



Converging Technologies

EDITED BY MAURITS DOORN

STT 71



STT Netherlands
Study Centre for
Technology Trends



Converging Technologies

STT Netherlands
Study Centre for
Technology Trends



The Netherlands Study Centre for Technology Trends (STT) was founded in 1968 by the Royal Institution of Engineers (KIVI). STT has the following aims:

- To evaluate technological trends from the viewpoint of the engineering sciences and to explore their interaction with other developments in society as a whole.
- To give wide publicity to its findings as a contribution to a more integrated picture of the future of society in the Netherlands and elsewhere.

STT addresses itself to industry, government, science, and the interested layman.

STT visiting address is: Prinsessegracht 23, The Hague, the Netherlands.

Correspondence address:

P.O. Box 30424

2500 GK The Hague

The Netherlands

Telephone +31 70 302 98 30

E-mail: info@stt.nl

Website: www.stt.nl

Converging Technologies

INNOVATION PATTERNS AND IMPACTS ON SOCIETY

EDITED BY MAURITS DOORN

2006

STT

THE HAGUE, THE NETHERLANDS

COLOPHON

English translating and proofreading Justine Stoop, The Hague

Editor Maurits Doorn, Amsterdam

Book design Salabim Design Consultancy BNO, Rotterdam

Cover design Salabim Design Consultancy BNO, Rotterdam, with thanks to Peter Clevestig from DEZ3D, Stockholm, for providing the neuron shader

Printing DeltaHage bv, The Hague

ISBN-10: 90-809613-3-7

ISBN-13: 978-90-809613-3-3

STT Publication no 71

NUR 950

Key words nanotechnology, biotechnology, life sciences, information technology, converging technologies, regenerative medicine, nanoelectronics, innovation, technological change

© 2006 STT, The Hague, the Netherlands

Justification of the illustrations. The utmost care has been taken to find the proprietors of the pictures. Those who think to still have claims to certain rights are requested to contact STT.

All rights reserved under international copyright conventions.

No part of this work may be reproduced in any form by print, photo print, microfilm or any other means without written permission from the publisher.

Inquiries to Stichting Reprorecht Amstelveen, the Netherlands.

Contents

Preface	10
Management Summary Maurits Doorn	14
CONVERGING TECHNOLOGIES	18
Introduction Maurits Doorn, Arie Rip	18
Anticipating the Dynamics of Converging Technologies Maurits Doorn, Arie Rip	28

CASE STUDY REGENERATIVE MEDICINE	46
Introduction	46
John Jansen, Maurits Doorn	
Future Perspectives of Regenerative Medicine	58
Gert Meijer, Clemens van Blitterswijk	
Spinal Fusion	74
Diyar Delawi, F. Cumhuri Öner, Wouter Dhert	
Cardiac Cell Therapy: To Mend a Broken Heart	92
Brian Fernandes, Marc Hendriks	
Tissue Models	118
Carlijn Bouten	
From Laboratory to Practice: Learning about normative issues	134
Klasien Horstman	
Discussion and Conclusions	156
John Jansen, Maurits Doorn	
CASE STUDY NANO ELECTRONICS	166
Introduction	166
Fred van Roosmalen, Maurits Doorn	
Nanoelectronics and Society	178
Fred van Roosmalen, Maurits Doorn	
Innovation from Within the Existing Nanoelectronics Value Chain	186
Ivo Raaijmakers	
More than Moore and Heterogeneous Integration	200
Chris van Hoof	
Large-Area Printable Electronics	224
Frank Simonis, Herman Schoo	

Architectural Innovations in Perspective	244
Kees Eijkel, Erik Knol, Steven T. Walsh	
Discussion and Recommendations	266
Fred van Roosmalen, Maurits Doorn	
CONVERGING TECHNOLOGIES	274
Discussion and Conclusions	274
Maurits Doorn, Hans de Wit	
Index	282
Survey Organization	290
Project Cooperation	294
STT Publications	298
Financial Support STT	304

Preface

Innovation is about creating value in a complete value chain. The innovation process may start off with just a vague but potentially brilliant and creative idea, the outcome can be the solution to a societal problem or a product or service fulfilling a market need. All phases of the innovation process and every link in the value chain may be the source of new insights and knowledge that can be used to create value. Innovation processes are therefore not just about science, technology or R&D. Nevertheless, a new technology is an important and often essential factor in the innovation process, but it will only be fruitful if embedded in societal developments.

At an early stage of an innovation process, the value chain is often not clear, incomplete or changing at a high rate. Innovation at this stage can be a hazardous process with many failures and frustrations, increased by expectations that are too high. Because of the uncertainties about eventual outcomes it is difficult to make a realistic planning defining the steps to be taken.

At a later stage in an innovation process, the objectives — products, process technologies — become better defined, and actors can use planning tools, such as roadmapping, to anticipate developments and to coordinate their activities. One example is the use of roadmapping in the electronics sector discussed in the case study about nanoelectronics. Although innovation remains a journey into the future with ever-changing conditions and with a moving target, roadmapping is a useful exercise, which helps to anticipate future innovations as it allows to analyse, integrate and act upon the information available.

Roadmapping is even more difficult and sometimes impossible at an earlier stage. In case of printable large-area electronics, — discussed as part of the nanoelectronics case study — and regenerative medicine — the second case study in this book — the value chains are incomplete. Additionally, there may be social, ethical or institutional issues increasing the complexity.

Although planning innovations remains difficult and there is always the risk of hypes, well-expressed expectations can lead to a wise selection of technological options: We can call this dynamic process evolutionary but of course without the blind variation of options of the neo-Darwinian theory. Options are selected and shaped by the actors in the innovation process, increasing the success rate.

The relatively new paradigm of open innovation also reflects that the problems to solve, the products to design and produce and the development processes of innovative solutions are becoming more and more complex. No-one can cope on their own anymore. Various parties, big and small companies, universities, RTOs, NGOs and government, should cooperate as responsible partners mutually respecting their places in the value chain and stimulating each others strongholds.

Complex issues are characterized by an abundance of not entirely independent parameters, and we can only deal with these if we combine various disciplines. In fact, this is the main theme of this book: How to innovate by converging technologies?

In this book, the route of an innovation is mapped as a trajectory in a matrix with changing capabilities — technological or organisational — and linkages — between actors in value chains. With hindsight, organisations can learn from such patterns, and then use such insights to anticipate the future. Most are slow transition processes composed of many small, but fast and disruptive creative solutions, which are driven by visionary individuals with a deviating perception of our world. These creative minds are essential for any innovation process. The so-called European innovation paradox is not so much the result of a lack of translation of novelties into applications, but of the presence of a suffocating ambient for creative minds. Risk-taking is not a typically European habit, which is alarming since any creative process, wherever in the value chain, is breathtakingly risky!

‘Converging technologies’ is a label nowadays used to point at synergies between originally separate fields leading to revolutionary innovations. It is clear from the above that any complex issue can only be solved by converging technologies in an open innovation context. I am convinced that in 10 years time we will no longer use this term. It will be the standard in technological developments or, even better, the standard in societal transitions.

In this book, the mentioned patterns are simple and clear in the case study about nanoelectronics, less so in the case study about regenerative medicine. This reflects the different stages in the trajectories of the chosen topics. These differences do add to the educational power of the book. The case studies, together with the generic chapters on innovation and converging technologies, explain how the dynamic evolution processes work, describe the risks and factual failures in time and finally show the possible innovative outcome.

It teaches us not to shy away from planning, to open up to creative minds, not to believe that the prospected outcome is the sole solution, but to profit from the abundance of possibilities which pop up during the process, to adapt the planning at every dynamic crossover of a diversity of ‘converging’ capabilities and to use communication skills in order to arrive at a future with an even better than expected outcome.

We hope that the book will help policy makers, technology managers and R&D specialists to interact in designing innovative schemes for cooperation in order to create value for society.

Last but not least, we hope you will enjoy reading this book.

The Hague, October 2006



A handwritten signature in blue ink, corresponding to Prof dr J.H.W. de Wit. The signature is highly stylized and cursive.

A handwritten signature in blue ink, corresponding to Ir W. Draijer. The signature is highly stylized and cursive.

Prof dr J.H.W. de Wit
Chairman of the steering committee
Converging Technologies STT

Ir W. Draijer
Chairman STT

Management Summary

Maurits Doorn¹

CONVERGING TECHNOLOGIES

Recently, ‘converging technologies’ has become a fashionable label, pointing out emerging interactions between previously separate fields of research and technological development. Such shifts result in qualitatively new technological possibilities, with potentially revolutionary impacts. Whether or not the label converging technologies is used, there is definitely a shift going on in how different fields of technology interact. In the present shifts, nanotechnology plays an important role as an enabling technology, that, in combination with information technology, biotechnology and cognitive and neuroscience, can create major changes, for example in chips technology, drug delivery or implants (including electronic brain stimulation). Similar shifts occurred in the past, for instance in fields like materials science, mechatronics and information technology. These earlier examples illustrate that convergence is associated with changing innovation patterns, industry structures and broader developments in society.

¹ STT, Den Haag, the Netherlands.

In a recent series of high-level policy reports in the United States and Europe, the idea of converging technologies was adopted and associated with expected revolutionary improvements in human performance (US) or with a ‘next technology wave’ (EU). Critical commentators stress the possibility of undesirable outcomes. The result is a lot of hype and counter hype.

THE STT PROJECT

This book is one result of the STT foresight project about converging technologies. Starting point for this study is that the label converging technologies does refer to important qualitative changes in technological development and that similar changes occurred before. Insight into the dynamics of such earlier changes can help to cut through the rhetoric and hype to some extent, so as to better understand what is actually happening in particular technological domains today. Converging technologies present a twofold challenge. The first challenge is for actors to better understand the complex dynamics of converging technologies. The second challenge is to use such insight into the dynamics to actively shape the developments.

The book discusses two particular domains, nanoelectronics and regenerative medicine, which were the subjects of two case studies. These case studies constitute the core of this book. The case study approach was chosen to base the analysis on concrete developments. By doing so, we have attempted to step back from the current dynamics of expectation and hype.

We have asked practitioners from academia, public research institutes and industrial companies for each of the two domains to reflect on developments, sharing and at the same time furthering their understanding. Additionally, to deepen the analysis we have used insights from studies of innovation and the dynamics of technological change. The results of this process are reflected in the chapters of this book, written by the participants of the study.

RESULTS

The results of the study are twofold. On the one hand, insight into the dynamics of converging technologies. On the other hand, clues as to what are conditions that allow converging technologies to develop to the benefit of society. Here, we highlight a selection of the results of the study, integrating the results of the case studies.

INSIGHTS

- The dual-promise of converging technologies. Expectations about possible performance improvements or novel functionality (ambient intelligent information and communication systems, recovery or improvement — possibly at an early stage — of the ‘natural’ function of impaired tissue) are attributed to underlying actual technological developments that remain largely invisible (integrated multifunctional electronic devices and flexible interfaces, control of physiological processes underlying tissue development) but have their own dynamics. This dual-promise dynamics carries the risk of hype. Promises, as a way to articulate expectations, are necessary to start a process of agenda-setting, prioritization and resource mobilization. However, there is a risk of oversimplification, resulting in over-extended expectations and unrealistic requirements, and in the end in disappointment about otherwise promising technological options.
- The result of an agenda-setting process is emerging path dependencies, i.e. difficulty to move away from the path because it is a stabilized pattern of interactions. The actual shape of such trajectories depends on the context. Trajectories in health, electronics, architecture, agriculture will differ as they are shaped by different factors. In order to anticipate on future path dependencies, and maybe even influence them, it is interesting to characterize the actual factors that shape these trajectories. Such factors include not only the technological developments but also sector-structural developments — such as reconfigurations of value chains — or broader societal developments — of for instance regulatory or normative frameworks.
- Insight in such trajectories, both in technological developments and in the associated sector-structural developments, can be used to map the development path of a technology in time, both retrospectively and anticipatorily. Such maps can serve as a ‘roadmapping’ tool to articulate visions about future developments, to commit stakeholders and to define a course of (collective) action.

CONDITIONS

- Broad, multidimensional and dedicated research programmes are needed to stimulate a creative tension between a realistic assessment of what is possible and a desirable future. Such programmes should not only pay attention to science and technology, but also take into account contextual social and economical issues including regulatory, economic, and ethical issues. Considering the open-ended character and complexity of the developments — where structured foresight is not a possibility — a way forward can only be found if the non-technological issues are addressed simultaneously with research and technological development, in a step-by-step learning process that includes all relevant actors.

- At the start of a trajectory, a value chain starts to emerge and roadmapping becomes possible. Roadmapping is a tool to articulate a shared vision of the future in order to timely address a problem or to fulfil a market need. A good roadmap emphasises the commitment of all stakeholders. The coherence between various levels of abstraction, such as technology, product and marketing planning, are made explicit in the roadmapping process in order to steer the planning and decision-making. Aspects of scenario planning are taken up in this process, so that for instance relevant societal issues and sector-structural developments can be placed on a time scale and clearly specified future milestones can be defined. Then, backcasting to the present, a course of action can be defined. A roadmap is not a static plan: It should be regularly updated to incorporate new insight and adapt to changing circumstances.
- Cooperation across the entire value chain is essential, for small and large companies alike. Realising that it is impossible to predict which products will be winners and when the associated volume markets will take off, well-organised R&D ecosystems are necessary that foster parallel emerging technology developments. Such ecosystems should enable cross-fertilisation in an open innovation atmosphere while protecting the intellectual property rights of the actors involved in a responsible manner. ‘Responsible partnering’ is an essential success factor in open innovation. Both internal and external communications are essential throughout the ecosystem to enable the actors to decide at the right time on the continuation of winner technologies and the discontinuation of less promising options. In the ideal ecosystem, very innovative R&D infrastructures are in close proximity to traditional production methodologies; this will stimulate the convergence of know-how from all domains and reduce the inevitable struggle of innovative concepts to become accepted in volume applications. Ideally, the R&D ecosystem will be a fusion of large and small industry, notably start-ups, together with universities and institutes. It requires a different way of thinking about cooperation, also between small firms and larger corporations.

Introduction

Maurits Doorn¹, Arie Rip²

CONVERGING TECHNOLOGIES

Whether the label of ‘converging technologies’ is used or not, there is definitely a shift going on in how different fields of technology interact, and in doing so introduce qualitatively new possibilities, with perhaps revolutionary future impacts. Mechatronics, the combination of mechanical and electronic engineering, was an earlier example. And materials science, now one domain, can be seen in itself as the outcome of the convergence between chemistry, physics and materials engineering. In the present shifts, nanotechnology plays an important role as an enabling technology, which, in combination with information technology, biotechnology and cognitive and neuroscience, can create major changes, for example in chips technology, drug delivery and implants (including electronic brain stimulation).

These shifts are characterised in policy-oriented reports as ‘converging technologies’. The report ‘Converging Technologies for Improving Human Performance’ on the convergence of Nanotechnology, Biotechnology, Information Technology and Cognitive Science [Roco and Bainbridge, 2003; Roco and Bainbridge, 2002] has been particularly influential. The report is based on a conference in June 2002 that was sponsored by the USA National Nanotechnology Initiative which is presided by one of the editors,

¹ STT, Den Haag, the Netherlands.

² Universiteit Twente, Enschede, the Netherlands.

M.C. Roco. In Europe, it was deemed necessary to articulate a response, and an expert group produced a report on converging technologies for the European knowledge society [Nordmann, 2004]. Other responses come from critical commentators, such as the ETC group, which reformulated the NBIC (Nano, Bio, Info and Cogno) message of Roco and Bainbridge as the Little BANG, because the elementary building blocks Bits, Atoms, Neurons and Genes were now to be combined to give rise to a Big Bang of unprecedented and possibly undesirable options for intervention [ETCgroup, 2003].

A lot of hype, and counter-hype (about negative impacts), is involved in these discussions. Thus, the use of the label ‘converging technologies’ — as we do in this book — is risky: One can become associated with the hype. But we think the label does indicate an important qualitative shift, as well as a shift which has occurred before. We have already mentioned materials science & engineering and mechatronics. Reference can also be made to the convergence of computing, communication and media technologies, for which the label of convergence was actually already used in the late 1990s (see, e.g., [Castells, 2000]). These examples show that convergence, in terms of synergistic new combinations of knowledge and technological capabilities, can indeed open up new and unexpected spaces for technological development with, potentially, enormous impacts on society. Since there are earlier examples of converging technologies, one may inquire into their nature and the dynamics of their development. This is one of the challenges taken up in this book: Can we use insights drawn from studies of such developments (and from innovation studies and technology dynamics more generally) to better understand what is actually happening in particular domains today? To that end we have selected two domains, nanoelectronics and regenerative medicine, on which this book focuses.

In the chapter ‘Anticipating the Dynamics of Converging Technologies’, we will draw on specific insights from innovation and technology dynamics studies indicating the elements from these studies that have to be taken into account so as to better understand the dynamics of converging technologies in general and that in the case studies in particular. But we will first introduce two key issues about converging technologies in general.

First, the evolution over time of converging technologies, i.e. the way that different technological trajectories get linked up, become entangled and deliver new technological options. And coupled to this, the difference between, on the one hand, the performance at system level, serving actual or potential needs and demands — about which the promises are made — and, on the other hand, what may be called the ‘physical layer’ that underpins such a

performance, but has its own possibilities and limitations (see the section ‘Dynamics of development’ hereafter).

Second, how various actors start to reflect on ongoing developments, with the promise of converging technologies as an entrance point. Insight into the combination of technical possibilities and changing innovation patterns, industry structures and broader developments in society can then be used to better shape (or modulate) such developments. The aim of this book is to contribute to such analysis and reflection (see the chapter of Doorn et al. ‘Anticipation the Dynamics of Converging Technologies’).

DYNAMICS OF DEVELOPMENT

First, the dynamics of the development of converging technologies. Looking back, there appears to be a pattern of links between fields which are more than supply and uptake, as is the case, for example, with analytical chemistry and pharmaceuticals or environmental monitoring. The supplying field creates new possibilities for the receiving field, while the latter actively engages with the supplying field. Electronic engineering started out as a simple supplier to mechanical engineering but with the development of robotics, an integrated trajectory started and was labelled mechatronics. Kodama [Kodama, 1991] who studied this case and the earlier case of materials science, speaks of ‘fusion’ of technologies — and adds that Japan’s focus on fused technologies explains part of its (then) leading edge. For the present combination of nanotechnology, neuroscience and cognitive science, the beginnings of such an integrated trajectory built around the electro-stimulation of the brain can be observed.

The broader version of the notion of converging technologies pushed by Roco and Bainbridge is more programmatic. With them, the notion has become an umbrella term for a variety of entanglements of technological trajectories. Part of its impact has to do with the idea that these NBIC technologies will become the leading edge technological domains of the 21st century, exactly because they are converging. Our approach in this book is to look closely into specific entangled trajectories – in nanoelectronics and in regenerative medicine – but we will come back in the Discussion and Conclusions chapter to the broader issues of conditions for such innovations.

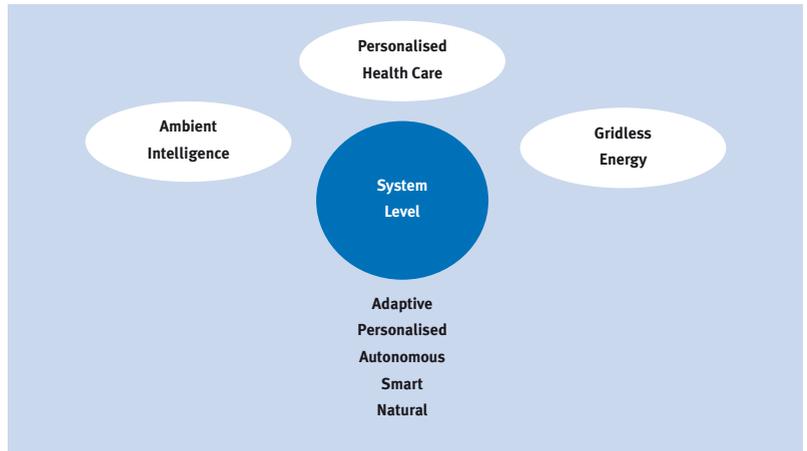
There is the risk of a hype when emphasising the broader, programmatic notion of converging technologies and their impact, without checking what is actually happening ‘on the ground’. However, the possibility of hype is in a sense built into the dynamics of new and emerging science and technology: Without promises, new options and applications cannot be further articulated nor selected. The structure of this situation, promises and actual performance

versus the invisible technologies achieving them, can be visualised in the three diagrams below.

In the first diagram, we take ambient intelligence, personalised health care and gridless energy as exemplary overall entrance points. The performance is put upfront, the technology remains invisible — in some way the system does what is expected of it.

Figure 1

Expectations about performance improvements and new functionalities.



Then there is that what can be called the physical layer (which includes software and orgware), where all these wonderful things have to actually be made possible. Different fields, trajectories and actors are involved, and even when there is interaction and coordination, there is no guarantee that the expected performance at system level will actually be realised.

Figure 2

The physical layer that makes possible – or not – the high level promises.

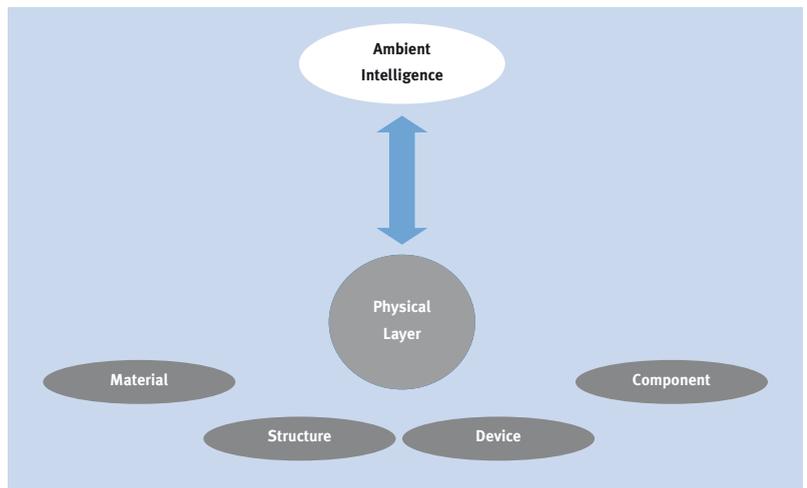
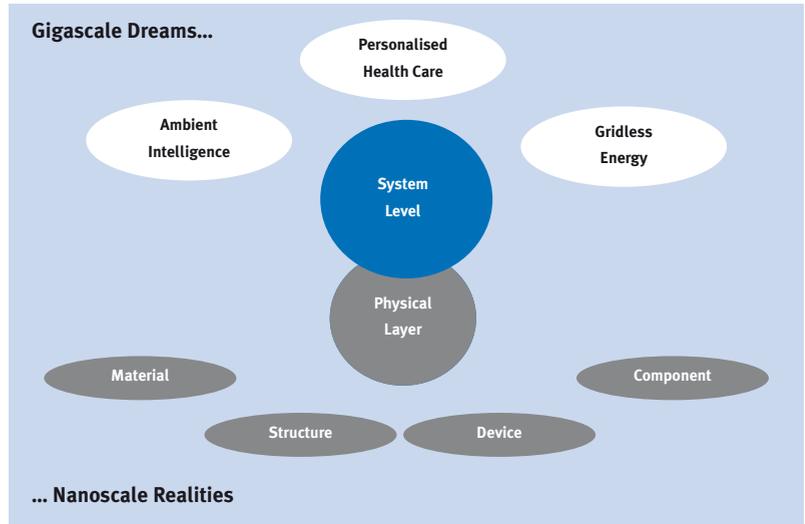


Figure 3

Dual promise of converging technologies: gigascale dreams and nanoscale realities. Bron: [De Man, 2005].

The two layers have their own dynamics. Together, they show how the dual promise of converging technologies (interactions between technological fields, impacts on society) should be positioned.



The two domains studied in the body of this book, nanoelectronics and regenerative medicine, show the dual promise dynamics: the promise of hoped-for performance and the promise of ongoing technological and sector-structural developments. In addition to learning about the specificities of the two domains, we can thus also learn about the patterns in the dynamics of converging technologies.

ANTICIPATION OF CONVERGING TECHNOLOGIES

The second key issue is that of anticipation. How do actors attempt to understand the dynamics of the domains they are involved in, and how do they use such insights to actively shape developments?

The introduction of a new label, while this starts out as the action of one actor pushing his interests (as when Roco and Bainbridge organised their conference in 2002 and put ‘converging technologies’ in the title), can be an incentive for other actors (like the authors of this book) to try and understand what is happening. The introduction of the label ‘mechatronics’ had such an effect, and ‘converging technologies’, when accepted as more than rhetorics to create visibility, will have such an effect. That is a reason why we continue to use the reference to the umbrella term ‘converging technologies’ in this book: There might be patterns that one can learn from, for the next steps in one’s own domain, or for other domains.

THE STT STUDY ‘CONVERGING TECHNOLOGIES’

The purpose of the STT project ‘Converging Technologies’ was to discuss how fields of research and technology link up in practice and promise, to see how actors can use the resulting insights to better anticipate and to point out under which conditions converging technologies can productively develop and achieve their promises.

We have selected two particular domains, nanoelectronics and regenerative medicine, as subjects for the two case studies. These case studies constitute the core of this book. The case study approach was chosen to help us to base our analysis on concrete developments. By doing so, we have attempted to step back from the current dynamics of expectations and hype.

We have asked practitioners from academia, public research institutes and industrial companies for each of the two domains to reflect on developments, sharing and at the same time furthering their understanding. Additionally, we have used insights from studies of innovation and the dynamics of technological change (as outlined in the chapter ‘Anticipating the Dynamics of Converging Technologies’) to deepen the analysis.

This book reports on the results, drawing out possible futures and allowing further learning from the comparison of the two case studies. The book can then feed back into further reflection on and analysis of ongoing developments and help different actors to articulate their strategies. It will become part of the reflexive co-evolution of converging technologies and society.

INTRODUCING THE CASE STUDY

REGENERATIVE MEDICINE

Regenerative medicine refers to the development of therapies for the treatment or replacement of impaired tissue. The long-term objective of regenerative medicine is to combine results from different fields in life sciences and medical biotechnology and translate these into regenerative therapies for impaired tissue. From time to time, a process of trial-and-error results in a step forward, but the results cannot comply with overheated expectations.

One example, tissue engineering, refers to the option of in vitro manufacturing of tissues (see the chapter of Jansen et al. ‘Introduction’, and the chapter of Meijer et al. ‘Future Perspectives of Regenerative Medicine’). This field of

research emerged in the 1990s but could not meet the overheated expectations, with a classic hype-disappointment cycle (see the chapter of Doorn et al. ‘Anticipating the Dynamics of Converging Technologies’) as a result. Tissue engineering was, for instance, associated with the image of a future body shop where tissue and organs can be manufactured on demand and then implanted to replace defective tissue. However, researchers, clinicians and industrial actors were confronted with an unanticipated complexity — not only technological but also with respect to the introduction into clinical practice and broader societal issues. In the case study, the underlying dynamics are investigated, in order to identify what can be learned in anticipation of new developments.

Recent findings in genomics, proteomics, stem cell research and biomaterials research offer new hope at the end of tissue regeneration. The case study discusses two examples, cell therapy as a treatment option for heart failure (see the chapter of Fernandez et al. ‘Cardiac Cell Therapy’) and the use of growth factors in orthopaedic surgery of the spine (see the chapter of Delawi et al. ‘Spinal Fusion’). These examples not only serve to illustrate the possibilities of tissue regeneration with all the related complexity but also discuss other factors — cost-effectiveness, insurability, regulation, normative issues — that together shape and are shaped by the development of these potential therapies. Integrating the lessons learned from the study of tissue engineering and examples of therapies that emerged more recently, the chapter discusses conditions as to how the field can be moved forward. One aspect that requires special attention is the open-ended character of the developments, full of surprises, contingencies, branching and feedback. The idea of in vitro tissue manufacturing is now explored for its application in tissue models (see the chapter of Bouten ‘Tissue Models’). The uncertainty about possible outcomes means that, for instance, ethical dilemmas that arise in the course of the development trajectory cannot be dealt with upfront but need to be dealt with in a step-by-step learning approach (see the chapter of Horstman ‘From Laboratory to Practice’). Finally, the chapter provides clues on how to improve the process of agenda-setting and other conditions for research programs to more productively develop the possibilities in this field (see the chapter of Jansen et al. ‘Discussion and Conclusions’).

NANOELECTRONICS

The label of nanoelectronics encompasses a multitude of newly emerging technologies, some of which will eventually make possible the physical layer of future electronics products and systems. Expectations about the future of electronics, such as Ambient Intelligence, assume not only an ongoing improvement of the existing technological trajectories such as, for instance,

the trajectory of logic and memory ICs described by Moore's law, but also the development of a range of new technological possibilities.

This case study discusses two fields, 'More than Moore' and 'Polymer-based Large-Area Electronics', that are part of the nanoelectronics field. In the More than Moore domain technological options emerge to permit the integration of, for instance, MEMS or biosensors with logic and memory functionality into one electronic device, 'on-chip' (System-on-Chip, SoC) or 'in-package' (System-in-Package, SiP). The other field, printable large-area electronics, is a field of technological options that promise to make possible the seamless interaction between an electronic device or system and its users and the environment of ambient intelligence. Examples of such interfaces are flexible displays, signage, tags, thin-film power, sensors, that can be integrated on a large variety of surfaces such as packaging materials, building materials, textiles, etc.

Even with this delineation, the nanoelectronics field features a proliferation of technological paths, constituting a veritable maze in which it is difficult to chart a way toward the future. Two chapters in the case study discuss the technological developments in More than Moore (see the chapter of Van Hoof 'More than Moore and Heterogeneous Integration') and Large-Area Electronics (see the chapter of Simonis 'Large-Area Printable Electronics'). The purpose of these chapters is not to provide an inclusive overview of all technological options in these fields but to provide a more in-depth analysis of selected technological paths, and to use these insights to anticipate future developments. The authors make use of a mapping tool, the Abernathy and Clark transience map — introduced in the next chapter (see the chapter of Doorn et al. 'Anticipating the Dynamics of Converging Technologies', section The Abernathy and Clark model and its generalisation, Figure 3 'Four types of innovation') — to map technology paths and associated application and technology roadmaps. Two other chapters discuss the dynamics from the perspective of sector-structural developments, studying how innovation can be promoted from within the existing value chain (see the chapter of Raaijmakers 'Innovation from within the Existing Nanoelectronics Value Chain') or from start-ups aiming at disruptive innovations (see the chapter of Eijkel et al. 'Architectural Innovations in Perspective').

REFERENCES

- Castells, M. (2000). *The Rise of the Network Society. 2nd Edition*. Malden, MA Oxford, UK, Blackwell Publishers
- De Man, H. (2005). *Ambient Intelligence: Gigascale Dreams and Nanoscale*

Realities. Solid State Circuits Conference, 6-10 February

- Etcgroup (2003). *The Little Bang Theory*. <http://www.etcgroup.org/en/materials>
- Kodama, F. (1991). *Emerging Patterns of Innovation: Sources of Japan's Technological Edge*. Boston, Harvard Business School Press
- Nordmann, A. (2004). *Converging Technologies - Shaping the Future of European Societies Foresighting the New Technology Wave*. HLEG Foresighting the New Technology Wave. Report to to European Commission Research. Brussels (http://ec.europa.eu/research/conferences/2004/ntw/index_en.html)
- Roco, M.C., Bainbridge, W.S. (eds.) (2003). *Converging Technologies for Improving Human Performance: Nanotechnology, Biotechnology, Information Technology and Cognitive Science*. Kluwer Academic Publishers. (Also available at <http://www.wtec.org/ConvergingTechnologies/>)

Anticipating the Dynamics of Converging Technologies

Maurits Doorn¹, Arie Rip²

PATTERNS IN TECHNOLOGICAL CHANGE AND INNOVATION

As discussed in the chapter of Doorn et al. 'Introduction', converging technologies are synergistic new combinations of scientific and technological fields that open up new spaces for technological development and create promises of value creation. These promises influence strategies of R&D actors, firms and governmental actors. In due course, there will be changes in industrial networks and, more generally, in the socio-economic context, where these technologies are produced. In addition to the economic effects, the emergence of converging technologies is reflected in changes in the organisation of scientific and technological disciplines, new approaches for the organisation of research and development, the dynamics of industrial sectors and even in broader socio-economic developments.

¹ STT, Den Haag, the Netherlands.

² Universiteit Twente, Enschede, the Netherlands.

If ‘converging technology’ refers to a recurrent phenomenon in processes of technological changes with significant, and potentially revolutionary, impacts on society, it is important to understand this phenomenon in order to anticipate future developments. Are there patterns that will be repeated? And, if so, can actors use their knowledge of these patterns to anticipate future changes? Could an improved understanding of the dynamics of converging technologies help the actors to go beyond an ad-hoc approach to the developments and to base their actions on a more integrative picture of the factors determining the dynamics?

These are ambitious questions. In this chapter, we will limit ourselves to offering building blocks for answers. The first section will present insights and analytical tools derived from studies of the dynamics of technological change and innovation. In the second section, we will look at the expectations about the possible function and value of new technological options, and how such expectations fuel the dynamics, and lead to specific trajectories of development. In the third section, we will present an approach to map such trajectories as they unfold. In the concluding section, we will indicate how these building blocks will be visible in the two extended case studies of converging technologies.

TECHNOLOGICAL CHANGE AND INNOVATION PROCESSES

Innovation processes are often presented as linear, with innovations progressing through a number of successive stages, from basic research through technical development and engineering toward final commercialisation. The underlying assumption is that innovation processes gradually develop toward a pre-defined goal, progressing along a logical trajectory and within a stable, well-controlled environment. While such a picture may be retrospectively presented as a kind of streamlined history, which filters out failures and other contingencies that happened along the way, it does not reflect the actual dynamics. There is more complexity: There are feedback and feedforward loops, setbacks and other contingencies of the innovation ‘journey’ [Van De Ven, 1999]. In addition, innovation journeys are embedded in larger patterns: of expectations about the right direction when developing further products and of sector structures, which make certain innovations easier than others (for example, capacity-maintaining innovations rather than potentially disruptive innovations).

These larger patterns can be captured by the concept of a technological regime, the rule-set or grammar that shapes efforts at technological change

to realise process or product innovation. Nelson and Winter (1977) [Nelson et al., 1977] introduced this notion, and used as an example the Douglas DC-3 aircraft of the late 1920s, with its metal skin, low wings and piston engines under the wings. It became the model, or dominant design, for subsequent generations of aircraft [Anderson et al., 1990; Tushman et al., 1986]. As Nelson and Winter emphasised, such a regime relates to “*technicians’ beliefs about what is feasible or at least worth attempting*”. Aircraft engineers held strong notions regarding the potential of the DC-3 design, and subsequent innovations essentially exploited this potential. Thus, a technological regime gives rise to (and is visible in) a technological trajectory. As Dosi (1984) [Dosi, 1984; Dosi, 1982] noted, economic evaluations then become superfluous: Following the trajectory means that a market is assured.

However, such regimes can be superseded, as when jet engines were introduced in the 1950s leading to a modified design from the DC-9 generation onward. A regime can also be replaced, as when CDs made gramophone records obsolete (except in certain niche markets). Based on the nature of the technological change involved, innovations can be differentiated in regime-following and regime-challenging. This distinction is usually phrased as ‘incremental’ innovation versus ‘revolutionary’ innovation, sometimes with a normative overtone that ‘revolutionary’ is better — and anyway more exciting — than ‘incremental’. We prefer more operational characterisations, such as regime-following versus regime-challenging, or capacity-maintaining innovation versus capacity disrupting innovation. This last-mentioned distinction will be taken up again when we discuss the Abernathy and Clark model [Abernathy et al., 1985].

First, we will discuss the dynamics of innovation in further detail. For an invention to develop into an innovation, the new idea has to be combined with other (existing and new) knowledge, capabilities, skills and resources. A firm needs access to manufacturing capabilities, access to markets, a distribution system, financial resources, etc. to turn an invention into an innovation. Complementary inventions/innovations are needed to successfully put an idea into practice. This is one of the causes of the considerable time lag that may occur between the new idea and its practical application. In the enthusiasm about the new idea, such complementary requirements are not always taken into account. Very early attempts to treat malfunctioning body parts by replacing them with body parts from slaves were not successful and could not be successful, given our present knowledge of the issues of sterility, immunology and wound healing (see the chapter of Jansen et al. ‘Introduction’ in this book). The present promises about human enhancement, including connecting chips to the brain, suffer from the same combination of enthusiastic projec-

tions and lack of knowledge of what is required for an actually successful functioning.

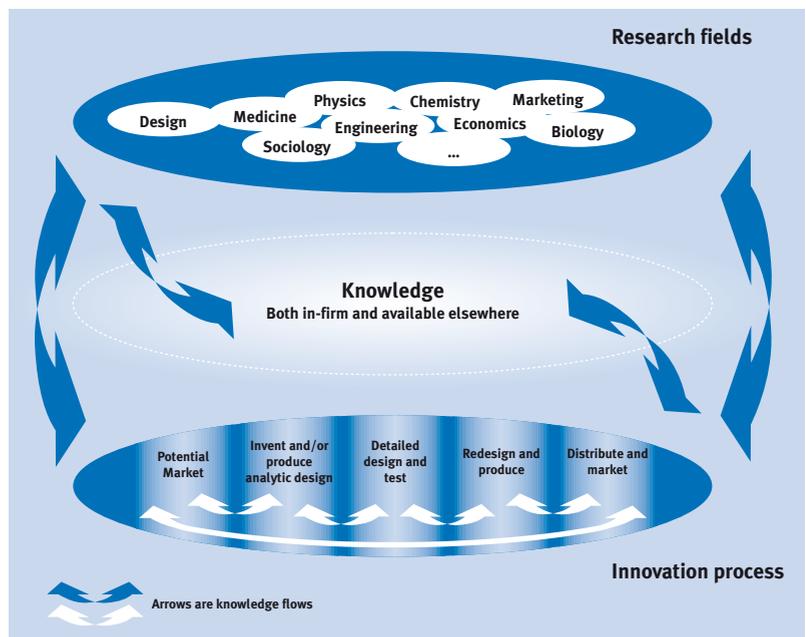
When an invention is developed, it will change as it is combined with existing context and with complementary inventions and innovations. Kline and Rosenberg pointed out the implications:

“It is a serious mistake to treat an innovation as if it were a well-defined, homogenous thing that could be identified as entering the economy at a precise date — or becoming available at a precise point in time. (...) The fact is that most important innovations go through drastic changes in their lifetimes — changes that may, and often do, totally transform their economic significance. The subsequent improvements in an invention after its first introduction may be vastly more important, economically, than the initial availability of the invention in its original form” ([Kline et al., 1986] p. 283 cited in [Fagerberg, 2003]).

Kline and Rosenberg also suggested a general pattern for innovation processes and their links to relevant knowledge, the chain link model. A version of this model is shown in (see Figure 1 ‘The chain link model of innovation’ (adapted from [Phillips, 2003]).

This model does three things. Firstly, in this chain link model, the various stages of the innovation process are shown as interconnected in a web of feedback loops, rather than as a linear, sequential cycle. This indicates the variety

Figure 1
The chain link model of innovation.



of types of knowledge that are relevant for a successful innovation, including market knowledge and knowledge of complementary inventions. Secondly, the model also shows the links of the innovation process with ongoing research processes that have their own dynamics. These links not only reflect the contribution of scientific research to innovation processes, but also the reciprocal dependence of science on innovation, for agenda-setting and for tools and equipment. For instance, the technological challenges related to the space race and the cold war required a better understanding of the structure–property relationships of materials, and this was the motivation to create materials science as an interdisciplinary field of academic research. Soon, other issues in innovation processes defined the agenda of materials science, for instance the need to better understand materials processes and properties that were important for semiconductor devices, as discussed in the case study nano-electronics, but also the need for biomaterials for implants, as discussed in the case study regenerative medicine [Brooks, 1994; Cahn, 2001]. Finally, the chain link model indicates that such knowledge can come from within or without an organisational unit, such as a firm. How exactly knowledge is linked to innovation processes will depend on how innovation processes are organised in the various fields. Patterns of linkages in industry, services, health, etc. can differ significantly. Moreover, such patterns may evolve in response to changes. For example, in an industrial setting, the mode of organisation of R&D significantly changed in the course of the twentieth century, most recently toward open innovation settings (see, e.g., [Chesbrough, 2003]).

Note that converging technologies appear twice in this model: at the research side, where new and promising technological options are created, and at the innovation side, where new processes and products are introduced in the market in the hope they will realise their promised impacts.

Terminology: Innovation, technological change

Three characteristics of innovation:

- Value is created as an invention, is put into practice, and becomes tradable in a market or in other ways, e.g., use in the health sector.
- This requires new combinations of knowledge, capabilities, skills and resources.
- Innovation is a continuous process of de-alignment in an existing order, to create space for the novelty and re-alignment to make the new configuration work.

While innovation is often related to new products and production technologies, innovation can also be based on changing supply chains, access to new markets, customers or users or new organisational forms. It will be clear that not all innovation is technological. Product innovation — based on new or improved products — and process innovation — based on new or improved production technologies

— are often directly related to new technological options, whereas other innovation types are not necessarily directly or exclusively related to technological change.

While technology can be used to distinguish a production technology from a product ('chips technology' versus 'chips'), its use is broader. The word 'technology' may be used to depict an artefact (a spoon, hammer or space station), the skills and techniques involved in producing these artefacts or the abstract idea of technology as a force in society (e.g. 'technology as boon or bane'). Rip and Kemp (1996) discussed these and other uses in depth and then proposed a definition for technology as 'a configuration that works' which captures the key aspects. It combines form ('configuration') and function (it works). It does not predefine what is part of the configuration and what is not, recognising that the working of a technology is generally based on its links with other artefacts. Nor does it limit the elements of the configuration to material ones; there can be educational technologies, such as curricula and the discipline of schooling.

Technological changes consist of changes in technology and the dynamics of such changes. It is often conceived as a force impinging on our societies. While it may be experienced as an external force, this is so because it is difficult to influence its direction, not because it is external to society. Technology is developed and influenced all the time, but the net effect depends on interactions and shifts of many actors in many places. The emergence of a dominant design is an example of where such dynamics can be traced in detail.

There are more patterns in innovation processes, and in technological change, for that matter. In the next two sections, we shall specifically look at expectations, and at the extent of change anticipated by an innovation. The concept of pattern, as we use it here, is somewhat stronger than the common-sense notion. Patterns can be observed in ongoing actions and interactions, and in how developments are shaped in a more or less recurrent manner. Moore's Law in microelectronics is a well known example of such regularities. Although it is called a 'law', it is actually continually achieved (i.e. constructed) through the efforts of many actors joined together in a strategic game of competition and partial coordination. This exemplifies a general point: Patterns are constructed, but the regularities involved may be used to anticipate. That is why we can tell something (precariously, since it is about the future) about emerging technologies even if at a very early stage.

An evolutionary perspective is particularly relevant for technological change and innovation, where novelties are introduced. The introduction of a novelty can be compared with a variation (a mutation in the case of the neo-Darwinian biological evolution theory), and its subsequent fate is determined by how it is

nurtured as well as challenged in overlapping selection environments. For our purposes, we do not have to go into great detail here. (See box ‘Patterns: an evolutionary perspective’). It is a way to integrate promises, and expectations more generally, into ongoing dynamics of technological change.

Patterns: an evolutionary perspective

Technological change and innovation are full of contingencies, while at the same time patterns emerge. Evolutionary theories can address this because they combine contingent variation and selection leading to stability in due time (for example, biological species). This is how evolutionary economics (and the related sociology of technological change) attempts to understand the dynamic characteristics of innovation, something that is out of reach of the equilibrium theories of mainstream, neo-classical economics. (Note that the term ‘evolutionary’ is not used here, denoting step-by-step, gradual change, contrasting it to revolutionary change but in the sense of biological evolution.) The evolutionary view recognises that innovation always implies the introduction of novelty, whether technological or not, into an existing order. Such novelty is then seen as a variation, just as mutations in neo-Darwinian evolutionary theory are variations. The context in which a novelty emerges (say, a firm) acts as an early selection environment, and when accepted (‘surviving’), as a retention mechanism. The eventual wider selection environment is more than a market, where firms compete with products. There are further selections taking place: The degree of compatibility with existing technical systems and infrastructures, institutions such as the patent system and the way it is applied, various regulations, a broader public acceptance of new technologies and products. The combination of retention and more or less stable selection environments is the mechanism behind the emergence of irreversibilities and patterns – species in biology, trajectories, regimes and dominant designs in economics and sociology of innovation.

The evolution of technology in society differs from neo-Darwinian evolutionary theory because here variation is not blind and the selection environment is not independent of variation generation. Actors develop and select technological options based on expectations: of their promise, linked to eventual chances of survival. And they actively shape the new option so as to create a better fit with the expected selection environment, for example in test-labs and with user tests. At the same time, the selection environment might be influenced. For example, when the synthetic dye industry emerged, and technological innovation became routine in the labs of German companies such as Bayer, spokespersons for the industry attempted to change the rules of the patent system to allow routine discoveries (as with azo dyes) to be patented. In the course of time, further changes occurred because the dyers became dependent on the manuals developed by the dyestuff producers, rather than that they set requirements on the dyes to be developed.

A further application of the evolutionary theory is the notion of punctuated equilibrium: A period of relative stability (in terms of emergence of new species) is broken ('punctuated') somehow, an explosion of variations occurs with partial survival and changing selection criteria. In microelectronics, there are the dominant CMOS regime and its development following Moore's Law as a dynamic equilibrium, which is now punctuated because of new technological opportunities as well as broader search strategies, given the expectation of a 'brick wall' limiting the continuation of Moore's Law.

EXPECTATION DYNAMICS AND PATH DEPENDENCIES

Why discuss expectations separately? Expectations as such are an important feature because they articulate the possible future value of a new technological option or a fledgling innovation. This can be done in a structured but limited way as when venture capitalists calculate the potential return on investment in a technology in order to make better decisions.

Expectations are a bridge between explorative work on improved product performance and better production processes on the one hand, and the exploitative interests of economic actors (firms, venture capitalists) to create innovations that will find a market on the other hand.

Expectations anticipate, and an effort can be made to better anticipate. There is a tradition of forecasting, but for a large part of the examples of technological changes we are considering, the situation is too open-ended for systematic forecasting. We are looking at earlier stages, where the rhetoric of expectations and promises serves to set agendas and to mobilise.

In a sense, promises are necessary to create visibility and interest for new technological options [Van Lente, 1993]. At the same time, it is inevitable that there will be some exaggeration, in some cases hype. Scientists and technologists contribute to the promising, whereas at the same time they are concerned about hype — it is not an easy balance. They expect there to be hype and, because there is no way to distinguish hype from justified hope at an early stage, the expectation is that there will be a lot of hype, followed by a reaction leading to realism. There are different strategies, for example in nanotechnology, between the United States, where a 'third industrial revolution' is promised and the idea of converging technologies serves to articulate this promise [Roco et al., 2002; Roco et al., 2003], and Europe, where 'making things smaller and faster' is the key phrase.

The stage model of a hype followed by realism is now widely recognised as the

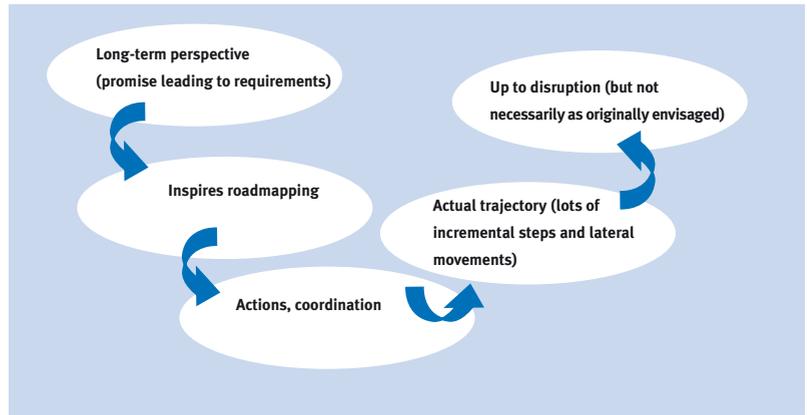
hype-disappointment cycle that was famously adopted by the Gartner Group, a consultancy. They used it, for example, in a 1999 report that supposedly anticipated the bursting of the ICT bubble in 2000 [Gartner]. This is an example of a meta-expectation — an expectation not so much about the actual technology but about the way the technology will develop — used by actors to position themselves and to define their strategies. Meta-expectations can be structured further, for example, with the notion of new generations, an example of a prospective chronology [Schaeffer, 1998]. One example is the idea of a succession of therapeutic approaches in orthopaedics (see the chapter of Delawi et al. ‘Spinal Fusion’). Once adopted by actors, such meta-theories start to steer the developments.

Agenda-building is important for focusing efforts on a limited set of options, while other (competing) possibilities are abandoned, at least temporarily. Foresight exercises attempt to do this explicitly (not always with sufficient authority to make a difference). Agenda-building is a broader process and will have effects because of ongoing strategic choices. Promises initially made to mobilise resources now become obligations. This agenda-setting and resource mobilisation process constrains the option for further developments, as alternative options are abandoned, but at the same time it opens up new spaces for further development as new energy is put into the project, and new questions and challenges come on the agenda.

When expectations stabilise, they will start to shape the direction of further developments. This may be the start of trajectories, for instance defined through successive generations of products that shape further developments, as in the case of the DC3. After a certain time, the promises take on substance, not only in the shape of the concrete technologies, but also in the shape of the associated structures, routines, agreements, etc. that serve to produce these technologies and define the technological regime. Such trajectories and the associated regimes can be actual, based on working products — such as the CMOS-based integrated circuit that gave rise to Moore’s law — or potential — such as the tissue-engineering programme that promises a next step in the overall tissue replacement approach.

At present, fashionable roadmapping exercises are based in the phenomenon of emerging trajectories. Once a trajectory is established, roadmapping becomes useful as a way to indicate how a trajectory can be further exploited. Through involvement of relevant actors in the roadmapping process, the roadmap is also a way to coordinate activities and to get commitment. A good example is the ITRS roadmap (see www.itrs.net/about.html), the product of involvement of all relevant parties in the worldwide electronics sector.

Figure 2
Realisation of a perspective.



Hype or no hype, the net result is that paths emerge with some path dependency, i.e. difficulty to move away from the path, because it is a stabilised pattern of interactions. The actual shape of such trajectories depends on the context. Trajectories in health, electronics, architecture, agriculture will differ, because they are shaped by different factors. In order to anticipate future path dependencies, and maybe even to influence them, it is interesting to characterise the actual factors that shape these trajectories. Such a characterisation is possible through the mapping of capabilities and linkages, an analysis first introduced by Abernathy and Clark for the automobile industry.

THE ABERNATHY AND CLARK MODEL AND ITS GENERALISATION

Abernathy and Clark, in their seminal 1985 article ‘Mapping the winds of creative destruction’ [Abernathy 1985], argue that it is not product features as such that determine what happens, but the underlying competencies enabling firms to develop and market such products. It then becomes important to characterise potential innovations as to whether they conserve such competencies, or make them obsolete (or just irrelevant for the potential innovation). This is why they develop a mapping tool, and one which is broader than the one-dimensional distinction between conservative innovations and disruptive innovations. They distinguish two dimensions related to different types of competencies: capabilities and linkages.

Capabilities

Technical and production capabilities, but also scientific and technological knowledge and knowledge embedded in organisational processes, systems and procedures.

Linkages

Linkages to users, customers and markets, not only comprising commercial

Domain of innovative activity	Range of impact of innovation	
I Technology/Production		
Design/embodiment of technology	improves/perfects established design	offers new design/radical departure from past embodiment
Production systems/organisation	strengthens existing structure	makes existing structure obsolete; demands new system, procedures, organization
Skills (labor, managerial, technical)	extends viability of existing skills	destroys value of existing expertise
Materials/supplier relations	reinforces application of current materials/suppliers	extensive material substitution; opening new relations with new vendors
Capital equipment	Extends existing capital	extensive replacement of existing capital with new types of equipment
Knowledge and experience base	builds on and reinforces applicability of existing knowledge	establishes links to whole new scientific discipline/destroys value of existing knowledge base
II Market/Customer		
Relationship with customer base	strengthens ties with established customers	attracts extensive new customer group/creates new market
Customer applications	improves service in established application	creates new set of applications/new set of customer needs
Channels of distribution and service	builds on and enhances the effectiveness of established distribution network/service organisation	requires new channels of distribution/new service, after market support
Customer knowledge	uses and extends customer knowledge and experience in established product	intensive new knowledge demand of customer; destroys value of customer experience
Modes of customer communication	reinforces existing modes/methods of communication	totally new modes of communication required (e.g. field sales engineers)

Table 1
Capabilities and linkages in the automobile industry.

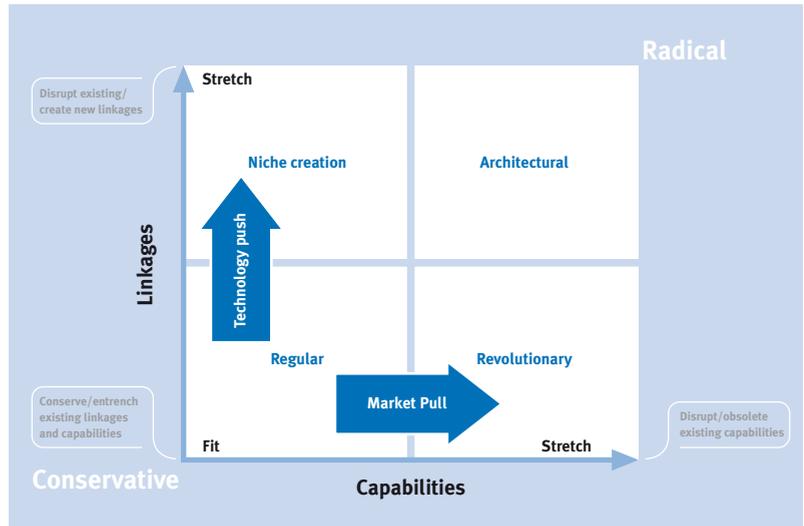
relations, but also deeper linkages, for instance at the level of (user-specific) application knowledge, customer experience, etc.

As an example, the technological capabilities and linkages to customers and markets that Abernathy and Clark identified for the automobile industry are presented in Table 1 ‘Capabilities and linkages in the automobile industry’.

Distinguishing between smaller and larger changes (disruptions) in the two types of competencies, they created a 2x2 matrix and labelled each of the four cells in the matrix as a particular type of innovation (architectural, niche, regular and revolutionary). See Figure 3 ‘Four types of innovation’.

The specific labels chosen by Abernathy and Clark are less important than the dynamics they attempt to capture. For example, the label ‘revolutionary’ now

Figure 3
Four types of innovation.



stands for the introduction of novel capabilities (new product, existing market), while it is often used to indicate disruptive changes in both dimensions. For this cell in the matrix, Abernathy and Clark chose to use the label ‘architectural’. In their eyes, such innovations were characteristic for the creation of new industries as well as the reform of old ones:

“Innovation of this sort defines the basic configuration of product and process, and establishes the technical and marketing agendas that will guide subsequent development. In effect, it lays down the architecture of the industry, the broad framework from within which competition will occur and develop” (p. 7).

Abernathy and Clark pointed out that the four different types of innovation require different strategies (‘fit’ versus ‘stretch’ with respect to the environment) and management approaches and structures. It goes without saying that the dichotomisations leading to four distinct types is a simplification, as innovation always involves some disruption of linkages and capabilities: The degree of change on the two dimensions is continuous.

A further point should be made. Abernathy and Clark’s analysis, based on the automobile industry, is relevant for large, integrated firms with an in-house R&D capability, their own manufacturing capacity and (more or less) direct access to end-customers. However, other industrial sectors, such as the micro-electronics sector, have a different structure. The competitive power of this industry is based on a highly differentiated value chain, where networks of highly specialised firms add value in a strategic game of cooperation and competition. In addition, more generally, broader linkages in business networks became more relevant in the course of the previous decades, as the ‘traditional’ model of closed innovation was left in favour of an open innovation

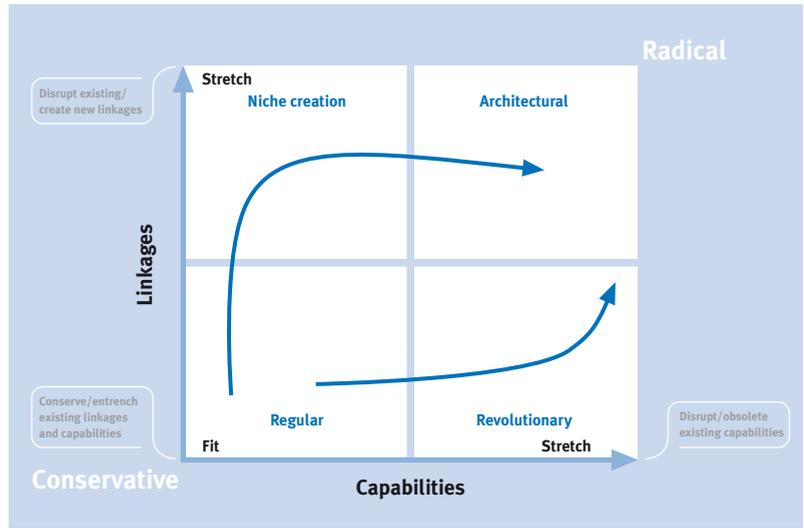
paradigm (also in the automobile industry) [Chesbrough, 2003]. The integrated firm with in-house manufacturing capacity and R&D is transformed as firms increasingly outsource activities, starting with production capacity (capital), but increasingly also basic research and product development (knowledge). Not only for the microelectronics industry, but also for open innovation in general, innovation takes place in an evolving network, where players build linkages, aligning their activities to optimise added value. Especially in the case of innovations, where radically new technological capabilities have to be implemented, firms will often not be able to develop these capabilities in-house. Broader alliances are needed to spread risks and to achieve economies of scale.

For the purpose of our analysis, in particular in the nanoelectronics case study, we use the method of Abernathy and Clark to map the de- and re-alignments of competences associated with an innovation process, as such and in due course. We can therefore map trajectories retrospectively, so as to understand what happened, and prospectively, so as to derive strategy and management implications. Typically, an innovation starts with the introduction of a new capability or with the formation of a new market linkage. This may be a first step in a further process of re- and de-alignment of competencies and may eventually result in an architectural innovation that (re)defines an industry. However, other innovation trajectories survive in niches or are selected-out before they have a real impact. What happens as well is that an innovation project starts with the promise of being architectural, but then it turns out that the necessary re-alignments are too difficult, and the focus shifts to changes in linkages or in capabilities only.

It is therefore important to add time as a parameter to the Abernathy and Clark maps, locating the various innovations and stages in one innovation trajectory on one map, thus depicting a trajectory (see Figure 4). In doing so, a further complexity is introduced, viz. changes in context in the course of time (cf. our earlier observation, when discussing the evolutionary theory, that selection environments will change in due time, partly in response to the introduction of an innovation). Such a trajectory can be mapped both retrospectively, but also prospectively, as is the case, for example, in roadmapping. The prospective map guides and coordinates actions, and might be realised thus, as a sort of self-fulfilling prophecy. In many cases, however, there is another outcome (cf. Figure 2 in section ‘Expectation dynamics and path dependencies’).

A further extension of the Abernathy and Clark model is necessary considering the increasing importance of linkages at a societal level. One example is

Figure 4
Abermathy and Clark framework adapted for trajectory mapping.



regulation, for instance product safety, risk regulation in health care, product trials in the health sector, environmental protection, competition, but also the increasing importance of public acceptance, such as the backlash in agricultural biotechnology, nuclear energy, stem cell research. At this level one can see the co-evolution of technological change and the selection environment at work, for instance, as the regulatory regime for medical products that changes in response to the introduction of so-called ‘hybrid’ tissue-engineering products.

This extension of the notion of linkages illustrates that processes of de- and re-alignment play a role at multiple levels. It can be used to describe the dynamics at the level of an individual innovation project, but it can also be worked out at the level of firms, networks of organisations, sectors and at the level of the broader socio-economic landscape. Variation and selection mechanisms are active at all these (interrelated) levels.

CONVERGENCE REVISITED

What is then the relationship between converging technologies and the foregoing general observations about the dynamics of technological change and innovation? And how can these concepts and tools be used in the analysis of the case studies?

Converging technologies are new technological options, made possible through the synergistic combinations of knowledge and technological capabilities derived from various fields. Two characteristics stand out: the synergistic character and the interactions between the fields.

First the synergistic character. The promise of qualitatively new possibilities of converging technologies is not based on random combinations but on a new principle, such as a design rule or a new scientific paradigm that makes the new technological option possible. In the case of materials science, this was the idea of structure-property relationships, at a later stage extended to the structure-property-processing triangle, allowing a better control of materials properties [Bensaude-Vincent, 2001]. In the microelectronics revolution, it was the promise of integrated manufacturing of semiconductor electronic components that let Gordon Moore make his famous prediction about the evolution of the semiconductor industry [Moore, 1965]. The microelectronics revolution made the later convergence possible, at system level, of communication, computer and content technologies, which was based on the idea of an underlying unity of information [Castells, 1996]. (Note the interaction between the dynamics of the physical layer, in this case microelectronics, and at a later stage the dynamics at system level of ICT systems described in the chapter ‘Introduction’.)

Secondly the interactions between fields. Just like technological changes in general, converging technologies are not external developments impacting on the various actors, as the actors actively work to create these new combinations; in the case of converging technologies, in particular through the creation of new linkages between normally separate fields of research or innovation. This reflects the power of the concept ‘converging technologies’: When actors subscribe to the promise of converging technologies, they will then be forced to open up their fields to new interactions. Without such interactions, it will not be possible to mount the necessary expertise, mobilise the resources and fulfil all other necessary conditions to fulfil the promise of converging technologies.

Note that these two dimensions of converging technologies are directly reflected in the two axes of the Abernathy and Clark diagram — technological options as new capabilities on the horizontal axis, the interactions required to realise the promise of these options as linkages on the vertical axis. The promises of converging technologies have a regime-challenging character.

The next two parts of this book will discuss the case studies — about nano-electronics and regenerative medicine — that form the core of this book. The concepts, insights and analytical tools discussed in this chapter can serve as a possible guide for the reader to work through the case studies.

REFERENCES

- Abernathy, W.J., K.B. Clark (1985). Innovation: Mapping the Winds of Creative Destruction. *Research Policy* 14, 1, 3-22
- Anderson, P., M.L. Tushman (1990). Technological Discontinuities and Dominant Designs — a Cyclical Model of Technological-Change. *Administrative Science Quarterly* 35, 4, 604-633
- Bensaude-Vincent, B. (2001). *Materials Science and Engineering: An Artificial Discipline About to Explode?*
- Brooks, H. (1994). The Relationship between Science and Technology. *Research Policy* 23, 477-486
- Cahn, R.W. (2001). *The Coming of Materials Science*. Elsevier Science Ltd., Oxford
- Castells, M. (1996). *The Rise of the Network Society*. Blackwell Publishers, Malden, MA, Oxford, UK
- Chesbrough, H. (2003). *Open Innovation: The Imperative for Creating and Profiting from Technology*. Harvard Business School Press
- Dosi, G. (1982). Technological Paradigms and Technological Trajectories: A Suggested Interpretation of the Determinants and Directions of Technical Change. *Research Policy* 11, 3, 147-162
- Dosi, G. (1984). *Technical Change and Industrial Transformation*. St. Martin's Press, New York
- Fagerberg, J. (2003). *Innovation: A Guide to the Literature*. Workshop The Many Guises Of Innovation: What we Have Learnt and Where we Are Heading, Ottawa, October 23-24, 2003
- Gartner. *Understanding Hype Cycles*
- Kline, S.J., N. Rosenberg (1986). An Overview of Innovation. In: Landau, R., N. Rosenberg (eds). *The Positive Sum Strategy: Harnessing Technology for Economic Growth*. National Academy Press, Washington D.C., 275-304
- Lente, H. van (1993). *Promising Technology. Dynamics of Expectations in Technological Developments*. University of Twente, Delft
- Moore, G.E. (1965). *Electronics* 38, 8
- Nelson, R.R., S.G. Winter (1977). In Search of a Useful Theory of Innovation. *Research Policy* 6, 36-76
- Phillips, P.W.B. (2003). *The Challenge of Creating, Protecting and Exploiting Networked Knowledge: Ip Management Challenges in Genome Canada*. GE3LS Conference, Kananaskis, April 25-27, 2003
- Roco, M.C., W.S. Bainbridge (2002). Converging Technologies for Improving Human Performance: Integrating from the Nanoscale. *Journal of Nanoparticle Research* 4, 4, 281-295

- Roco, M.C., W.S. Bainbridge (eds.) (2003). *Converging Technologies for Improving Human Performance: Nanotechnology, Biotechnology, Information Technology and Cognitive Science*. Kluwer Academic Publishers
- Schaeffer, G.J. (1998). *Fuel Cells for the Future. A Contribution to Technology Forecasting from a Technology Dynamics Perspective*. PhD thesis, University of Twente, Enschede
- Tushman, M., P. Anderson (1986). Technological Discontinuities and Organization Environments. *Administrative Science Quarterly* 31, 439-465
- Ven, A.H. van de (1999). *The Innovation Journey*. Oxford University Press, New York

WEBSITE

- www.itrs.net/about.html

Introduction

John Jansen¹, Maurits Doorn²

INTRODUCTION

In this case study we will focus on regenerative medicine, an emerging area of fundamental research, technology development and innovation in health care. This field is expected to make possible a broad range of therapeutic approaches directed towards the treatment of congenital and acquired problems of tissue loss and organ failure. The shared objective and distinguishing characteristic of these regenerative approaches is that they try to build on physiological principles for maintaining or restoring a normal functioning of human bodies. Whereas traditional therapies treat conditions, the revolutionary potential of regenerative medicine lies in its claim to cure pathologies and to restore a 'normal' body functioning. Regenerative medicine involves novel combinations of cells, biomaterials, drugs, or genes that may be designed, manufactured and delivered either synchronised or chronologically as a customised therapy. The regenerative approach is considered as an alternative for simple replacement and is based on the intrinsic self-healing capacity of natural tissues. Although some body tissues, such as bone and skin, have a large self-healing capacity, other tissue types and organs lack this property.

.....
¹ Radboud University Nijmegen, Nijmegen, the Netherlands.

² STT/Beweton, Den Haag, the Netherlands.

For example, cartilage repair is impossible, and damage to muscle tissue will result in scar tissue formation. The same is true for large defects and traumata. The aim of regenerative medicine is to seduce the body into self-healing, which can only be achieved by a good fundamental understanding of structure-function relationships in normal and pathological tissues. This implies that the regenerative approach builds on the convergence of the knowledge of engineering sciences, life sciences and clinical sciences and requires a multi-disciplinary approach. Regenerative medicine combines new knowledge and technological capabilities coming from nanotechnology and life sciences but is also based on and competes with existing therapies using implants, organ transplantation and, more recently, tissue engineering.

There is an increasing optimism that nanotechnology will provide new options for the diagnosis, treatment and prevention of diseases. The improved understanding of physiological processes, such as tissue development at biomolecular and cellular levels, is often attributed to advances in nanotechnologies. Such understanding underlies the technological options currently evaluated in regenerative medicine research programmes. Therefore, regenerative medicine is positioned by proponents as a part of ‘nanomedicine’, a broader area of health-related technological development (see, e.g., [ESF, 2005]). However, nanomedicine as defined here is broader than regenerative medicine, as it also comprises developments in two other areas:

- diagnostics and imaging;
- targeted drug delivery and release.

Expectations about the potential of regenerative therapies are often based on assumptions about progress to be made in these two other fields.

In addition, the developments in regenerative medicine can be located in the context of wider developments in biotechnology and its applications in health care. As such, they provide an illustration of issues that come up as such biotechnologies become embedded in society, e.g. ethical dilemma’s, regulation, risk assessment, scientific uncertainty.

This chapter presents a brief overview of the development of regenerative medicine from the early days up till now. In addition, the field of regenerative medicine is defined, and the problems met in the emergence of this field are discussed.

A HISTORY OF REPLACEMENT

The ability to replace malfunctioning body parts has long been an issue of fiction and vision throughout the development of medical practice. One of the most striking examples is the legend of St. Cosmas and St. Damien, which describes the replacement of a man's gangrenous leg with the limb of a dead black man [Schultheiss et al., 1997].

Apart from this legendary example, the more realistic replacement of lost or damaged body tissue started in dentistry. The French surgeon Ambroise Paré (1510-1590) described the replacement of missing teeth by donor teeth, which were taken from 'serfs'. It goes without saying that this kind of early transplantation was prone to failure due to the existing lack of knowledge about immunology and sterility as well as the underlying biological phenomena of wound healing. In view of this, the actual innovations in the replacement of tissue and organs originated from the end of the 18th century and the beginning of the 19th century.

The discovery of the sterility principles by Lister meant an enormous step forward in surgical therapy. In addition, the introduction of cell and tissue culture techniques in the beginning of the 20th century, with a considerable expansion in the 1950s, provided detailed information about the proliferation, migration and differentiation of a wide variety of different cell types.

At about the same time, proper examples could be found of the use of synthetic materials for whole organ replacement. For example, Greenfield (1913) [Greenfield, 1913] fabricated a hollow basket of iridium wires as artificial replacement of dental roots. The absence of any adverse effect of fragments of plastic aircraft canopy in eye injuries of World War II warplane pilots resulted in the use of plastics for corneal replacement. With the progress in materials sciences, new materials became available for the manufacturing of these so-called implants, which finally resulted in the current relatively successful use of implants for the replacement of teeth, hips, knees, blood vessels, etc. Apart from the development of implants, the first detailed descriptions of experimental organ transplantation also date from the beginning of the 19th century. However, it was only as late as 1954 that organ transplantation became successful and repeatable. Then, the transplantation of a kidney in identical twins was stunning news (Merrill 1956), which was followed by the first heart transplantation by Barnard (1968).

Although current practices using medical implants as well as organ transplantation procedures are rather successful, both therapies are also associated with problems and disadvantages. Organ transplantation is prone to rejection and the patients have to use immunosuppressive drugs on a long-term

basis. Furthermore, there is a continuous shortage and lack of available donor organs. Implants are prone to failure due to a non-physiological response resulting from the contact between body tissues and the synthetic device. Therefore, the suggestion that with the aid of regenerative medicine a body-shop can be developed, allowing the on-demand production of tissues and even organs is very appealing [Garr, 2001].

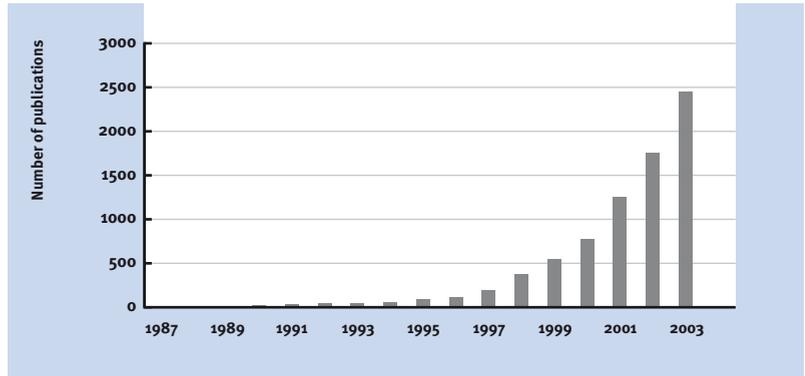
EARLIER ATTEMPTS — THE TISSUE-ENGINEERING PROGRAMME

The promise of regenerative medicine has already attracted a lot of attention from scientists, clinicians, patients and investors, starting at the beginning of the 1990s with the emergence of a tissue-engineering approach. The expectation that many patients might benefit from relatively simple structural new tissue-replacing devices gave rise to ambitions as well as hope. Anticipating the potential market and stimulated by much too optimistic views of the scientists involved, research efforts expanded rapidly and were almost immediately followed by the foundation of new companies. Riding the wave of IT technology and fed by speculation in a rapidly growing stock market, everybody became blinded by imaginative visions about the huge medical potential and suggested profitability of approaches based on tissue engineering. This resulted in a hype. It is interesting that the media played an important role in this process. Tissue engineering became a popular example of the potential of technology to fix medical problems. Especially so, as both the medical problems it promised to solve and the advantages for patients were easily recognizable for the public, while the engineering solutions proposed were conceptually easy to understand. However, during the first decade, the deadlines for marketable products were constantly extended due to both underestimated problems in research and regulatory issues. As a consequence, in the early 21st century, commercial ventures in tissue engineering were confronted with setbacks. Many of these new companies were shut down and some were even put into liquidation. Other companies merged, were bought up or radically changed their company philosophy and product strategy. For example, Genzyme Biosurgery was reduced in size and merged into its parent corporation (Genzyme). Only the potentially profitable part of the Advanced Tissue Sciences was acquired by Smith and Nephew [Lysaght et al., 2004]. At the same time, the setbacks in business development were not reflected in the research activities. On the contrary, the number of scientific publications dealing with tissue replacement and regeneration has increased during the last 5 years.

In view of these developments, the question could be asked why the introduction of innovations based on tissue engineering was commercially unsuccessful,

Figure 1

Bar graph showing the steep increase in the number of tissue-engineering publications from 1987-2003.



while at the same time research programmes seemed to prosper. The failure of the tissue-engineering programme to meet expectations can be attributed to a combination of factors. First, a lot of the start-up companies suffered from bad management. They were managed by scientists who had no experience in the management of a company and the development of a market-ready product. Second, most of the company managers had a biased view of the marketing opportunities, because they were involved both in the scientific research underlying product development and the final marketing of these products. They lacked a clear vision about what was needed by and of interest to medical practitioners and their patients. As a consequence, the distance between expectation and reality became huge. These unrealistic expectations were reflected in misleading advertisements that set customer expectations too high: Although these products were advertised as tissue equivalents, they did not show any similarity to original tissues, leaving patients and doctors disappointed with the results. But the market projections were also far too optimistic as they did not take into account that a majority of the patients could still be effectively treated with conventional methods. In addition, because many of the tissue-engineering products developed were radically different from existing products, they did not conform with existing medical practices. The application of these products therefore required adaptations of these practices, resulting in complex and frequently delayed application procedures during patient treatment. An additional disadvantage was the inconvenience in availability: In contrast to conventional implants, tissue-engineered products could not be manufactured in-stock and required an exact fit of patient treatment with manufacturing and delivery schedules. Evidently, this lack of an 'assembly line' approach, which had made the automobile industry so profitable in the past, became a bottleneck for the application of tissue-engineered products [Mason, 2003]. All these factors resulted in a much slower and much more limited adaptation of the new products in medical practice. As a result, while manufacturing costs remained high and health insurance companies were reluctant to reimburse the newly developed, costly medical procedures,

the new products did not provide a satisfactory revenue and profitability. A further complication was the character of the regulatory regime for medical products (Kent, 2006). Existing regulation essentially addressed two broad product categories — medicinal products and medical devices — both with their own regulatory regimes. Tissue-engineering products do not easily fit either of these categories. From a regulatory perspective, these products are at best seen as borderline cases but they could probably more appropriately be described as hybrids, combining characteristics of both medicine and devices. The last but absolutely no least compromising factor was that the composite nature of regenerative products requires a real interdisciplinary approach and due to a lack of participation and co-operation of all relevant disciplines progress in product development was not promoted. Moreover, the extrapolation of the obtained animal results into the final clinical situation was not as straightforward as supposed and some of the used animal models were not even useful at all. These unsolved technological and scientific challenges were perhaps the most significant reasons that the deadlines for marketable products have never been met (see also [Pangarkar et al., 2003]).

Nowadays, the regenerative medicine industry is being rebuilt after the collapse in the first years of this century [Lysaght, 2004; Pangarkar, 2003]. Improvements are now made so as to achieve the improved levels of maturity and productivity necessary for a successful commercial development. The following issues are now attracting attention:

- Management: Large medical companies are entering the tissue-regeneration field. These companies not only provide significant financial support, but they also contribute to the development of a clear business strategy, management, regulatory approval, marketing and advertising. Quite often, multidisciplinary scientific boards are formed and patient interest groups are involved.
- Need for automation: The necessity of automated production processes and the availability of in-stock products have been understood and have resulted in an extension of new product developments along these lines. Efficient, cost reducing scale-up techniques will improve the market potential of the new treatment concepts.
- Focused research programmes: Governments have worldwide established research programmes that are based on the promises and imageries of regenerative approaches. However, the programmes have emphasised the importance of nanotechnology and converging sciences to make real progress in technical complex questions, like tissue and organ regeneration. Intensive collaboration of multidisciplinary composed teams is promoted.
- Regulation: In Europe, a new regulatory regime for risk management of combination products is emerging in the space between medicinal products,

medical devices and biologics [Kent et al., 2006]. This will enable industrial parties to make more informed investment choices, effectively facilitating commercialisation and trade. However, new regulation could also disturb the precarious balance between the need for harmonisation of regulation and effective risk management present in the existing regulatory environment. Regulation also helps to build up public trust, because regulation suggests some level of government control over developments and the existence of competent officials who are able to develop and uphold these laws. But here again there is the other side of the coin. New regulation may also invite stakeholders with different outlooks and interests to become involved in the regulation process, making the new space a contested one and inviting political and ethical debates about risk management but also about other normative and ethical aspects.

ENABLING SCIENCE AND TECHNOLOGY: GENOMICS AND STEM CELLS

The field of regenerative medicine is currently one of the most exciting areas of science and engineering. This subject is boosted by new energy from the results of the human genome project and the advances in human adult and embryonic stem cell research. The genome project provides a lot of information and fundamental understanding of the building blocks and mechanisms underlying the development of tissue structures and organs. Gene expression and the subsequent encoding of signalling peptides are known to play a crucial role in the initiation of morphogenesis and final organ formation. This knowledge is required for the application of the regenerative technologies in an effective way, where effectiveness means reproducibility, reliability, safety, and efficacy.

In the area of stem cell research announcements of new breakthroughs are to be seen almost every week. Such discoveries accelerate science, but a proper translation of the obtained knowledge in applicable and effective products has not yet been achieved. The cell therapies suggested that are based on these results in stem cell research involve the delivery of cell doses to patients as well as the incorporation of the stem cells into a 3-dimensional scaffold material. Which approach should be preferred depends on the final clinical application. Given the currently available knowledge, stem cells harbor a high potential and have to be considered as one of the enabling sciences/technologies for regenerative medicine. Apparently, this technical drive is the major explanation for the continuous increase in scientific output in the fields of tissue engineering and regenerative medicine.

DEFINITION OF THE FIELD

Regenerative medicine holds the promise of revolutionary advances for health care. Whereas medicine always focused on the replacement of damaged tissues and organs, advances in regenerative medicine provide promising options for the regeneration of damaged tissue. In the very long term, such therapies for tissue regeneration might even substitute current replacement or implantation therapies. In replacement medicine, mainly materials are used that are carefully selected but not specifically designed for biomedical application. Although these materials have offered a wide variety of new medical treatments, there are also problems with respect to their biocompatibility and ultimate clinical life.

The goal of regenerative medicine is to regenerate living tissue equivalents in order to replace or enhance lost tissue functioning or structure. In order to achieve this, cells or tissue have to be implanted in such a way that they 'believe' that they are in their natural environment. Subsequently, they have to receive all the necessary signals from this environment to trigger the natural processes of differentiation, proliferation and organisation. Critical components in this process are the structural material, which provides a shape to the tissue defect that has to be regenerated as well as to direct the cell signalling events that regulate cellular activities, such as gene expression, protein synthesis, and the release of autocrine and paracrine factors that lead to the desired responses at the cellular and tissue levels. In nature, the so-called extracellular matrix (ECM) acts as a support material for residing cells. This ECM is produced by the cells and is constantly degraded, remodelled and resynthesised. From this perspective, the technological scope of regenerative medicine covers an 'opportunity space' where cellular, biomolecular growth factors (defined biomolecules that can lead to the formation of new tissue), and biomaterial systems can be combined to trigger tissue regeneration. The biomolecules are placed on the biomaterial and implanted at the damaged site. The growth factors have the ability to diffuse out of the material and to direct the functioning and growth of cells already present at that site, thus promoting the formation of the desired tissue type and structure. However, this matrix function requires the development of completely new materials, which possess intrinsic properties to support cell differentiation as well as the ability to release medicines in a controllable and standardised way. In addition, these materials have to degrade slowly and predictably within a limited time during their presence in the body.

A similar approach involves the delivery of a gene instead of a biomolecular growth factor. This gene encodes the factor that stimulates tissue formation in

the cells present at the site. These cells will then start to produce the required growth factors. Several studies have already confirmed that cells are able to take up DNA fragments involved in the production of specific biomolecules (transfection) and to produce these factors in sufficient amounts to promote tissue formation [Franceschi, 2005].

Finally, the ‘holy grail’ in regenerative medicine is the development of ‘smart’ materials that do not require additional biologically active factors. Such materials are alleged to exactly mimic the natural ECM and serve as a scaffold for the orchestrated activation of the local cellular processes. Recent studies have already confirmed [Habibovic et al., 2005] that such a tissue-inductive approach without the addition of committed agents is indeed feasible for the regeneration of bone tissue. Scaffolds made of calcium phosphate ceramic and possessing a specific microporosity and macroporosity have been shown to induce the formation of bone tissue. However, the amount of induced bone is very limited (about 1-2% of the total scaffold volume). In addition the current understanding of underlying processes is still too limited for controlled and standardised bone tissue induction to be possible.

REGENERATIVE MEDICINE IN CONTEXT

Supported by the prediction of Time Magazine that tissue engineering will be the number one job by 2010 [Rawe, 2000], the main stimulant for the industry is the increasing number of elderly people in the Western population coupled with an increasing life expectancy and an increasing need for a good quality of life up to an advanced age. For example, it is supposed that by 2050 life expectancy at birth will be increased by 10 years compared with 2005. Moreover, the proportion of people over 80 will increase by 10% by 2050. This expansion in the number of elderly persons is associated with, for instance, a rising demand for orthopaedic, neurodegenerative and cardiac treatment. The strategy to win and to develop innovative products seems to be the focus on highly specialised niches where treatment can be hugely improved. Examples are: cartilage for arthritic patients, living blood vessels and spinal fusion. After that, the market can be expanded and can gradually replace existing tissue-replacing devices.

Regenerative medicine, however, should not only be considered as a substitute and improvement of existing therapies. It also opens up new areas of indications for tissue defects, which are currently incurable with the existing therapeutic approaches. One possible direction is a shift in the disease spectrum toward preventive strategies. In view of this, it has to be emphasised that a successful application of regenerative medicine in medical practice will require complementary technological developments. To be specific, regen-

erative medicine requires diagnostics and imaging technologies to detect deviations and the malfunctioning of tissues and organs at a very early stage. In addition, biological tissue equivalents have to be available in order to regenerate the damaged or injured tissue/organ structure. The manufacturing of these tissue equivalents not only requires the development of bioreactors that support the differentiation and growth of stem cell clusters, but also the necessary logistical systems that allow a delivery of tissue at the required time and place. Moreover, the tissue equivalents have to be applied with minimal surgical damage at the proper place. In the optimal situation, all required medical procedures and handling can occur within one session.

Regenerative medicine belongs to the novel area of nanomedicine and is based on the interface between nano-diagnostics and targeted drug delivery and release. It will be clear that this requires the input from physicians, surgeons, pathologists, biologists, material scientists, physical, chemical and mechanical engineers, imaging, etc. However, there is more at stake than providing the right combination of disciplines. The point is that the pre-symptomatic use of regenerative medicine anticipates the developments in complementary technology areas, such as nanotechnology, diagnostics and imaging, and advanced surgical techniques, such as minimally invasive surgery. However, developments in these areas have their own independent dynamics that are only partially related to developments in regenerative medicine, and eventual outcomes are uncertain. A successful introduction of new regenerative therapies requires coordination and convergence with developments in these complementary technologies.

REFERENCES

- ESF (2005). *ESF Forward Look on Nanomedicine*. European Science Foundation
- Franceschi, R.T. (2005). Biological Approaches to Bone Regeneration by Gene Therapy. *Journal of Dental Research* 84, 1093-1103
- Garr, D. (2001). The Human Body Shop. *Technology Review*. April, 72-80
- Greenfield, E.J. (1913). Implantation of Artificial Crown and Bridge Abutments. *Dental Cosmos* 55, 364-369
- Habibovic, P. et al. (2005). 3D Microenvironment as Essential Element for Osteoinduction by Biomaterials. *Biomaterials* 26, 17, 3565-3575
- Kent, J. et al. (2006). Towards Governance of Human Tissue Engineered Technologies in Europe: Framing the Case for a New Regulatory Regime. *Technological Forecasting and Social Change* 73, 41-60
- Lysaght, M.J., A.L. Hazlehurst (2004). Tissue Engineering: The End of the

Beginning. *Tissue Engineering* 10, 1-2, 309-320

- Mason, C. (2003). Automated Tissue Engineering: A Major Paradigm Shift in Health Care. *Medical Device Technology* Jan-Feb, 16-17
- Pangarkar, N., D.W. Hutmacher (2003). Invention and Business Performance in the Tissue-Engineering Industry. *Tissue Engineering* 9, 6, 1313-1322
- Rawe, J. (2000). What Will Be the Hottest Jobs? *Time* 155, 54
- Schultheiss, D. et al. (1997). Rejuvenation in the Early 20th Century. *Andrologia* 29, 351

Future Perspectives of Regenerative Medicine

Gert Meijer¹, Clemens van Blitterswijk²

INTRODUCTION

Regenerative medicine is an exciting field in translational medicine. It attempts to translate the results of basic research into clinical applications and promises to bring about a paradigm shift to health care. In this new field, therapies are developed at the intersections of already existing disciplines, such as stem cell biology, immunology, tissue engineering, molecular biology, biomaterials, transplantation biology, and clinical research. For example, a stem cell-based therapy may develop into a new therapeutic platform to treat a vast array of clinical disorders. Blood transfusions and bone marrow transplantation are prime examples of the successful application of cell-based therapeutics; recent advances in cellular and molecular biology have expanded the potential applications of this approach. A success was recently reported in the treatment of skin ulcers [Mason, 2005], diabetes [Ryan et al., 2006] and liver disease [Strom et al., 1997], cartilage repair [Kuo, 2006] and bone repair [Cancedda et al., 2003]. Another example is recombinant genetic engineering, which is used to produce a variety of therapeutics, such as human erythropoietin and insulin.

.....
¹ Universitair Medisch Centrum
Utrecht, Utrecht, the Netherlands.

² Universiteit Twente, Enschede,
the Netherlands.

However, although these therapies proved to be successful, they are unable to completely correct or reverse pathological states, because most common disease processes are not due to the deficiency of a single protein but develop due to alterations in the complex interactions of a variety of cell components [Humes, 2005].

The challenge for regenerative medicine is not only to simply combine the results of these fields, but also to develop new philosophies of how to deal with diseases. Therapies developed in the past appear relatively simple but are — from a nanotechnological point of view — much more complicated. New challenges are to be met. Although regenerative medicine proposes therapies that are conceptually simple at first sight, researchers are again and again confronted with an ever increasing complexity and unexpected complications as they attempt to understand and control the biological processes and bio-materials that play a role at nanoscale.

Issues to be addressed before regenerative therapies can enter the clinics include identifying sources of suitable cells, developing new scaffolding bio-materials, and scaling up the production, not to mention discovering ways to preserve the tissue product and to prevent immune rejection [Lavine et al., 2002].

It can be imagined that a further development of this field may help to prevent birth defects, control abnormal tissue growth, slow the deterioration and aging of tissues and facilitate the repair, regeneration and replacement of injured tissues. It may also permit the in vitro production of replacement tissues and organs [Caplan, 2000]. Furthermore, the successful application of bioelectronics (bionics) in medical practice will also be connected with the progress made in the field of regenerative medicine.

As this newly emerging field gains a wider audience and as the experimental results in the field become more broadly based, the hope that its concepts and techniques can be applied to human diseases grows stronger. This hope is based on the profound need, which the new field may be able to improve [Vacanti, 1997]. In order to understand the emergence of the field and its hope for the future, it is helpful to place its roots in the context of the 'changing philosophies' in medicine.

A PARADIGM SHIFT IN HEALTH CARE

From ancient times till the nineteenth century, surgeons were mainly focused on manual procedures. Their first priority was to save lives; in case of a trauma resulting in a broken leg, the surgeon opened the soft tissue layers for inspection, removed the diseased bone, repaired the affected area and finally stabilised the bone fragments by splinting. In addition, infection could only be controlled by a surgical approach, by the drainage of pus and little else until the revolution of antibiotic therapies. Modern surgery, based on the introduction of sterile techniques, did not emerge until the germ theory of diseases became scientifically understood in the nineteenth century. With the addition of anaesthesia by the mid-nineteenth century, a rapid evolution of surgical techniques for extirpative surgery became possible. Examples include the surgical removal of tumours, surgical bypasses in case of obstructions and the surgical repair of life-threatening injuries.

With the advent of the modern concepts of sterility and anaesthesia, a new field of reconstructive surgery emerged too, aiming to improve the quality of life by replacing missing functions by re-building structures. To this end, tissue replacements were needed. The first choice for reconstruction were autografts (the patient's own tissue), despite the drawback that a second operation is needed for the harvesting of bone, thus introducing additional morbidity. Then, alternatives, such as allografts (human-human) and xenografts (animal-human), were developed. Nevertheless, these types of grafts are of lesser quality, because of the processing techniques used to reduce the patient's immune response (such as demineralisation, freeze-drying and irradiation). These processing techniques also alter the structure of the graft and thereby reduce its potential to induce bone healing, while at the same time the risk of disease transmission remains [Damien et al., 1991].

Initially, grafts were only used for posttraumatic abnormalities, later also for congenital malformations. Stabilisation of hard tissue grafts in relation to host area appeared to be a prerequisite for success; no movement is allowed to ensure adequate healing. Therefore, the use of stainless steel wires in the early 1950s was also a big step forward. A real breakthrough was accomplished by the introduction of plates and screws for solid fixation in the 1980s [Habal, 1992]. In retrospect, the idea of improving upon nature by using man-made materials may have been nurtured by the discovery, since World War II, of the new synthetics. These materials were introduced into the human body as replacement parts at a time when the possibility of biologically imitating nature was still unexplored, and many are still used. Thus, through a combination of scientific advance and improved surgical understanding, techniques

for restoring structure and function became integral to the advancement of human therapy. Eventually, artificial materials were developed for replacing limbs and teeth or for restoring partially lost functions, such as lenses for vision or devices for augmenting hearing.

In our time, modern techniques of transplanting tissue from one individual into another have been revolutionary and lifesaving. The molecular and cellular events underlying the immune response are now sufficiently understood. So that the immune response can be suppressed in the clinical setting of transplantation, and prolonged graft survival and functioning in patients is possible. However, as with many successful undertakings in health care, new problems have emerged. Techniques using implantable foreign body materials have produced dislodgement, infection at the foreign body tissue interface, fracture, and migration over time. Moreover, techniques for moving tissue from one position to another have produced adverse reactions because of the abnormal interaction of the tissue at its new location. For example, creating an imbalance of immune surveillance from immuno-suppression can cause new tumour formation. These constraints have produced a need for alternative solutions for tissue replacements and repair [Vacanti et al., 1997]. It is in this context of transplantation medicine and reconstructive surgery that the field of regenerative medicine has its roots.

With the aid of accelerating developments in biotechnology and life sciences, a new approach is now explored, which essentially provides a paradigm shift in the design and clinical application of tissue and organ replacements. Instead of using biological or synthetic implants to replace impaired tissues, the focus is on how biological and synthetic materials can be used to influence and control the processes of tissue development so as to regenerate healthy tissue function. Although the associated clinical issues appear easy to solve at a superficial level, at nanoscale researchers are confronted with a new world of biochemical and cellular processes, inhabited by proteins, cytokines, hormones, nutrients etcetera. What was previously called reconstructive surgery evolves into regenerative medicine as the design principles for tissue and organ replacements dramatically shift toward the biochemical and cellular processes on which tissue development is based.

THE DANGER OF MONO-DIMENSIONAL THINKING: IN MEDICINE

Because tissue repair and tissue regeneration are highly coordinated processes at a very complex surgical site, all of the various factors, components, parameters, and considerations should be taken into account. Therefore, mim-

icking these complex processes requires the coordination of a large number of variables. In the race to achieve results this complexity is sometimes neglected, and some approaches have been mono-dimensional for both their logics and the experimental results obtained thus far. There have been some good ideas, but the proposed solutions for clinical problems have been a bit too simple for dealing with the real-life complexities of tissue regeneration. Meanwhile, the basic principles concerning tissue fabrication, either in modes of repair or regeneration, have not been sufficiently understood [Caplan, 2000].

AN EXAMPLE OF OVER-SIMPLIFICATION

Autogenous bone has been the standard and the most successful method for bone reconstruction. However, drawbacks like donor site morbidity, prolonged operation times and limited bone volume have urged researchers to find bone substitutes. First, research was concentrated on pure biomaterials, such as metals, ceramics, polymers and composites. However, in order to deal with the performance limitations of these materials, it was proposed to incorporate growth factors and living cells so as to better mimic living bone.

Since Friedenstein's first publications in the eighties [Friedenstein et al., 1987], it has been recognised that mesenchymal stem cells (MSCs) may be used to engineer mesenchymal tissues, such as bone and cartilage. Therefore, scientists are worldwide working to provide the right carrier and the appropriate set of cells that, once re-transplanted, will ensure bone repair. Bone marrow has been claimed to be the most abundant source of MSCs, which have a high proliferative ability and great capacity for differentiation [Haynesworth et al., 1992]. Caplan and co-workers have combined MSCs with a scaffold, so as to allow paracrine and host-derived factors to produce bone matrix after implantation. However, bone formation mainly turned up at locations in tissues where originally no bone had been present, so-called ectopic locations, such as underneath the skin (subcutaneous) or within the muscles (intramuscular) [Caplan, 1991; de Bruijn et al., 1998; Haynesworth et al., 1992]. Subsequently, all the authors assumed that, if bone was formed at an ectopic location, the test material automatically was capable to restore osseous defects too.

However, the use of 'the ectopic rodent model' to underscore their 'proof of concept' appeared to be hard to defend; after 25 years of research, only 2 studies in bone tissue engineering, involving cells in humans, were published [Cancedda et al., 2003; Schimming et al., 2004]. Moreover, disputable results were presented, underscoring the limited importance of subcutaneously or intramuscularly creating bone. Recently Meijer [Meijer et al., 2006] conducted a human study to evaluate the benefit of MSCs seeded on a scaffold in restor-

ing an intra-oral osseous defect. Seven out of ten cultured constructs did show bone formation in mice after six weeks of subcutaneous implantation. Surprisingly, in contrast to the findings in mice, only in one patient bone formation was observed of which it was suggestive that it had been induced by the implanted cells. The point is that, although it seems to be miraculous to induce bone in a non-osseous environment, ectopic models offer a far more favourable biological environment for implanted cells. There are two main reasons for this. First, in the animal models, only a few small samples of stem cells were subcutaneously implanted. These were in direct contact with the surrounding well-vascularised tissues, thereby shortening the diffusion length, allowing the seeded stem cells to be optimally supplied with oxygen and nutrients. In bone, larger samples of stem cells were used, and the implants were isolated from vascularised tissue surrounding the bone. Second, implanted cells in osseous defects will die due to the high potassium concentration inside the wound [Bouhadir et al., 2001], which occurs during the first phase of the osseous wound healing process.

Such misinterpretations have to be corrected. By testing hypotheses, unknown natural repair mechanisms are revealed that subsequently need to be understood. For example, the success of bone formation in an ectopic model should be interpreted as underscoring the importance of adequate vascularisation. Therefore, translating its successful outcome into osseous defects is short-sighted, because in an osseous environment vascularisation is delayed by blood clot formation. To successfully apply cell-based bone tissue engineering techniques for reconstructing osseous defects, first the problem of cell death induced by insufficient oxygen and nutrient supply should be solved. Adding growth factors to stimulate vessel growth is one solution. Another option is to bypass the aspect of long diffusion depths induced by the haematoma by first applying the scaffold, and a few days later, injecting the MSCs in a secondary procedure. At that point, new blood vessels have already invaded the haematoma, guaranteeing a sufficient supply of oxygen and nutrients, thus securing the survival of the injected MSCs. This ongoing process of hypothesising and the subsequent confrontation with new barriers is inseparably linked to performing research.

THE DANGER OF MONO-DIMENSIONAL THINKING: IN FINANCIALS

Parallel to the overextended expectation at a medical level, financial markets also react overenthusiastically to the possibilities of new medical techniques. Regenerative medicine has a high intrinsic appeal not only to scientists, but also to investors, policy makers and the media. During the bull market of

the late 1990s, media attention became almost euphoric. Reports such as: *“Advances in tissue engineering and genetic medicine are likely to be the greatest scientific achievements of the twentieth century”* [Gillian, 1999] or *“Regenerative medicine is on a path to become a \$ 100 billion industry”* [Palmer, 2000] evoked high expectations. In 2003, even the normally sceptical Economist reported, *“These are exciting times for tissue engineers. The technology for growing human body parts is rapidly advancing. Already it is possible to cultivate sheets of human skin and huge efforts are underway to develop even more complex structures, such as heart valves, and whole organs, such as the liver.”* Such a highly favourable media treatment has its benefits, but research-minded professionals increasingly recognised a gap with reality, which rarely leads to a happy ending.

Despite the ‘hurrah stories’, by the close of 2002, only twenty tissue-engineered products have entered Food and Drug Administration clinical trials. Four have been approved: Apligraf (Organogenesis), Carticel (Genzyme Biosurgery), Dermagraft (ATS) and OrCel (Ortec) but none of these are commercially successful as yet. Six other applications have been either abandoned or failed to achieve product approval. Ten products are still in the phase of clinical trials, some of which are investigator-sponsored, and most of which are at the phase I/phase II stages. The field has yet to produce a profitable product despite an aggregate research and development investment exceeding \$ 4.5 billion [Lysaght et al., 2004]. Regenerative medicine is clearly having difficulties in transitioning from a development stage industry to one with a successful product portfolio.

The most difficult issue for industry enthusiasts is the poor market acceptance of those products that have been introduced into the market after FDA approval. Of the four firms whose products have entered the clinical market, one has filed for bankruptcy (Organogenesis), one has discontinued operations (Advanced Tissue Sciences; ATS), one has downsized and has been assimilated into a larger division of its parent corporation (Genzyme) and one is operating under a ‘going financial concern warning’ (Ortec). Dermagraft (ATS) continued to be marketed by Smith & Nephew, till in 2005 the decision was made to exit Dermagraft due to the receipt of a non-approval letter from the FDA. The argument for the withdrawal was that in effect more clinical work was required to bring the product on the market which in turn pushes the break-even date too far into the future for the product to have an ongoing economic viability [Thomson Finance, 2005]. Ortec expects to file an HDE supplement to obtain marketing approval for the use of OrCel(R) in patients with Recessive Dystrophic Epidermolysis Bullosa undergoing hand reconstruction by mid-July 2006. An HDE is an FDA clearance that authorises medical devices

providing a safe treatment to be available in a prescribed manner for patients with rare medical conditions that affect fewer than 4,000 individuals in the US per year.

Several factors can be identified to explain this rather unsatisfactory performance. In the first place, initial sales were disappointing because the improvements over existing therapies were either limited to small subsets of patients, or were not generally compelling enough to attract large numbers of customers. The lack of interest in these conceptually appealing products may be due to relatively modest advantages over traditional approaches, as well as the need for surgeons to retrain the procedure. Secondly, clinical trials that tested the product in young patients with traumatised joints — not really a representative pool of typical candidates — may have led to miscalculations regarding the market potential. Thirdly, although scientifically strong, the costs to produce tissue-engineered products were higher than expected whereas high regulatory costs and protracted approval processes (especially for Dermagraft) placed a high burden for return on investment on the fledgling products. Finally, reimbursement strategies were insufficient as, for example, assurance companies were reluctant to refund the more expensive regenerative medicine products.

Those in the field need to face the realities of the time frames and costs associated with bringing complex regulated products on the market. Shortcutting any of these areas is likely to result in failure during clinical trials or after approval, and few firms survive such failures. If regenerative medicine is to represent the basis for the next generation of organ replacement therapies, adequate funding and effective tactics for transitioning from research to product-based enterprises have to emerge and take form [Lysaght et al., 2004].

The initially poor performance of tissue-engineered products in the market and in latter-stage clinical trials is manifestly disappointing, especially to those involved with the firms and products that failed. But it is important to view these early-stage difficulties from a balanced perspective and to bear in mind that innovative medical therapies more often than not endure a period of ‘blood, sweat, and tears’ before a final triumph.

IN THIS PARADIGM SHIFT, REGENERATIVE MEDICINE SHOULD DEVELOP ITS OWN STRATEGY

Although in regenerative medicine some impressive advances have been produced and interesting experimental models have been invented, only a

very limited number of clinically successful regenerative therapies have been reported as yet [Caplan, 2000; Humes, 2005; Heng et al., 2005]. It should be emphasised that, although the translation of this discipline into medical practice has a tremendous potential, in many applications not only technological but also biological issues have still to be overcome.

For regenerative medicine, it is impossible to present one central strategy to solve clinical issues as long as this new exciting approach is only viewed by specialists depending on, and therefore limited by their specific training, backgrounds and experience [Caplan, 1998]. For example, biologists will copy how embryos fabricate tissues, point out the key events, and use these to stimulate the regeneration of organs or complex tissues in adult organism. Material scientists will focus on the material properties of adult tissues and concentrate on tissue substitutes whose material properties exactly match those of the adult tissue. Engineers will mimic the mechanical properties of tissues, and design a mathematical (finite element) model to predict how the tissue will change with age and change in various modalities. Surgeons will wish to continue performing manual tricks but now while using cultured cells and scaffolds. Molecular biologists will gather the sequencing information from the Human Genome Project on the promoter control elements involved in forming and/or repairing different tissues and use these to design vectors to transform primitive cells into cells which will fabricate the tissues we are interested in. Obviously, in order to succeed in regenerative medicine, the solution is to cross borders and to combine these various approaches [Caplan, 2000].

Moreover, each researcher should be stimulated to address clinical issues 'with a open mind'. It is well known that research that initially appeared totally irrelevant to any practical objective has yielded most of the major discoveries in medicine. For example, X-rays were discovered by a physicist observing discharges in vacuum tubes, penicillin came from enzyme studies of bacterial analysis, and the polio vaccine came from learning how to grow cells in culture. Cisplatin, a widely used drug in cancer chemotherapy, came about from studying whether electric fields affect the growth of bacteria and observing inhibition due to the unexpected electrolysis of the platinum electrodes. All these discoveries came from being curious about questions in physics, chemistry and biology, apparently unrelated at the outset to a specific medical or practical problem.

Technologies for biological research come about in multiple ways, through serendipity, through inspired insight, and through incremental advances, and they are tightly coupled to progress in engineering. The complex dynamics of technology and biology are based on the various motivations of those who

work in the two realms. Considering how methodologies emerge has implications for the planning of interdisciplinary centres and the training of the next generation of scientists [Fields, 2001]. As an alternative for creating new institutes based on scientific or technological rationales, another possibility for productive partnership is simply to recruit individuals of contrasting talents in existing structures.

Two examples of regenerative medicine

New insights in spinal cord repair

Regenerative medicine compels to find new strategies. Repair of the nervous system has long been thought impossible. A few years ago, the prognosis for recovery after spinal cord injury was bleak, and this field of research was labelled a lost cause. Now, at least from the research perspective, the situation has radically changed. Certain cellular, molecular and bioengineering strategies for repairing the injured spinal cord are showing encouraging results (either alone or in combination) in animal models, with a limited recovery of mobility reported in some cases [Zenner, 2002].

The spinal cord receives sensory information from the skin, the muscles, the joints and other tissues of the body. It transmits this information in the form of electrical impulses to the brain, along millions of nerve fibres that are grouped together in bundles. The motor commands that are subsequently generated in the brain are sent to the spinal cord along fast-conducting nerve fibres, which terminate in local spinal motor circuits. From here, the electrical impulses that will direct coordinated muscle contraction reach the muscles via the peripheral nerves.

Destruction of the spinal cord can be compared to a bomb exploding in a computer centre, and repairing the spinal cord is as complicated as trying to rebuild all of the computer connections. These last few years, there was an encouraging progress in animal models, with sufficient regeneration of the damaged spinal cord to enable some recovery of motor ability. When the spinal cord is injured, the first phase of injury involves mechanical tissue destruction. It is followed by a second phase of tissue loss, which is principally caused by a severe local disturbance of the blood supply [Dumont et al. 2001; Schwab et al., 1996].

Four regenerative strategies for repairing spinal cord lesions are now proposed: (1) promoting the re-growth of interrupted nerve fibre tracts, using nerve growth stimulatory factors or molecules that suppress inhibitors of neuronal extensions (neurotrophins); (2) bridging spinal cord lesions with scaffolds that are impregnated with nerve growth factors, which promote axon growth and reduce the barrier caused by scar

tissue; (3) repairing damaged myelin (the insulating sheath surrounding the axons) and restoring nerve fibre impulse conductivity in the lesion area; and (4) enhancing central nervous system (CNS) plasticity by promoting compensatory growth of spared, intact nerve fibres above and below the lesion [Schwab, 2002].

Convergence of bioelectronics and regenerative medicine: regeneration of hearing and vision

The close link between developments in the field of bioelectronics and the field of regenerative medicine is another example illustrating the emergence of new ways of thinking. Bioelectronic engineers use their tools to restore mobility to persons with missing or non-functional limbs. These tools include the latest materials, mini-electronics and mega-computers, advanced robotic mechanisms and algorithms. It goes without saying that bioelectronics is mainly focussed on technology. However, the need to incorporate these devices in living tissue is inseparably linked to the goal of restoring human parts. At this interface, regenerative medicine comes into view. In addition, before tissues with sensory functions can be stimulated by bioelectronic devices, these non-functioning tissues have to be regenerated first.

An example of 'new thinking' is the development of the cochlear implant (CI), a microelectrode array that directly stimulates the auditory nerve. Partial or total hearing loss has many different causes. On the one hand, defects in either the outer ear or middle ear (encompassing the tympanic membrane, ear drum and auditory ossicles) result in a conductive hearing loss that can usually be remedied by the insertion of the well known hearing aid, which purely amplifies sound vibrations. Profound deafness, on the other hand, is caused by loss of the sensory hair cells in the inner ear, or cochlea, which transducer sound waves into electrical impulses, which are then transmitted to the brain. Profoundly deaf individuals who still have an intact auditory nerve have profited from the dramatic advances made over the past 30 years in the field of cochlear implants [Rauschecker, 1999]. For some profoundly deaf individuals, however, even electrical stimulation of the inner ear with a CI is impossible due to the absence or destruction of the auditory nerve. Instead, an auditory prosthesis consisting of a microelectrode array that directly stimulates one of the auditory processing centres of the brainstem, bypassing the cochlea and auditory nerve, might restore hearing to these patients. The cooperation between these two types of engineers may be established by the interaction between, on one hand, the technical device and, on the other hand, the incorporation of the same device in living tissue. For example, nerve cells can be stimulated by growth factors or culturing techniques in improving the impulse transmission between microelectrode and brainstem.

A related clinical issue is blindness; a number of research groups are developing electrical implants that can be directly attached to the retina in an attempt to

restore vision to patients suffering from retinal degeneration. However, despite promising results in animal experiments, there are still several major obstacles to overcome before retinal prostheses can be clinically used.

Vision is an enormously complex form of information processing that depends on a remarkable neuroprocessor at the back of the eye called the retina. Seeing is initiated when light passing through the pupil of the eye is focused by the lens onto the retina's sensory neuro-epithelium. This results in the projection of a reduced, upside-down image of the object onto the roughly 130 million photoreceptor cells (rods and cones) in the outermost layer of the retina. The cones, providing chromatic (colour) images of high spatial resolution, and the rods, required for achromatic vision with less spatial resolution in dim light, transform local luminance and colour patterns of the projected image into electrical and chemical signals. These signals then activate a complex circuit of retinal neurons. Visual information from the retina's 130 million photoreceptors is compressed into electrical signals carried by 1.2 million highly specialised ganglion neurons, which form the optic nerve. The optic nerve transmits visual information to the brain.

Blindness can result when any step of the optical pathway (the optics, the retina, the optic nerve or other brain areas involved in the processing of vision) sustains damage. However, about 50% of all blindness is caused by damage to the retina. Although electrical devices can support or replace the function of defective tissues, such as cochlear implants for the hearing impaired or pacemakers for individuals with heart diseases, restoring vision with electrical devices implanted in the retina is much more difficult. It should be realised that, despite the technical effort in performing the optimal electrical signal, there is a point in which the created signal is transferred to neurons. The quality of such an interface will be determining for the end result. Therefore, restoring vision by bioelectronic techniques is just a 'narrow-minded approach', regenerative medicine should also be applied.

CONCLUSION

In order to meet the objectives of regenerative medicine, such as reconstituting tissues *in vitro* and repairing tissues *in vivo*, an understanding of tissue growth in its natural environment is the critical challenge. What instructions do cells need to organise into tissues? How are these instructions delivered? What materials are synthesised for extracellular transport as a result of signals received and how are the secreted materials assembled? How are cells of a specific tissue induced to increase their number, or how are stem cell resources tapped? How are cells primed to engage in the synthesis of tissue-specific products? How do the reconstituted tissues fare in the hosts in which

they have been implanted? These are all crucial but unanswered questions. The study of these questions should be subsumed not by a single discipline, but by many, including microanatomy, cell, molecular and developmental biology, by immunology, by materials science and by branches of engineering that are able to look into the modes of action of the physical forces on which many developmental phenomena depend.

So as to overcome the problem that every specialist approaches a clinical issue from their own limited scope, it is recommendable to recruit individuals of contrasting talents and bring them together in interdisciplinary centres. Referring to major discoveries of medicine, such as the invention of X-rays or penicillin, it should be stressed that research is not a mono-dimensional process. Ideal circumstances for researchers also implicate that they are allowed to spend sufficient time to address issues that might initially appear irrelevant.

Unrealistic ‘Star Track’ expectations of future opportunities in regenerative medicine caused the bull market of the late 1990s. Reports, indicating regenerative medicine as the greatest scientific achievement of the twentieth century and as such promising high financial profits, resulted in hype-driven research. Despite the ‘hurrah stories’ by the end of 2002 few tissue-engineered products entered the market, none of which are yet commercially successful. Regenerative medicine is clearly having difficulties in transitioning from a development stage industry to one with a successful product portfolio.

With a scientific foundation firmly established, regenerative medicine can move from an era of phenomenological observation and serendipity to one of commercially viable products that will improve the lives of millions of patients. But before successes are achieved, thorough research is necessary in a multidisciplinary approach. For this transition to succeed, the structure of the current short-term research programs should be lengthened. More effort is needed for successful products to evolve.

REFERENCES

- Bouhadir, K.H., D.J. Mooney (2001). Promoting Angiogenesis in Engineered Tissues. *J. Drug Target.* 1, 9, 397-406
- Bruijn, J.D. de, C.A. van Blitterswijk (1998). New Developments in Implant Coatings: Biomimetics and Tissue Engineering. In: Walenkamp, G. (ed.). *Biomaterials in Surgery*. Thieme, Stuttgart, 77-83
- Cancedda, R., M. Mastrogiacomo, G. Bianchi, A. Derubeis, A. Muraglia, R. Quarto (2003). Bone Marrow Stromal Cells and their Use in Regenerating

- Bone. *Novartis Found Symp.*, 249, 133-43; *Discussion* 143-7, 170-4, 239-41
- Caplan, A.I. (1991). Mesenchymal Stem Cells. *J. Orthop. Res.* 1, 9, 641-50
 - Caplan, A.I., D.J. Fink, S.P. Bruder, R.G. Young, D.L. Butler (1998). The Regeneration of Skeletal Tissues Using Mesenchymal Stem Cells. In: Patrick, Jr C.W., A.G. Mikos, L.V. McIntire (eds.). *Frontiers in Tissue Engineering*. New York, Elsevier Science, 471-480
 - Caplan, A.I. (2000). Tissue Engineering Designs for the Future: New Logics, Old Molecules. *Tissue Eng.* 6, 1, 1-8
 - Damien, C.J., J.R. Parsons (1991). Bone Graft and Bone Graft Substitutes: A Review of Current Technology and Applications. *J. Appl. Biomaterials* 2, 187-208
 - Dumont, R.J., D.O. Okonkwo, S. Verma, R.J. Hurlbert, P.T. Boulos, D.B. Ellegala, A.S. Dumont (2001). Acute Spinal Cord Injury, Part I: Pathophysiologic Mechanisms. *Clin. Neuropharmacol.* 24, 5, 254-64
 - Economist, the (2003). February 1
 - Fields, S. (2001). The Interplay of Biology and Technology. *Proc. Natl. Acad. Sci. USA.* 28, 98, 10051-4
 - Friedenstein, A.J., R.K. Chailakhyan, U.V. Gerasimov (1987). Bone Marrow Osteogenic Stem Cells: In Vitro Cultivation and Transplantation in Diffusion Chambers. *Cell Tissue Kinet.* 20, 263-272
 - Gillian, M. (1999). *Good Morning America*. April 29
 - Habal, M.B. (1992). Craniofacial Surgery. In: Habal, M.B., A.H. Reddi (eds.). *Bone Grafts and Bone Substitutes*. WB Saunders Company, Philadelphia. 316-365
 - Haynesworth, S.E., J. Goshima, V.M. Goldberg, A. Caplan (1992). Characterisation of Cells with Osteogenic Potential from Human Marrow. *Bone* 13, 81-8
 - Heng, B.C., H. Liu, T. Cao (2005). Transplanted Human Embryonic Stem Cells as Biological ‘Catalysts’ for Tissue Repair and Regeneration. *Med. Hypotheses* 64, 1085-8
 - Humes, H.D. (2005). Stem Cells: the Next Therapeutic Frontier. *Trans. Am. Clin. Climatol. Assoc.* 116, 167-83
 - Kuo, C.K., W.J. Li, R.L. Mauck, R.S. Tuan (2006). Cartilage Tissue Engineering: its Potential and Uses. *Curr. Opin. Rheumatol.* 18, 1, 64-73
 - Lavine, M., L. Robert, O. Smith (2002). If I Only Had a ... *Science* 295, 995
 - Lysaght, M.J., A.L. Hazlehurst (2004). Tissue Engineering; the End of the Beginning. *Tissue Engineering* 10, 309-320
 - Mason, C. (2005). Tissue Engineering Skin: a Paradigm Shift in Wound Care. *Med. Device Technol.* 16, 10, 32-3
 - Meijer, G.J., J.D. de Bruijn, R. Koole, C.A. van Blitterswijk (2006). *Cell-Based Bone Tissue Engineering; New Directions Need to Be Exploited!* PLoS Medine (accepted)

- Palmer, J (2000). Spare Body Parts. *Barron's*. May 15
- Rauschecker, J.P. (1999). Making Brain Circuits Listen. *Science* 10, 285, 5434, 1686-7
- Ryan, E.A., D. Bigam, A.M. Shapiro (2006). Current Indications for Pancreas or Islet Transplant. *Diabetes Obes Metab.* 8, 1, 1-7
- Schimming, R., R. Schmelzeisen (2004). Tissue-Engineered Bone for Maxillary Sinus Augmentation. *J. Oral Maxillofac. Surg.* 62, 724-9
- Schwab, M.E., D. Bartholdi (1996). Degeneration and Regeneration of Axons in the Lesioned Spinal Cord. *Physiol. Rev.* 76, 319-70
- Schwab, M.E. (2002). Repairing the Injured Spinal Cord. *Science* 295 (5557), 1029–1031
- Strom, S.C., R.A. Fisher, M.T. Thompson, A.J. Sanyal, P.E. Cole, J.M. Ham, M.P. Posner (1997). Hepatocyte Transplantation as a Bridge to Orthotopic Liver Transplantation in Terminal Liver Failure. *Transplantation* 63, 4, 559-69
- Thomson Finance (2005). *Conference Call Transcript SNN – Q3 2005 Smith & Nephew Earnings Conference Call*. Oct. 27
- Vacanti, J.P., A.V. Vacanti (1997). The Challenge of Tissue Engineering. In: Lanza, R., W.L. Chick, R. Langer. *Principles of Tissue Engineering*. Springer, New York. RG Landes Co. 1-5
- Zenner, E. (2002). Will Retinal Implants Restore Vision? *Science* 295 (5557), 1022–1025

Spinal Fusion

Diyar Delawi, F. Cumhuri Öner, Wouter Dhert¹

INTRODUCTION

The basic approaches in orthopaedic treatment have evolved during the last 150 years. As described by Thomas A. Einhorn in 1998, the evolution of orthopaedic surgery can be divided into three discrete ages [Einhorn, 1998]. First, there is The Age of Resection. Due to the limited surgical possibilities, treatment was often restricted to amputations of injured limbs and excision of damaged tissue. Although this was quite effective for certain disorders, it was also clearly a very primitive and disabling treatment. After several decades, surgeons started emphasising on the immobilisation of joints (*arthrodesis*) and the cutting and realignment of bones (*osteotomies*). With this, orthopaedic surgery had entered the second age of development, The Age of Reconstruction.

¹ Department of Orthopaedics,
University Medical Center Utrecht,
Utrecht, the Netherlands.

In the early 1960s, important steps were made in joint replacement (*arthroplasty*), especially by a very innovative surgeon, Sir John Charnley [Charnley, 1960]. Some of his ideas were so bold and creative that he was seriously questioned by many of his colleagues. He aggressively pursued and tried to solve the problems he encountered. The efforts of Charnley and others resulted in the introduction of joint replacement in orthopaedic surgery. With this therapy, the damaged joints of patients, most often knees or hips, are replaced by artificial joints (*prostheses*). During the last decades of the 20th century, joint replacements became a more and more popular medical intervention, and orthopaedic surgery has now entered the third age, The Age of Replacement. Joint replacements are currently one of the most successful treatments in surgical practice. However, there are some drawbacks. Joint replacements are mainly used in patients with damaged joint cartilage. This cartilage normally covers the bone ends of a joint and will allow virtually frictionless and pain-free movement. If this cartilage is damaged, the joints will become painful. Since articular cartilage does not regenerate by itself in the body, joint replacement therapy can be an option, but artificial joints unfortunately have no unlimited life span. A substantial percentage of the prosthesis will wear out, and the orthopaedic surgeon will have to remove the previously implanted joint. Replacement of a prosthesis (*revision*) is a challenge for both the patient and the orthopaedic surgeon. Such a revision requires the removal of the previous prosthesis, in many cases the cement in which the prosthesis was fixated, the surrounding tissue and dead bone, before a new prosthesis can be inserted. In addition to the complexity of the surgery, the outcome of revisions is often inferior to the results of primary joint replacement as well [Retpen et al., 1989].

It was anticipated that by the beginning of this millennium we would have entered the fourth age of development, The Age of Regeneration. Regenerative therapies have the potential to change the approach of the treatment by being used to repair specific tissues, like cartilage and bone. The treatment of cartilage damage can include the regrowth of cartilage instead of replacing the natural joint with an artificial one. The use of bone is necessary to restore bone defects or to fuse bone parts with each other. Despite the efforts of many scientists and clinicians, the clinical implementation of regenerative therapies is still limited. Spinal fusion is one of the few applications where a regenerative therapy is currently being investigated clinically, and this is the topic that will receive further attention in the present chapter.

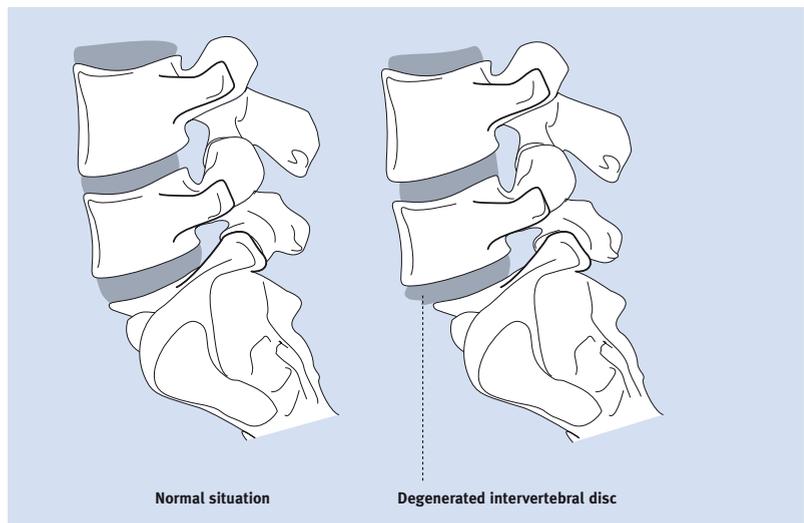
SPINAL FUSION SURGERY

One of the causes of low back pain is abnormal or excessive motion of the spine caused by degeneration of the intervertebral disc (Figure 1) or instability due to other degenerative causes. A treatment option for a carefully selected group of patients is spinal fusion. Spinal fusion is a surgical technique in which one or more of the vertebrae of the spine are joined (*fused*) through the formation of a bone bridge, so that motion cannot longer occur between them. The rationale for spinal fusion is based upon a successful use of surgical immobilisation (*arthrodesis*) of painful joints. The gold standard for achieving a fusion between the adjacent vertebrae is by using autogenous bone grafts (*autograft*). During surgery, the bone graft will be harvested from the patient's own pelvis and placed around the spine. The bone graft will stimulate the body to form bone tissue, and in several months the vertebrae will grow together – 'fuse' – into one long bone.

An autogenous bone graft stimulates bone formation, because it contains living cells, a structural framework into which bone can grow, and several growth factors [Muschler et al., 1992; Muschler et al., 1990]. The living cells are required for bone formation, since only living cells can make new bone tissue. The success of any bone grafting procedure depends on having enough potential bone-forming cells in the area (*osteogenicity*). In some situations, the healthy tissues around the graft site will contain a sufficient number of such cells. In many settings, however, the number of such cells in the surrounding tissues may be limited. Bone grafts can provide the required bone-forming cells or the precursor cells that can differentiate into bone-forming cells. In addition, autogenous bone grafts also provide a framework (*scaffold*)

Figure 1

A degenerated intervertebral disc: The disc has lost height and protrudes. This can cause back pain due to instability of the vertebral joint.

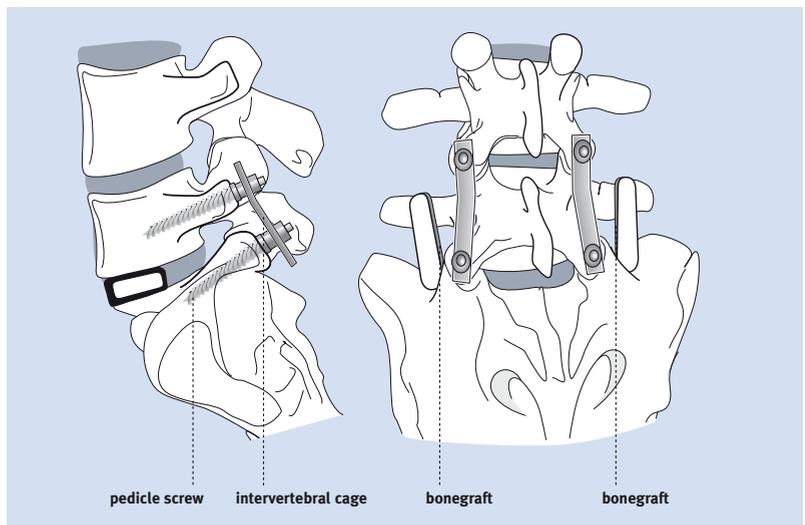


on which the new bone can grow (*osteoconduction*). Bone-forming cells generally function much better when they have a scaffold or matrix to attach to. Thus, the bone healing response is conducted through the graft site. Finally, autogenous bone grafts contain several growth factors, including bone morphogenetic proteins (BMPs) and transforming growth factor (TGF). Growth factors are vital to bone formation as they are part of the messaging or communication system, which tells cells what to do – grow (*proliferate*), or become a dedicated bone-forming cell (*differentiate*). In this way growth factors can initiate, or induce bone growth (*osteoinduction*). These three properties of autogenous bone grafts contribute to the successful use of autogenous bone grafts in procedures requiring new bone formation, such as spinal fusions. In addition to the use of autogenous bone grafts, the chances of achieving a successful fusion are enhanced when motion is prevented or minimised [Fischgrund, 2004]. Motion can be prevented by using hard plastic braces, or by internally immobilising the vertebrae with metal implants (*instrumentation*). Typically, these implants include rods, hooks, plates, screws, and more recently – threaded interbody cages (see Figure 2). The role of the metal implants is to correct deformity and to provide additional spinal stability while helping the fusion set-up. If bone fusion does not occur, the metal construct will fatigue and break. Thus, the metal implants are only an adjunct to successful fusion – they immobilise the spine while the body forms new solid bone. These metal implants may substantially increase the chance of successful fusion but are also associated with some risks, such as injury to nerves or blood vessels.

Although for many surgeons spinal fusion using autogenous bone in combination with instrumentation is the gold standard, it is associated with significant

Figure 2

Instrumented spinal fusion with the use of metal implants: The left drawing shows an intervertebral cage to correct the loss of height. Pedicle screws were placed at the back of the spine and connected by a plate. The right drawing shows a bone graft in situ between the two vertebrae. The bone graft will accelerate the formation of bone and in time the two vertebrae will unite (fuse).



complications. Failure to achieve such a fusion (*non-union*) has been reported to occur in more than 30% of the patients [Cleveland et al., 1948; Depalma et al., 1968; Stauffer et al., 1972; Steinmann et al., 1992]. The introduction of metal implants has decreased the rate of non-union [Fischgrund et al., 1997], but its incidence remains unacceptably high. In addition, the operative removal of bone from the iliac crest requires an additional surgical procedure with a distinct set of potential complications. In some cases the grafting procedure can even be more problematic than the primary surgical procedure itself. Major complications, such as pelvic fractures, nerve injuries, vascular injuries and infections, have also been reported [Arrington et al., 1996; Castelein et al., 1985; Fowler et al., 1995; Hu et al., 1994; Keller et al., 1987; Shin et al., 1996]. Although many severe and major complications are reported, the most common complication is persistent postoperative pain at the donor site. The reported incidence of chronic donor site pain after bone-grafting procedures from the pelvis ranges from 6% to 39% [Cockin, 1971; Fernyhough et al., 1992; Keller, 1987; Kurz et al., 1989; Laurie et al., 1984; Silber et al., 2003; Summers et al., 1989; Younger et al., 1989]. Another concern regarding autogenous bone grafts is that the amount available for transplantation can be insufficient. This is especially the case in children or when multiple levels need to be fused.

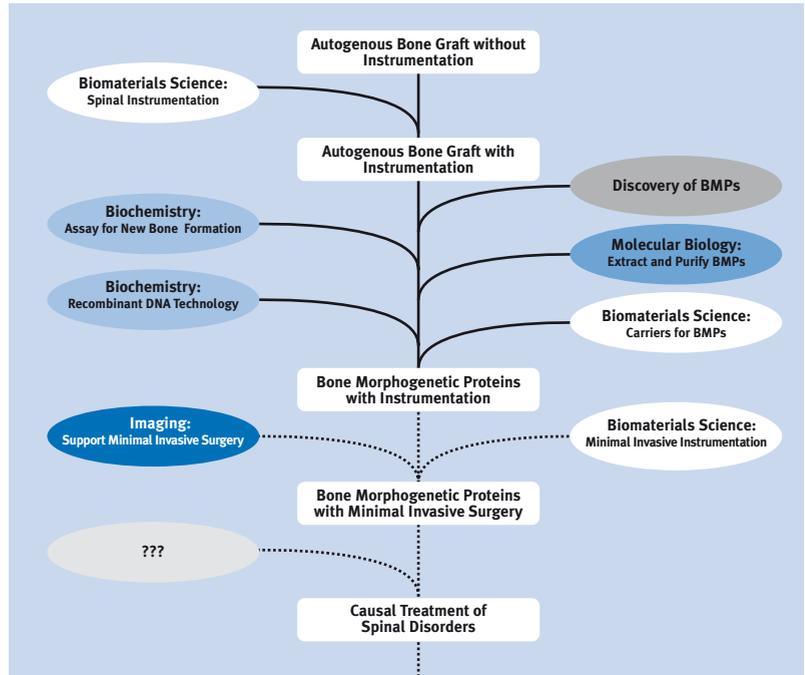
In an attempt to augment the limited quantity of autogenous bone that is accessible to the surgeon and to minimise the morbidity of grafting procedures, while maintaining an acceptable rate of fusion, several other strategies have been developed. One of the potential strategies is the use of growth factors, such as bone morphogenetic proteins (BMPs). BMPs are by nature present in bone. Nowadays, several human studies have reported the safe and effective use of BMPs as a replacement for autogenous bone grafts in spinal fusions.

BMPs FOR SPINAL FUSION: A NOVEL THERAPY THROUGH CONVERGING TECHNOLOGIES

Since Albee [Albee, 1911] and Hibbs [Hibbs, 1911] first described their series of spinal fusions in 1911, various technical advances have occurred and evolved leading to the introduction of spinal fusions with BMPs. The implementation of BMPs in the clinic could be achieved by combining the advances made by several distinct disciplines during the last century. Albee and Hibbs were not only the first to perform spinal fusions but also the first surgeons to employ autogenous bone grafts for the purpose of immobilisation of a joint. On the basis of the work of Albee and Hibbs spinal fusion utilising autologous bone became surgical standard procedures. Below, we will describe how the sequential converging of the technologies of biochemistry, biomaterial science, imaging and molecular biology has finally resulted in the development of a new, revolutionary regenerative treatment in orthopaedics. This is summarised in Figure 3.

Figure 3

BMPs for spinal fusion: a novel therapy through converging technologies. Spinal fusion started with the use of autogenous bone grafts without metal implants (instrumentation). During the last century, the influence of several distinct disciplines has led to the progression of spinal fusion techniques. Converging the knowledge of these disciplines has led to the introduction of BMPs for spinal fusion. In the near future, BMPs can be combined with minimal invasive surgery. In the long run, by further convergence of future advances, a more causal treatment of spinal degeneration can be achieved.



When spinal fusion was introduced, it consisted only of placing autogenous bone graft around the spine without the use of any additional metal implants. In the late 1950s, metal implants for immobilising the spine were introduced as a means of creating a faster and better fixation. In the following years, the use of metal implants for spinal fusion became more common, as surgeons saw the benefits for their patients. However, it was found that the devices applied were less than ideal in establishing rigidity and that the spinal forces were much greater than anticipated. As insights into biomaterials science progressed and metallurgy evolved, the metal implants were progressively strengthened. In the ensuing years, the implants were refined, and by the last decade of the twentieth century, instrumentation technologies had become common place.

The seminal discovery of BMPs was made by Urist in 1965 [Urist, 1965]. Urist was director of the bone research laboratory at the University of California, Los Angeles School of Medicine, and was a practicing orthopaedic surgeon. Bone consists of cells and a surrounding substance between these cells, the bone matrix. Urist showed that extracts of this matrix have the possibility to induce new bone formation when injected outside bone tissue (*ectopic site*). His research, however, was hampered by the fact that he was unable to isolate the agent that was responsible for the forming of the new bone, although he named the active component 'bone morphogenetic protein' or 'osteogenic protein'. The reason for this was that he did not have a test to measure bone

formation [Alper, 1994]. In addition, it was not conclusively determined that this protein was responsible for the formation of new bone rather than any other component of the bone matrix.

He and others struggled with this for nearly 20 years. Only after progress in biochemistry, Reddi and Sampath were able to develop a reproducible test for measuring new bone formation. With the aid of this test they were able to show that when the protein component was dissociated from the bone matrix, the remaining matrix in itself did not induce new bone formation [Sampath et al., 1981]. However, if the protein was returned to the matrix, the latter turned out to be as effective as the original matrix in inducing bone formation. This conclusively proved that the protein contained within the extract was responsible for bone formation. After identifying the active protein, the scientists needed to extract and purify it from the matrix. This required new molecular biological techniques. Due to technological progress in this discipline, it became possible to extract and purify these bone-inductive proteins from the matrix, which resulted in the identification of many types of bone morphogenetic proteins. Nowadays, over 20 different BMPs have been identified.

The next step was to find a way to produce these BMPs in large quantities. As bone contains only very small amounts of naturally occurring BMP, it would require hundreds of kilograms of donor (*cadaveric*) bone in order to obtain enough BMPs to be clinically useful. Therefore, the next challenge to the scientists was to find a way to synthetically produce BMPs. This became possible through further progression of recombinant DNA technology. Through this progress in biochemistry, segments of foreign DNA are transferred into another cell, and thus the substance for which they code may be produced. With this incorporated DNA the cells become 'factories' for the production of the protein. By using this technique, natural human BMPs can be produced in large quantities.

The final step before these proteins can be used in a clinical setting required the innovations made by biomaterial science during the last decades. This implied the identification of a suitable carrier to ensure a specific release of the protein in time. BMPs are water-soluble and are relatively low-molecular weight proteins that diffuse easily when administered at a surgical site. It is therefore necessary to contain the BMPs. In addition, bone-forming cells generally work better when a strong framework is available. In order to meet these two requirements, various carriers have been investigated both in the laboratory and in patients.

Combining the progress made by different specialties within life sciences resulted in the first clinical study by Johnson and associates with purified human BMP in 1992 [Johnson et al., 1992]. At present, BMPs have been investigated as an alternative to bone autograft in a variety of clinical situations, including spinal fusions, the internal fixation of fractures, treatment of bone defects, and reconstruction of maxillofacial conditions.

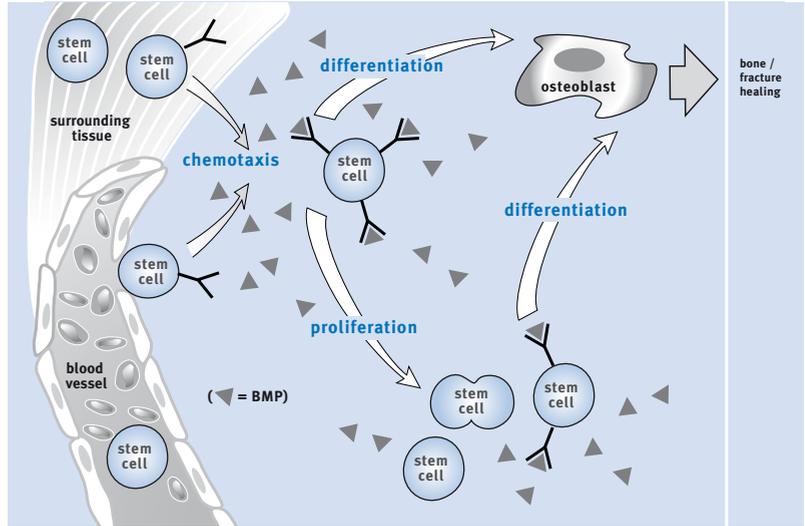
CURRENT STATUS OF BMPs FOR SPINAL FUSION

Soon after Sampath and Reddi invented a test to measure new bone formation and showed that the BMPs were responsible for the induction of bone formation, the development race was on. Two possible BMPs, identified in the bone extract, were 'chased' by two biotech firms, Genetic Institute and Creative BioMolecules [Alper, 1994]. Genetic Institute hired Reddi as a consultant, and Sampath joined Creative BioMolecules. The objectives of these firms were to identify the genes and complementary proteins that were responsible for the bone formation and to obtain the rights to this potentially lucrative market. In order to identify the responsible genes, the first step was to purify the protein, i.e. separate it from other proteins in the bone mixture. When they succeeded in purifying enough BMPs, they needed to determine the basic structural building units (amino acids) of the protein, the protein sequence. After having determined the partial protein sequence, both companies discovered that it contained a specific contribution of amino acids [Alper, 1994]. That pattern is characteristic of proteins belonging to the transforming growth factor- β (TGF- β) superfamily of regulatory proteins. This clue allowed the groups to fill in the blanks of the incomplete protein sequence with sequences from other members of the TGF- β superfamily and then to develop gene probes. Using the gene probes as bait, the two groups went fishing among a library of human fragments. Both companies found the complementary genes and proteins for various BMPs and applied for patents simultaneously. The determination of who owns the right to which genes and proteins was resolved by the court. Creative BioMolecules obtained the rights to produce BMP-7 (= Osteogenic Protein-1 (OP-1)) and associated with Stryker Corporation (Kalamazoo, Michigan). Genetics Institute started collaborating with Medtronic so as to produce BMP-2.

At present, these two recombinant human BMPs (rhBMPs) are commercially available. In the United States, rhBMP-2 is approved for long-bone fractures and for anterior spinal fusions. RhBMP-7 has a Humanitarian Device Exemption for recalcitrant long-bone non-unions and revision postero-lateral lumbar fusions. This Humanitarian Device Exemption is available to those devices intended for fewer than 4,000 patients per year. While the largest clinical trials and randomised studies demonstrate that rhBMP can be an alter-

Figure 4

Schematic depiction (simplified) of the working mechanism of BMPs. Under influence of BMPs undifferentiated stem cells are attracted from the surrounding tissue and blood vessels (chemotaxis). After being recruited, some of the stem cells multiply (proliferate), while others differentiate into bone-forming cells (osteoblasts). These osteoblasts start forming bone.



native to an autologous bone graft for interbody spinal fusion [Burkus et al., 2003; Burkus et al., 2005], treatment of tibial fractures [Govender et al., 2002] and fracture non-unions [Friedlaender et al., 2001], these results cannot be extrapolated to other clinical indications, because of the variations in carrier and delivery systems. To date, there are inadequate data to document efficacy in other clinical applications, and therefore other clinical trials need to be performed before expansion of the labelled indications.

HOW BONE MORPHOGENETIC PROTEINS WORK

Bone is unique compared to all the tissues in vertebral organisms. When injured, it heals by forming new bone. By contrast, most other tissues, such as the heart muscle, kidney and brain, heal by replacement of connective tissue rather than the original tissue. BMP is a protein existing by nature in our bodies and stimulates bone formation. The protein is essential for the healing of broken bones. BMPs are osteoinductive as they are able to stimulate new bone formation [Urist, 1965]. The principle of their working mechanisms is the initiation of a complex multistage cascade of events in promoting bone formation [Sakou, 1998] (See Figure 4).

Under the influence of BMPs, undifferentiated stem cells are attracted from the surrounding tissue. After being recruited from the surrounding tissue, some of the stem cells multiply, while others differentiate into specialised cells that are necessary for bone formation, bone-forming cells or blood vessel cells [Sakou, 1998]. Due to the ability of BMPs to transform cells from primitive undifferentiated stem cells into specialised ones, they are known as morphogens (from the Greek *morphê*, shape, and *genesis*, creation). The bone formed under influence of BMPs is biochemically and microscopically the same as

normal bone. A significant amount of the research into BMPs has been performed to elucidate the effects of individual BMPs at a cellular level, but up to now, unfortunately, the exact cellular mechanism is still unclear.

FUNDAMENTAL SCIENCE VERSUS APPLICATION

It is more than 4 decades ago since Marshall Urist made the seminal discovery that bone-derived proteins can induce bone formation, but so far BMPs did not have a major impact on orthopaedic surgery. Controlled clinical trials for each BMP, for each anticipated application/location need to be performed, not only to maximise clinical efficacy, but also to clearly define safety parameters for these highly osteoinductive compounds. One of the limiting factors is that the exact cellular mechanism targeted by BMPs, and the complete working mechanisms are not yet revealed. As mentioned before, laboratory studies have shown that under the influence of BMPs stem cells multiply and differentiate toward bone-forming cells. However, we do not know exactly what happens within the cells. With BMPs, we switch on the process of bone formation without actually knowing how to turn it off. In theory this could lead to excessive bone formation and even to an uncontrolled division of cells, although in practice this has not been observed. The question is, when do we know enough in order to allow clinical application, and which uncertainties can we accept in relation to the advantages obtained by this new therapy? Of course, in order to make progress in medicine, new potential therapies should be evaluated in human clinical studies, and here the difficulty remains to decide when it is safe to use it in a human clinical study. An example of a practical approach is total hip replacement. As mentioned in the introduction, modern artificial joints owe much to the work of Sir John Charnley. He pursued and tried to solve the problems encountered by replacing not only the femoral head (the ball) but also the acetabulum (hip socket). Charnley himself did suffer 'trials and tribulations' when developing his hip replacement, but he never gave up [Wroblewski, 2002]. Finally, in November 1962, the Charnley hip replacement became practical reality and it has become the gold standard for this form of treatment. Several decades had passed, when biomaterials science and biomechanics supplied more fundamental insights into and explanations of the working mechanism of the total joint prosthesis. We should, of course, first thoroughly explore the safety and efficacy in experimental models, but in order to make progress we should also dare to make the step toward clinical studies.

COST-EFFECTIVENESS

A major limitation of BMPs is their high price. Due to the ageing population and longer life expectations of the population in Western industrialised countries, it has become increasingly important to evaluate the economic impact of new therapies. The use of new technologies is generally presumed to be more expensive. Measuring the cost-effectiveness of a treatment is a tool that has been used as a decision-making aid for optimal societal resource allocation. Only one published cost-effectiveness analysis of BMPs for spinal applications is currently available, in which an economical analysis of BMP-2 (InFUSE, Medtronic Sofamor Danek) versus autogenous bone graft was performed in patients who underwent one-level fusions with the use of cages [Ackerman et al., 2002]. The authors suggested in a preliminary analysis that the price of BMP-2 is likely to be entirely compensated by reductions in the use of other medical resources. In other words, BMP-2 appears to be cost-neutral in this application. The cost reduction when using BMPs instead of autogenous bone grafts was largely attributed in this study to the prevention of pain and complications associated with autogenous bone harvest. Less obvious costs include decreased blood loss and obviated treatment of donor site complications, as well as potentially decreased transfusion requirements and shortened hospital length of stay. Additionally, by eliminating the need to harvest the autograft, anaesthesia time and surgeons' fees could compensate for the high price of BMPs. Last but not least, a reduction of the costs associated with fusion failures (*non-union*) largely contributed to the compensation of the price of BMPs. However, current literature has not indisputably shown that the use of BMPs provides this kind of reduction in non-unions, which could compensate for the high price of the product.

Although future research is needed to evaluate the cost-effectiveness of BMPs in the spine, it is possible that additional costs of BMPs may not be fully compensated. It is possible that the only advantage of BMPs will be elimination of chronic donor site pain and perhaps a slightly better fusion success, which is particularly relevant for patients 'at risk' (e.g. heavy smokers, diabetes etc.), or in combination with new surgical techniques to achieve fusion by less invasive methods. Currently, the economical analyses do not take into account the quality-of-life impact of pain. A difficult ethical question that needs to be considered is the appreciation of the iliac crest pain in terms of costs. In other words: What is pain avoidance worth? A more general discussion that needs to be addressed is whether these innovations have a place in a community of which the health care is not going to be affordable within a couple of decades due to the ageing population and longer life expectation. Should we only use regenerative medicine in certain indications? If so, will certain patients have more 'rights' to the new treatment, e.g. those patients 'at risk', the young pro-

Figure 5

The operation room of the future will contain special medical equipment, making minimal invasive surgery possible. This equipment may include fibre optic cables, miniature video cameras and special surgical instruments handled via tubes inserted into the body through small openings in its surface.



ductive sector of the population, or will this be equally accessible to everyone undergoing a spine fusion?

FUTURE TREATMENT OPTIONS WITH BMPs

Clinical application of osteoinductive factors is still in its infancy. Current studies are mainly focussed on avoiding morbidity associated with the harvesting of autogenous bone grafts from the pelvis. A greater advantage of BMPs can be established by using these inductive proteins in combination with a minimal invasive medical procedure, also known as 'keyhole' or percutaneous surgery. This procedure is carried out by entering the body through the skin, but with the smallest damage possible to these structures. Special medical equipment may be used, such as fibre optic cables, miniature video cameras and special surgical instruments handled via tubes inserted into the body through small openings in its surface (Figure 5).

Minimally invasive surgery results in less operative trauma for the patient. It is also less expensive, reduces hospitalisation time, causes less pain and scarring, and reduces the incidence of complications related to the surgical trauma. Without the use of BMPs, spinal fusions using a minimal invasive technique will still require an additional procedure to harvest the autogenous bone graft. This procedure will limit the advantages of the minimal invasive surgery, since an additional 'open' procedure is required. Nowadays, the first studies evaluating the combination of minimal invasive surgery with BMPs are being published and they show promising results [Boden et al., 1999; Villavicencio et al., 2005]. Minimal invasive surgery in combination with BMPs

will presumably be introduced in orthopaedic practice in the near future. In order to optimise the bone-forming capacities of BMPs, a combination with other growth factors and scaffolds should be considered. The synergistic effect of several factors stimulating bone-formation will result in higher fusion rates and a more successful treatment. By increasing the success of the treatment, the cost-effectiveness will increase. Also less BMPs may be required, which leads to a lower price of the bone graft substitute.

FUTURE FOR REGENERATIVE MEDICINE IN THE SPINE

Although the use of BMPs to establish a fusion between two vertebrae can increase the success rate of the treatment, spinal fusion remains a ‘salvage’ treatment. The patient has back pain due to degeneration of the spine and the therapy consists of immobilisation. When we look at the ages of development in orthopaedic surgery, spinal surgery has mainly remained in the Age of Reconstruction.

Ever since artificial hips and knees were introduced in the 1960s, scientists have also explored the idea of prosthetic replacements for damaged or degenerated intervertebral discs. Currently, several intervertebral disc prostheses are commercially available. One major intended benefit of artificial discs over spinal fusion is that potentially it does not change the biomechanics of the spine. Spinal fusion causes a decreased motion at one or more levels of the spine and will cause more stress to be transferred via the adjacent levels. This increased stress can create new problems at the other spinal levels. The artificial disc will facilitate the spine to maintain its normal range of motion and thereby reduces the risk of degeneration in adjacent segments. However, there are also drawbacks for the use of artificial discs. As mentioned before, intervertebral disc degeneration is a common cause of back pain in younger adults (age 30 to 50) and the demands for artificial discs will be great. Therefore, a substantial percentage of the patients will need revision surgery. Since this surgery is nearby vascular structures and scar tissue from the original surgery, revision procedures for artificial discs are complex and can be dangerous. In addition, the long-term outcomes of artificial discs are not well-known as yet.

In an attempt to improve the disadvantages of the current surgical treatment options for disc degeneration, spinal fusion or disc replacement, a more causal treatment of degenerative disc disorders is desired. Current treatment of disc degeneration aims at relieving the consequences of disc degeneration rather than at focusing on the cause of the disease. A potentially promising technique that is currently under the attention of several groups is to restore the intervertebral disc by regenerative strategies. The extensive research

performed on BMPs in the last decades has given scientists more insight into regenerating mechanisms of bone and cartilage. We do not yet know all of the growth factors that are involved in disc cell regeneration, but it appears that BMPs are a key component. In the long run, this may lead to new therapies which can stop and maybe partially reverse the degenerative process in the spine. New therapies could focus on stimulating the synthesis of the disc by injecting stem cells or by injecting growth factors. As compared with the commonly used 'salvage' treatments, this causal approach of disc degeneration has many advantages: It requires no surgery other than the injection of specific agents into the disc and therefore limits the risk for surgical complications, whereas the demand for hospitalisation and rehabilitation is expected to considerably decrease. Furthermore, long-term complications of fusion or prosthetic placement will be absent, as the proposed technology aims at restoration of original function and mobility.

Another important aspect that needs to be solved is the diagnosis of low back pain due to disc degeneration. Over the last 15 years, advances in biomedical imaging have resulted in the widespread use of magnetic resonance imaging (*MRI*) as an evaluative tool in the diagnosis of patients with back pain. Degenerative changes seen on the MRI could account for the chronic back pain disc. However, there is no 1:1 correlation of disc degeneration to pain. As we age, the disc normally also undergoes degenerative changes. The MRI is a relatively sensitive test for the detection of degenerative changes within the intervertebral disc, but it is incapable of providing a pain association. In order to prevent procedures from being performed for the wrong reasons and to improve diagnostic accuracy, a reliable diagnostic tool for painful disc degeneration is required.

As discussed above, the implementation of these new technologies will likely be accompanied with higher costs. In order to keep health care affordable in the upcoming decades, cost effectiveness will play an increasingly important role in determining whether a new therapy will be implemented in clinical practice. This seems to clash with the rising quality-of-life demands of society. For instance, patients with low back pain wish to be able to continue practicing their sports. As a result of the emphasis on cost-effectiveness, these people will not receive treatment as it is calculated that the costs do not warrant the benefit to their quality of life. Furthermore, when determining the cost-effectiveness of a new treatment, we should realise that it is generally presumed that all new technologies are more expensive in the beginning. However, the costs can decrease after the initial development costs are compensated. Additionally, after the implementation of the new treatment on a broader scale, the reduction of the production costs will also count for a

decrease in the price of the new treatment. This can eventually lead to a cost-effective treatment, while initially the treatment was accompanied with higher costs.

In addition to the focus on cost-effectiveness of new treatments, it is also important to realise that innovations often give insight into the mechanism of diseases and can lead to other treatment options. The current application of BMPs for spinal fusion could be more expensive than the regular treatment with autogenous bone grafts. However, after the safety and efficacy of BMPs in spinal fusion has been shown, it is feasible that BMPs will be used in combination with minimal invasive medical procedures. Minimal invasive surgery is associated with less complications, shortened hospitalisation and less work absenteeism, thus leading to a reduction of health care utilisation. Finally, BMPs have given insight into the mechanism of diseases, like intervertebral disc degeneration. This brings a causal treatment option for patients with low back pain a bit closer. Since low back pain is associated with high costs of health care utilisation, a new treatment will reduce the impact of this major health and socioeconomic problem.

REFERENCES

- Ackerman, S.J. et al. (2002). Economic Evaluation of Bone Morphogenetic Protein Versus Autogenous Iliac Crest Bone Graft in Single-Level Anterior Lumbar Fusion: An Evidence-Based Modeling Approach. *Spine* 27, 16 Suppl 1, S94-9
- Alper, J. (1994). Boning Up: Newly Isolated Proteins Heal Bad Breaks. *Science* 263, 5145, 324-5
- Arrington, E.D. et al. (1996). Complications of Iliac Crest Bone Graft Harvesting. *Clin. Orthop. Relat. Res.* 329, 300-9
- Boden, S.D. et al. (1999). Posterolateral Lumbar Intertransverse Process Spine Arthrodesis with Recombinant Human Bone Morphogenetic Protein 2/Hydroxyapatite-Tricalcium Phosphate after Laminectomy in the Nonhuman Primate. *Spine* 24, 12, 1179-85
- Burkus, J.K. et al. (2003). Is Infuse Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the Lt-Cage Lumbar Tapered Fusion Device. *J. Spinal Disord. Tech.* 16, 2, 113-22
- Burkus, J.K. et al. (2005). Use of Rhbmp-2 in Combination with Structural Cortical Allografts: Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Surgery. *J. Bone Joint Surg. Am.* 87, 6, 1205-12
- Castelein, R.M., A.J. Sauter (1985). Lumbar Hernia in an Iliac Bone Graft Defect. A Case Report. *Acta Orthop. Scand.* 56, 3, 273-4

- Charnley, J. (1960). Surgery of the Hip-Joint: Present and Future Developments. *Br. Med. J.* 5176, 821-6
- Cleveland, M. et al. (1948). Pseudoarthrosis in the Lumbosacral Spine. *J. Bone Joint Surg. Am.* 30, 302-311
- Cockin, J. (1971). Autologous Bone Grafting: Complication at the Donor Site. *J. Bone Joint Surg. Br.* 52, 153
- Depalma, A.F., R.H. Rothman (1968). The Nature of Pseudarthrosis. *Clin. Orthop. Relat. Res.* 59, 113-8
- Einhorn, T. (1998). *Orthopaedic Surgery in the 21st Century: The Role of the Bone Morphogenetic Proteins*. American Academy of Orthopaedic Surgeons 65th Annual Meeting New Orleans, Louisiana
- Fernyhough, J.C. et al. (1992). Chronic Donor Site Pain Complicating Bone Graft Harvesting from the Posterior Iliac Crest for Spinal Fusion. *Spine* 17, 12, 1474-80
- Fischgrund, J.S. et al. (1997). 1997 Volvo Award Winner in Clinical Studies. Degenerative Lumbar Spondylolisthesis with Spinal Stenosis: A Prospective, Randomized Study Comparing Decompressive Laminectomy and Arthrodesis with and without Spinal Instrumentation. *Spine* 22, 24, 2807-12
- Fischgrund, J.S. (2004). The Argument for Instrumented Decompressive Posterolateral Fusion for Patients with Degenerative Spondylolisthesis and Spinal Stenosis. *Spine* 29, 2, 173-4
- Fowler, B.L. et al. (1995). Complications Associated with Harvesting Autogenous Iliac Bone Graft. *Am. J. Orthop.* 24, 12, 895-903
- Friedlaender, G.E. et al. (2001). Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in the Treatment of Tibial Nonunions. *J. Bone Joint Surg. Am.* 83-A Suppl 1, Pt 2, S151-8
- Govender, S. et al. (2002). Recombinant Human Bone Morphogenetic Protein-2 for Treatment of Open Tibial Fractures: A Prospective, Controlled, Randomized Study of Four Hundred and Fifty Patients. *J. Bone Joint Surg. Am.* 84-A, 12, 2123-34
- Hu, R.W., H.H. Bohlman (1994). Fracture at the Iliac Bone Graft Harvest Site after Fusion of the Spine. *Clin. Orthop. Relat. Res.* 309, 208-13
- Johnson, E.E. et al. (1992). Resistant Nonunions and Partial or Complete Segmental Defects of Long Bones. Treatment with Implants of a Composite of Human Bone Morphogenetic Protein (BMP) and Autolyzed, Antigen-Extracted, Allogeneic (Aaa) Bone. *Clin. Orthop. Relat. Res.* 277, 229-37
- Keller, E.E., W.W. Triplett (1987). Iliac Bone Grafting: Review of 160 Consecutive Cases. *J. Oral Maxillofac Surg.* 45, 1, 11-4
- Kurz, L.T. et al. (1989). Harvesting Autogenous Iliac Bone Grafts. A Review of Complications and Techniques. *Spine* 14, 12, 1324-31
- Laurie, S.W. et al. (1984). Donor-Site Morbidity after Harvesting Rib and

Iliac Bone. *Plast. Reconstr. Surg.* 73, 6, 933-8

- Muschler, G. et al. (1990). The Biology of Spinal Fusion. In: Cotler, J.M., H.P. Cotler (Eds). *Spinal Fusion Science and Technique*. Springer-Verlag
- Muschler, G., J. Lane (1992). Orthopedic Surgery. In: Habal, M.B., A.H. Reddi (Eds). *Bone Grafts and Bone Substitutes*. 375-407
- Retpen, J.B. et al. (1989). Clinical Results after Revision and Primary Total Hip Arthroplasty. *J. Arthroplasty* 4, 4, 297-302
- Sakou, T. (1998). Bone Morphogenetic Proteins: From Basic Studies to Clinical Approaches. *Bone* 22, 6, 591-603
- Sampath, T.K., A.H. Reddi (1981). Dissociative Extraction and Reconstitution of Extracellular Matrix Components Involved in Local Bone Differentiation. *Proc. Natl Acad. Sci. USA* 78, 12, 7599-603
- Shin, A.Y. et al. (1996). Superior Gluteal Artery Injury Secondary to Posterior Iliac Crest Bone Graft Harvesting. A Surgical Technique to Control Hemorrhage. *Spine* 21, 11, 1371-4
- Silber, J.S. et al. (2003). Donor Site Morbidity after Anterior Iliac Crest Bone Harvest for Single-Level Anterior Cervical Discectomy and Fusion. *Spine* 28, 2, 134-9
- Stauffer, R.N., M.B. Coventry (1972). Posterolateral Lumbar-Spine Fusion. Analysis of Mayo Clinic Series. *J. Bone Joint Surg. Am.* 54, 6, 1195-204
- Steinmann, J.C., H.N. Herkowitz (1992). Pseudarthrosis of the Spine. *Clin. Orthop. Relat. Res.* 284, 80-90
- Summers, B.N., S.M. Eisenstein (1989). Donor Site Pain from the Ilium. A Complication of Lumbar Spine Fusion. *J. Bone Joint Surg. Br.* 71, 4, 677-80
- Urist, M.R. (1965). Bone: Formation by Autoinduction. *Science* 150, 698, 893-9
- Villavicencio, A.T. et al. (2005). Safety of Transforaminal Lumbar Interbody Fusion and Intervertebral Recombinant Human Bone Morphogenetic Protein-2. *J. Neurosurg. Spine* 3, 6, 436-43
- Wroblewski, B.M. (2002). Professor Sir John Charnley (1911-1982). *Rheumatology (Oxford)* 41, 7, 824-5
- Younger, E.M., M.W. Chapman (1989). Morbidity at Bone Graft Donor Sites. *J. Orthop. Trauma* 3, 3, 192-5

Cardiac Cell Therapy: To Mend A Broken Heart

Brian Fernandes, Marc Hendriks¹

Imagine this article in all major newspapers of 1 March 2025:

First case of heart failure reported since 2020

“A case of heart failure was reported last month. It is the first case reported since 2020, and the first since cell therapy has found general use as the standard of care in the repair and regeneration of cardiac disease. The recent case is remarkable because it is so unusual. Particularly, since clinicians have achieved major progress and outstanding success in effective cardiac disease therapy as a result of the steadfast efforts of the scientific community and private public funding.”

Can this be possible?

¹ Medtronic Bakken Research Center BV, Maastricht, the Netherlands.

BACKGROUND

Heart diseases due to lack of oxygen encompass heart conditions that include myocardial infarction (heart attacks) and heart failure. It is the predominant cause of death and disability, accounting for about 20% of the deaths in Europe, Canada and the US. In 1997, heart disease resulted in nearly 2 million deaths across Europe [BHF, 2000]. The European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic Heart Failure estimates that at least 10 million people have some degree of heart failure [Remme et al., 2001]. It is projected that worldwide the rates on incidence and prevalence will continue to go up as the population ages and lives longer, and these increasing trends will place a large economic burden on health care systems.

Heart failure is an advanced form of heart disease, often progressing from heart attacks. Heart attacks lead to localised cell death. The body is incapable of replacing these specialised heart muscle cells, at least not to any significant clinical extent. After the damage to the heart cells, the body recruits non-conducting, non-contractile fibroblast cells. These replacement fibroblasts ultimately form scar tissue that interrupts the heart muscle and compromises the ability of the heart to contract and pump blood. With time these areas of damage continue to expand, eventually leading to heart failure.

Heart failure is a rapidly fatal, very expensive, and prevalent disease. The majority of heart failure patients are aged 65 years or older when diagnosed with this progressive disease. Heart failure therapy is expensive: During 2004, the estimated total costs for treating heart failure in the US were more than \$ 25 billion; in the UK, the same costs were estimated to exceed the equivalent of \$ 1.2 billion US dollars [www.chestpainperspectives.com].

Despite advances made in the management of heart attacks, heart damage is an increasing cause of heart failure in the Western world. While different existing therapies have improved the survival rate after heart attacks, they have also resulted in an increased prevalence of heart failure, as approximately half of all heart failure patients enter the morbid spiral of cardiac muscle disease as result of a heart attack. At the time of terminal heart failure, heart transplantation has long been considered as the only viable alternative.

CURRENTLY AVAILABLE THERAPIES

Despite the availability and application of drug and medical device therapies, heart failure patients still experience an average five-year mortality rate of 50%.

This mortality rate reflects the fact that most existing therapies only treat heart failure symptoms and are incapable of reversing the original heart muscle damage, as well as its gradual advancement over time.

Current therapeutic options for heart attacks include drug therapy — often with proven but limited benefit — various catheter and surgical procedures — many with restricted applicability and/or incomplete benefits, and electrical stimulation. The table below summarises various heart failure therapies [Euro PCR, 2004].

Table 1

Various heart failure therapies.

Therapy	Limitations
medical treatment: pharmaceuticals	terminal heart failure becomes resistant to drug therapy
electrical stimulation	technically demanding, applicable to a subset of patients
surgical cardiomyoplasty	limited clinical practice
mechanical assist devices (pumps)	expensive, not proven for long-term use, associated with significant complications
artificial hearts	first designs associated with numerous complications, subsequent designs still experimental
heart transplantation	limited number of organ donors, life-long immuno-suppression therapy

CELL THERAPY

In contrast to established dogma, very recently evidence has emerged of the adult heart being capable of a certain degree of self-repair. However, in most cases any demand for repair exceeds the capacity of the heart to respond after injury. The existence of these inherent repair mechanisms, albeit small, suggests that cardiac repair may be achieved therapeutically, i.e. it can be promoted by external means.

Accordingly, these last few years have witnessed a growing interest in the regeneration of the failing heart by cell therapy. This approach consists of transplanting cells into the injured area of the heart in the expectation that the transplanted cells will (i) increase or preserve the number of existing cells in the injured tissue, (ii) improve the blood supply in the injured region, and (iii) augment the contractile (beating) function of the injured tissue.

New, cell-based therapies are being developed in response to the limitations caused by the fact that available therapies cannot replace injured heart cells. These therapies entail removing cells from some source and then delivering these into diseased areas of the heart. The goal of these emerging therapies is to improve and perhaps repair the underlying heart muscle in particular and the overall cardiac function in general. And if the improvement in cardiac function is sufficient, to decrease the mortality among transplantation patients. In general, cardiac cell therapy approaches comprise three main categories:

- Using various cell sources to augment the function of heart muscle and/or create new heart muscle ('myogenesis' or 'cardiac regeneration').
- Using various cell sources to increase the flow of blood to the injured heart muscle ('angiogenesis' or heart muscle revascularisation).
- Using various cell sources and/or cell modifications to accomplish both: Regenerate heart muscle and generate increased blood flow to the injured heart muscle.

Cell therapy has entered the clinical field with promising results, but many hurdles still need to be overcome before cell therapy can be fully integrated into the armamentarium of regenerative medicine techniques. Several of these hurdles, technical and other, will be highlighted in this document.

CHOICE OF CELL TYPE

While the simplest and most direct form of cell therapy entails the delivery of cells alone to the injured sites, other more complex approaches can be envisioned as well. Some examples include tissue-engineered constructs, involving cell-biomaterial tissue substitutes, and the use of signalling molecules to mobilise cells from certain regions to migrate and home to affected regions for the purpose of engaging in self-repair. Regardless of the approach, the most basic and fundamental unit of the envisioned therapy will still be the cell, and the selection of the appropriate cell type will therefore be critical.

An ideal cell type to serve in replacement therapy has not yet been identified. For cell therapy to be successful, the following general criteria are at the very least required:

- Cells must be easy to harvest.
- Cells can be expanded to generate sufficient numbers.
- Immature cells can be converted (differentiated) into the desired cell type(s).
- Transplanted cells do not elicit an immunogenic response from the host that will reject the cells.

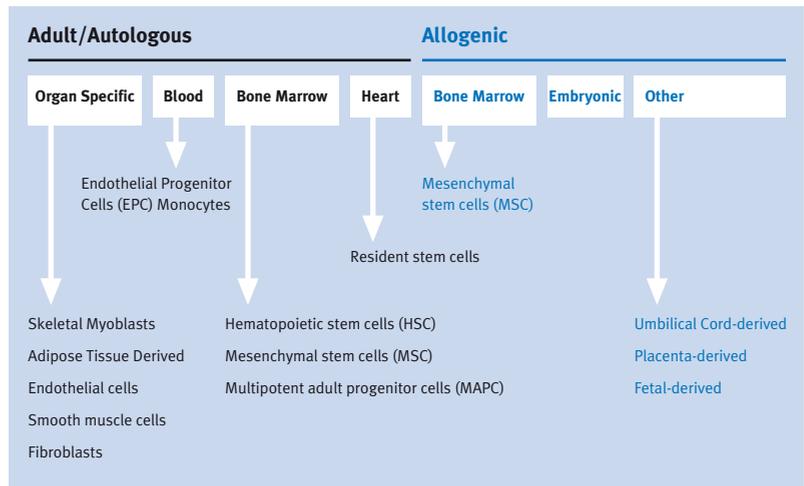
- The cells will survive in the recipient after transplant.
- The cells will integrate into the host tissue after transplant.
- The cells will effectively function for the duration of the recipient's life.
- The cells are not harmful to the patient.

The cell therapies under development generally vary by patient source and cell type. Sources of cells for transplantation can be autologous or allogenic. *Autologous, i.e. from the same patient.* The advantage is that the transplanted cells are well tolerated. Depending on the cell type of interest, however, a potential limitation is the availability of the cells and/or the lack of adequate numbers of cells. While this can be remedied by external expansion of cells to generate sufficient numbers, it can also lead to a delay between cell isolation and application, as well as potentially induce unwelcome changes in the cells as a result of external manipulation. Autologous cells tend to primarily come from adult sources (Figure 1).

Allogenic, i.e. from the same species. There can be a greater supply of this type of cells as they can be banked or stored for future applications. An important limitation is the immune reaction that these cells will likely elicit when being transplanted from one patient to another. While the immune rejection can be suppressed through the use of immunosuppressive agents, long-term use of immunosuppressive therapy can have undesirable and debilitating side-effects. The use of some allogenic cell sources, such as foetuses and embryos, also raise ethical and moral questions.

Fundamentally, stem cells are considered as master cells, which are capable of generating other types of cells. Stem cells have three general characteristics that distinguish them from other types of cells. They can renew themselves for long periods of time, are unspecialised, and they can give rise to one or more

Figure 1
Autologous cells tend to primarily come from adult sources.



specialised cell types under certain conditions. The property by which stem cells can generate different cell types is generally classified into three groups, namely totipotent, pluripotent, and multipotent.

- A fertilised egg is considered totipotent, meaning that its potential is total. It gives rise to all the different types of cells in the body.
- Pluripotent stem cells can give rise to any type of cell in the body except those needed to develop a fetus.
- Stem cells that can give rise to a small number of different cell types are generally called multipotent.

Adult stem cells have been identified in many organs and tissues. They are usually present in very small numbers and it is believed that their primary role is to repair and maintain normal conditions by generating the varied cell types that are specific to the tissue in which they reside. Researchers are trying to find ways to grow adult stem cells and manipulate them to generate specific cell types for treating different injuries and diseases [<http://stemcells.nih.gov/info/basics>].

Adult sources for stem cells are generally free of controversy. Currently, the adult sources, and the adult cell types most studied are the following:

- Bone marrow-derived cell populations.
- Blood-derived cells.
- Skeletal myoblasts from skeletal muscle.
- Fat-derived cell populations.
- Umbilical cord blood-derived cells.
- Most recently, several research groups have identified resident stem cell populations in the heart, which can be isolated, cloned and expanded.

Allogenic sources of cells tend to primarily come from non-adult sources, such as foetal, embryonic and umbilical cord blood, except for mesenchymal stem cells, which are derived from bone marrow. Mesenchymal stem cells are sparsely present in the marrow and need to be expanded for several weeks before sufficient cell numbers have been obtained for therapeutic purposes. These cells are multipotential, generating completely different cell types under different culture conditions [Caplan, 2005]. While mesenchymal stem cells have shown to lead to improved beneficial effects following delivery, the strong belief that they can generate heart cells, as demonstrated in small animal models, has not entirely lived up to expectations in larger animal species [Shake et al., 2002]. However, mesenchymal stem cells have the special characteristic of immune privilege, enabling them to survive in an allogenic setting [Zhao et al., 2004]. This property is particularly attractive as it suggests the possibility of an off-the-shelf approach. In this case the cells can be expanded,

banked, and shipped to the point of use when required, thereby allowing for reductions in cost and effort for cell production and quality control. Following experimental work, a clinical trial is underway for intravenous delivery allogenic mesenchymal stem cells following a heart attack [Price et al., 2005].

Based on experimental data, it is generally believed that the gold standard for cardiac regeneration is the transplantation of foetal heart cells rather than adult heart cells [Reinecke et al., 1999]. However, sufficient availability and the accompanying ethical and political issues associated with the source of these foetal cells will prove too high a hurdle to overcome for these cells to be adopted for clinical evaluation. The one source of cells that has pluripotential properties is embryo-derived stem cells. Although research in human embryonic stem cells only began 7 years ago, tremendous technical progress has already been achieved in several areas [Laflamme et al., 2005]. In addition, several small animal studies in rodents have revealed engraftment and repopulation of injury areas with embryonic heart cells [Hodgson et al., 2004], and more recently encouraging data have emerged with large animals as well [Menard et al., 2005]. For many, embryonic stem cells represent the holy grail of regenerative medicine. However, clinical adoption of these cells will require in the first place that the ethical and political issues associated with usage are overcome, and, in the second place, that outstanding technical challenges like purity of cell populations, tumourgenicity, and immunogenicity, to name a few, are addressed. These daunting challenges have not dampened the spirits or enthusiasm of the scientific community and currently, in spite of the restricted and regulated environment in many countries, research is continuing at a frenetic pace.

Experimentally, the results from a wide range of animal studies have been less than discriminatory, as almost every purported stem cell type tested, including non-stem cells, has demonstrated improved therapeutic efficacy. These positive results have been generated in varied animal species, with varied injury models, and with varied cell types and concentrations [March et al., 2004]. Clinically, the cell selection has been limited to either bone marrow derived cells, blood derived cells and skeletal myoblasts. Currently, the cell selection is essentially based on timing of application, that is either very early after injury (acute) or in patients with injuries that have taken place in the past (chronic). Thus far, acute patients have been exclusively treated with either bone marrow derived cells or blood derived cells. On the other hand, skeletal myoblasts have been exclusively used for chronic heart failure patients [Taylor, 2004]. More recently, bone marrow derived cells have also been used for chronic heart failure patients as well [Perin et al., 2004].

Collectively, the results that have emerged from the pre-clinical and clinical settings have not resolved the question as to which cell type is the most appropriate. The understanding of the actual working mechanisms of the applied cell therapy has been equally elusive, thus far. The previous dominant hypothesis, based on a cell-contractile based mechanism, has instead given way to alternate, more complex, mechanistic actions [Reinecke et al., 1999]. It has been hypothesised, and to some degree demonstrated, that the bone marrow-derived cells and the blood-derived cells give more direct contributions to the process of the formation of new blood vessels. The extent to which this may occur will likely depend on the cell type and the type and stage of cardiac injury [Dimmeler et al., 2005].

While the search for the ideal cell type continues, one common occurrence plaguing each and every cell type, regardless of the cell source, is the poor cell survival that is observed following transplantation into the damaged tissue [Laflamme et al., 2005]. A number of reasons can be identified for this phenomenon, the most notable of which are lack of oxygen, lack of blood supply and lack of optimal tissue present in the damaged zone. This is another indication that cells should perhaps not be thought of as isolated and that a different approach may be needed, one that pays attention to the environment of the cells as well. With this in mind, it is strongly believed that if the true potential of cell therapy is going to be realised much greater cell survival and cell integration are essential. At the moment, different strategies aimed at enhancing cell survival are being actively investigated [Huang et al., 2005; Tambara et al., 2005; Souza et al., 2004; Dib et al., 2005].

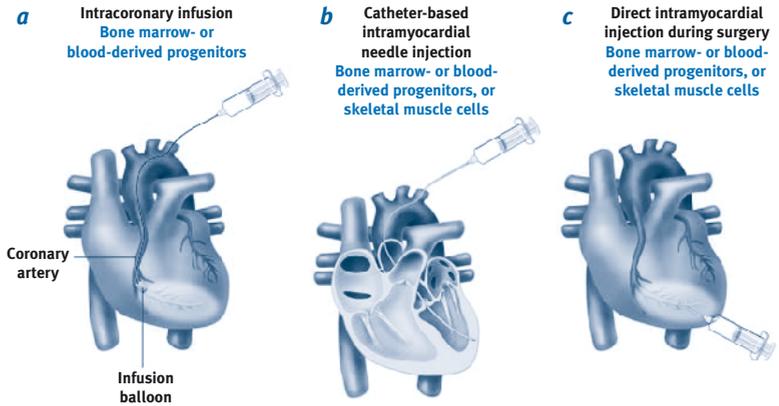
ROUTE OF DELIVERY

The success of cardiac cell therapy will also depend on the availability of suitable cell delivery techniques that allow the well-controlled local administration of cell concentrations in the target zone. Generally, there are three components involved in cell delivery: the cells, the delivery device (syringe or catheter), and the target localisation and navigation system. The selection of the appropriate administration route depends on a variety of factors including the disease state, the patient condition, the cell type and physician preference.

The most direct and simplest system for cell delivery is through the use of hypodermic syringes (Figure 2C). This approach is only employed during open heart surgical procedures, where the chest cavity has been opened. For then the affected area is in plain view and easy to visualise, and therefore, no specialised localisation/navigation instrumentation is required.

Figure 2

Catheter cell delivery. Republished from [Dimmeler et al., 2005].



However, open chest surgical procedures make up a very small percentage of total heart-related hospital procedures. The exponential increase in minimally invasive interventional procedures has had a direct effect on continually shrinking surgical volumes [Advisory Board Company, 2004].

As a result, intra-coronary artery delivery represents a minimally invasive procedure that offers the simplest route for catheter cell delivery (Figure 2A). With this approach the cells are delivered into the blood stream slightly upstream of the affected area. The delivery catheters employed tend to be unsophisticated, standard coronary angioplasty balloon catheters that are used off-label (i.e., outside the intended use). With this approach, the cells are delivered to a general area rather than a discrete location. However, with this approach greater reliance is left on the ability of the cells to migrate through the blood vessel walls and into the compromised ischemic zones. Intravenously infused cell delivery is a variation of the intra-coronary approach, which uses the coronary venous blood vessel system to direct the cells to the ischemic zones. A very real limitation of the delivery (infusion) of the cells into the blood vessels is the relatively poor retention of the transplanted cells within the affected area [Wollert et al., 2005].

An additional non-surgical, minimally invasive approach involves cell injections directly into the damaged heart tissue by using endoventricular catheters (Figure 2B). Such an approach, while minimally invasive, needs supporting visualisation, localisation and navigation instrumentation to reach the target areas. Ultrasound, fluoroscopy and electromechanical mapping are some of the modalities that are used for guiding the endoventricular catheters. Endoventricular catheters tend to be highly engineered devices, capable of enhanced articulation as well as containing retracting needle assemblies and features to interface with the localisation and navigation system.

A thorough examination and comparison of the various delivery modalities has thus far been lacking. The selection of a delivery system is essentially based upon various factors, including but not restricted to acute or chronic application, device availability, device complexity, physician preference/capabilities, and cost.

There are several issues that are common to each of the systems described. The most notable is the poor cell retention that is observed at the targeted sites in the periods immediately after delivery. Depending on the delivery modality, cell loss can be due to ‘backflow’ through the needle tract or ‘wash-out’ through the different blood vessels present in the receiving tissue [Dow et al., 2005]. Methods that can enhance the local retention of cells may improve overall cell survival. Where exactly to deliver the cells is equally important with regard to cell survival. Will better cell survival be ensured in the border regions (infarct periphery), as opposed to the centre of the injured sites? And, if so, are the available catheter systems smart enough to detect or identify these border regions?

CLINICAL STUDIES

So far, a flurry of small, mostly uncontrolled and non-randomised clinical studies have been conducted with a myriad of different cell types, cell preparations and delivery mechanisms. The primary objective of these studies has been to establish safety and feasibility [Wollert et al., 2005].

In the case of the bone marrow cells, the majority of the clinical studies have suggested that the procedure is feasible and safe. Encouragingly, various aspects of cardiac function were observed to improve following cell therapy. The relative ease, quickness and lower costs with which a cell population can be isolated from a bone marrow aspirate have contributed to these cells being readily used in acute clinical applications in about 14 European countries. In addition, the extensive prior clinical experience with bone marrow transplantation has reduced the regulatory burden and facilitated clinical adoption of bone marrow derived cells [Murry et al., 2005]. Larger and better designed clinical studies for bone marrow cells are currently being performed in order to attempt to definitively demonstrate safety and efficacy.

In the case of skeletal myoblasts, over 100 patients in 7 different studies have been treated in Phase I feasibility studies. While improvements in cardiac function have been reported, with all cases there have also been reports of arrhythmia (irregular electrical conduction) in the early periods following

myoblast therapy. One large randomised, double-blind, placebo-controlled multicentre Phase II trial to assess the efficacy of skeletal myoblast treatment in ischemic heart failure patients was prematurely halted due to the lack of efficacious findings with the treatment groups.

Similarly, after encouraging preclinical test results, stem/progenitor cell therapy has had mixed results in humans, with some studies showing positive effects and others showing marginal to no effects at all [Janssens et al., 2006; Kuethe et al., 2004; Wollert et al., 2004]. In addition, the assessment of efficacy and the functional interpretation of the results obtained are confounded by the fact that the cell therapy is generally applied together with standard procedures, such as surgical bypass procedures and stent-based procedures. The majority of the clinical studies have been initiated and conducted by specialised academic hospitals in Europe. Large size trials are invariably very expensive, and adequate funding is a never-ending issue. At this stage, continued activity in the field is essentially dependent on and driven by governmental and charitable sources [Wollert et al., 2005]. For example, the REPAIR-AMI study, which is the world's largest placebo-controlled study, is principally investigator-driven and has no central sponsor. It has partially received support from the J. W. Goethe University, Dept. of Cardiology (trial logistics), and the Institute for Transfusion Medicine (financed production and transportation of bone marrow aspirate and the study medication, respectively). In addition, the following non-profit research organisations have provided support for cell isolation procedures: Leduq Foundation, Alfried Krupp Stiftung, German Research Foundation and European Vascular Genomics Network. Guidant, Inc. provided the balloon catheters, used for infusing the study medication and provided an unrestricted research grant. Lilly provided abciximab co-administered with the study drug in the first part of the trial. All further costs related to the trial were covered by the individual participating study centres [American Heart Association, 2005].

Another potential factor for the relative absence of intermediate to large-size clinical trials is the lack of industrial participation in the sponsorship of these trials. The hesitancy on the part of some companies may be attributed to the want of convincing evidence on the clinical benefits of the therapy, and/or a lack of the perceived commercialisation value of such a therapy. While some medical device companies have become involved by focusing on products relating to cell processing and delivery devices, the question remains whether these companies will expand their roles by sponsoring and driving the much needed larger studies. There are a few examples where companies, because of their involvement with catheters and cell processing, have sponsored clinical trial activity. A larger skeletal myoblast-based trial (MAGIC) was co-sponsored by MGB Biotherapeutics, a joint venture between Medtronic, Inc., and

Genzyme Corporation. There are other examples of industrial sponsorship of cell therapy trials, but these all tend to be on a smaller scale [Dib et al., 2005].

SAFETY

One of the major concerns with cell therapy is whether the process is safe both short-term and long-term. Several issues have been highlighted that could possibly compromise the success of this therapy. The manifestation of life-threatening arrhythmias (abnormal electrical disturbances) during the early stages, especially with the use of skeletal myoblasts, has cast a shadow over the application of these cells [Menasche, 2004]. Currently, some myoblast studies are proceeding forward on the condition that the patients have an implantable device, such as an implantable cardioverter defibrillator (ICD), to provide protection against the potential for arrhythmias. There are several reasons why arrhythmias could be generated. Curiously, this phenomenon is not apparent in every clinical skeletal myoblast study [Herrerros et al., 2003]. Additional prospective research will need to be performed in order to determine whether arrhythmia generation post-transplantation is related to, for example, cell dose, cell placement or even cell preparation.

Although it is preferable that a certain degree of proliferation takes place following cell transplantation in order to repopulate the damaged tissue, controls need to be in place to ensure that the proliferation is not continuous and uncontrolled, so as to not generate tumour like structures. The delivery of immature cells, or partially differentiated cell types, as in the case of embryonic stem cells, has been shown to generate tumours [Laflamme et al., 2005]. This reinforces the need, as in the case of embryonic stem cells, for highly purified preparations of cells that reflect a differentiated state that is compatible to the milieu in which they are placed. Additional arguments for generating pre-differentiated cells prior to transplantation are to prevent aberrant cell differentiation, such as calcification, which make the cells incompatible with the environment they find themselves [Yoon et al., 2004]. Equally relevant to the tumour concern is the widespread distribution of cells, even following localised cell delivery [Aicher et al., 2003]. Several studies have now demonstrated that the majority of cells tend to localise in other organ systems such as the lungs, liver, kidneys, and spleen. Currently, increased efforts are made to increase delivery efficiency and to enhance localised cell retention. Other safety concerns that have been raised relate to the generation or enhancement of pathological conditions, such as atherosclerosis, in-stent restenosis, and infarct generation [Caplice et al., 2005].

CELL TECHNOLOGIES/PROCESSING

In order to bring cell therapies further on the market, GLP/GMP infrastructure will need to be in place to maintain the quality control that will be mandated by the regulatory authorities.

Cell processing facilities will need to demonstrate core expertise in varied areas, such as cell isolation, cell sorting, cell expansion, cell characterisation, cell storage, cell transport and bio-burden testing. And depending on the scale of production, investments may need to be made in cell factories and bioreactors for mass production.

Cells are complex elements and, whether differentiated or undifferentiated, need optimal conditions (milieu) for survival and integration. Stem cells are increasingly transplanted in tissues that are different from those from which they have been derived and in tissues that are damaged. Depending on sub-optimal local signals in damaged areas to influence differentiation toward a specific phenotype may not be the best approach. Therefore, there will be a greater reliance on ex vivo pre-differentiation processes. The potential issues that can be envisioned with ex vivo manipulation are: controlling differentiation, obtaining homogeneous cell populations, maintenance of the achieved phenotype, and ensuring persistence over time. Robust protocols will need to be generated and tested.

REGULATIONS

The use of cells as active substances poses new and unknown risks. As these cell therapy products gradually develop there is a general concern that the

Country	Reproductive cloning prevented by national law	Research authorised by national law on			Ministries in charge
		Stem cells	Human embryos	Aborted foetuses	
AUSTRIA	Yes	No law	No law	No law	Justice & Health
BELGIUM	No	No law	No law	No law	Public Health & Research (W) Justice & Health (F)
CYPRUS (•)	Yes	No law	No law	No law	Health & Law Office
CZECH REPUBLIC (•)	No	No law	No law	No law	Health
DENMARK (•)	Yes	In preparation (end 2002)	In preparation (end 2002)	In preparation (end 2002)	Science, Technology and Innovation

existing regulatory framework for medical and/or medicinal products are inadequate. Thus, there is a strong imperative and desire for new regulations and restrictions to be generated with regard to the development and use of these future therapies [Heinonen et al., 2005].

Different regulatory frameworks apply depending on the final mode of action of the therapy. For example, a distinction is made between those treatments (non-medicinal) where stem cells are used primarily to replace or augment normal tissue function and those treatments (medicinal) where the stem cells produce a therapeutic substance. Currently, within the European Community some relevant regulations include The Medicinal Products Directive (2001/83/EC), which includes an amendment for some cell therapy products (2003/63/EC), The Medical Device Directive (93/42/EEC), with recent amendments (2000/70/EC), and The Human Tissues and Cells Directive (2004/23/EC) which establishes standards for safety and quality regarding donation, procurement, testing, processing, storage, distribution and preservation of human tissues and cells [Dib et al., 2005; Parliamentary Office of Science and Technology, 2004].

While attempts are being made in the European Commission to generate one common regulatory framework, there is some concern amongst researchers and clinicians that such European-wide regulation might be bureaucratic, slow and subject to ethical and religious influences that may stifle progress and clinical application [Heinonen et al., 2005]. At the moment, it is up to each member state in Europe to legislate the use of stem cells. Table 2 (on pages 390-395) outlines the current legal and regulatory status in various countries of the European community [European Science Foundation, 2002].

Table 2

Regulations on the use of human stem cells in research in European countries.

Specific National Committee(s)	Competences of the Committee members	Communication
No	–	Yes
National Committee of Bioethics ¹	National Committee of Bioethics ¹	Yes
No	–	No
Bioethics Committee of the R&D Council & Ethical Committee of the Ministry of Health ¹	Biologists, physicians, ethicists, theologians, philosophers, lawyers	Yes
The Central Scientific Ethical Committee ¹	20 members (9 specialists, 11 lay persons)	Yes

Table 2 (continued)

Country	Reproductive cloning prevented by national law	Research authorised by national law on			Ministries in charge
		Stem cells	Human embryos	Aborted fetuses	
FINLAND (•)	Yes	Yes	Yes	Yes	Social Affairs and Health
FRANCE (•)	Yes	Yes (somatic and foetal stem cells) * No (embryonic stem cells)	No	Yes	Employment and Solidarity
GERMANY	Yes	No (embryonic stem cells) * No law (somatic and foetal stem cells)	No	No law	Federal Ministry of Health Central Ethics
GREECE (•)	No	No law	No law	No law	Development and Health
HUNGARY (•)	In preparation	Yes	No	No	Health
ICELAND (•)	Yes	No	No	No	Health and Social Security
IRELAND	No	No law	No law	No law	Dept of Health and Children
ITALY (•)	Yes	Yes	No	Yes	Health
LUXEMBOURG (•)	In preparation	No law	No law	No law	Health
NETHERLANDS (•)	Yes	Yes	Yes on left-over embryos	Yes	Health Welfare and Sports
NORWAY (•)	Yes	In preparation	No	Yes	Health
POLAND (•)	No	No law	No law	No law	Health and Social Affairs & National Education & Science
PORTUGAL (•)	Yes	No law	No law	No law	Health
SLOVAK REPUBLIC (•)	Yes	No law	'Non-therapeutic', 'interventional' research on living human embryos prohibited	Yes	Health

Specific National Committee(s)	Competences of the Committee members	Communication
Sub-committee on Medical Research Ethics of the National Advisory Board on Health Care Ethics ¹	10 members (6 physicians, 2 lawyers, 1 ethicist and 1 representative of patient organisations) and a chair (lawyer)	Yes
National Consultative Bioethics Committee for Health and Life Sciences ¹	39 members (5 philosophers and theologians, 15 scientists and physicians, 19 lay persons with competence in bioethics)	No
Commission for Stem Cell Research ¹	18 members (biology, ethics, medicine, and theology)	Yes
No	–	No
National Scientific and Ethical Committees ¹	24 members (medical doctors, lawyers, priests, journalists, ethicists, members of the Parliament, representatives of the Ministry of Health) and a chair	Yes
National Bioethics Committee ¹	5 members (health sciences, scientific ethics and human rights)	No
No ¹	–	No
National Committee of Bioethics ¹	Clinicians, pharmacologists, ethicists, scientists, lawyers, representatives of patient rights	Yes
National Consultative Bioethics Commission for Health and Life Sciences & Committee for Research Ethics (Ministry of Health)	Lawyers, theologians, social workers, teachers, doctors, representatives of social security department	No
Central Committee on Research involving Human Subjects ¹	Lawyers, physicians, nurses, methodologists, pharmacologists, psychologists, ethicists, & 3 advisors on research on embryos	Yes
National Committee for Research Ethics ¹	At least 9 members (physicians, geneticists, ethicists, lawyers, lay persons)	Yes
No ¹	–	Yes
National Committee for Reproductive Medicine & National Council of Ethics for the Life Sciences ¹	5 members (1 member of Medical Reproduction Society, 1 medical genetics expert, 2 specialised physicians, 1 biologist) & 21 members (physicians, legal experts, ethicists, philosophers, geneticists, 1 theologian)	Yes
Central Ethics Committee of the Ministry of Health ¹	Multidisciplinary (experts and lay persons)	Yes

Table 2 (continued)

Country	Reproductive cloning prevented by national law	Research authorised by national law on			Ministries in charge
		Stem cells	Human embryos	Aborted fetuses	
SLOVENIA (•)	Yes	Yes (somatic stem cells and embryonic stem cells from spared embryos)	Yes on embryos which are no longer part of a parental project (14 days)	Yes if authorised by the NMEC	Health
SPAIN (•)	Yes	No law	No	Yes	Health
SWEDEN (•)	Yes	No law	Yes (14 days) ²	Yes	Health and Social Affairs & Education
SWITZERLAND (•)	Yes	No	Yes	No	Federal Office for Public Health & Federal Office for Justice
TURKEY (•)	No	No law	No law	No law	Health
UNITED KINGDOM	Yes	Yes	Yes (14 days) ²	Yes	Department of Health

* The questionnaire was sent to the Heads of ESF Member Organisations. Replies were received from agencies in 25

(•) Among the 25 respondents' countries, 20 have signed the Convention on Human Rights and Biomedicine (Oviedo,

¹ Apart from national committee(s), when existing or not, there are local and/or regional ethical committees.

² Research is permitted on human embryos up to 14 days old.

ETHICAL DILEMMAS

In the case of embryonic stem cells the primary ethical and moral questions relate to whether the process of isolating stem cells from an embryo results in the destruction of a potential human life. Stem cells are generally harvested from embryos that are 5 days old. In the UK, research is permitted on human embryos that are up to 14 days old. This restriction is based on the observation that in the first 14 days there is no suggestion of a nervous system and the embryo is not conscious [Jain, 2001]. Although adoption of this cell type is not imminent, issues relating to it will need to be addressed and clarified.

Specific National Committee(s)	Competences of the Committee members	Communication
The National Committee for Medically Assisted Reproduction (MAR) & the National Medical Ethics Committee	5 members (1 MAR expert, 1 lawyer, 1 ethicist 1 psychologist and 1 ombudsman's representative) & 13 members (7 physicians, 1 psychologist, 1 social scientist, 1 lawyer, 1 theologian, 1 ethicist, 1 lay person)	Yes
National Commission for Human Assisted Reproduction ¹	22 members (scientists, lawyers, psychologists, social representatives, members of the Department of Health)	Yes (few)
No ¹	–	Yes
National Ethical Committee ¹	18 to 25 members (ethicists, members of the medical profession, scientists, lawyers, lay persons)	Yes
Central Ethical Committee ¹	20 members (3 medical pharmacologists, 3 clinicians, No 1 pharmaceutical chemist, 1 pharmaceutical technologist, 1 toxicologist, 1 pharmacist, 1 dentist, 4 specialised physicians, 4 representatives of Ministry of Health, 1 lawyer) and a chair (advisor of the Health Minister)	
Human Fertilisation and Embryo Authority (HFEA) & Human Genetics Commission (HGC) ¹	21 members (1/2 medical and scientific expertise, 1/2 lay expertise) & 22 members (the chair of HFEA, scientists, lawyers, ethicists, members of the medical profession, of industry, a journalist, a member of the	Yes
National Consumer Council		

out of 27 ESF national groups.

04/04/97) and the Protocole on the prohibition of cloning human beings. Only 9 have ratified them.

Banking of umbilical cord blood for use as a source of stem cells has been associated with a set of ethical issues. Questions have been raised over the ownership of the blood, and although the infant owns his or her blood, the parents are the child's legal guardians and owners of the cord blood, if preserved at birth, until the child reaches 18 years of age. A working group on ethical issues with regard to umbilical cord blood banking by the American Medical Association has generated some working guidelines at a Consensus Conference [Sugarman et al., 1997]. Ethical aspects have been generated along similar lines for placental blood banking as well [Sugarman et al., 1995].

Therapeutic use of adult stem cells raises very few of the ethical issues that accompany the use of foetal and embryonic stem cells. However, the question that can be raised is whether it is ethical to enter into clinical testing without adequate preclinical testing. Skeletal myoblasts underwent almost 15 years of preclinical testing in various animal species and injury models before entering the clinical realm. On the other hand, bone marrow derived cells made a rapid transition from rodent studies to clinical testing. Previous clinical experience with bone marrow transplant programs has largely facilitated the rapid transition and acceptance, even in the absence of a clear understanding of underlying mechanisms. In the interim, while clinical studies are ongoing, newer experimental animal studies, with enhanced and robust methodologies, have either contradicted earlier findings or have failed to reproduce them. Additionally, testing in larger animal species has generated mixed results [Zhao et al., 2004]. Together with the other advantages highlighted earlier, the absence of reported adverse side-effects in ongoing clinical studies has led to ever increasing trials in about 25 countries.

For newer cell types and cell technologies, a measured and methodical translational process from bench to bedside has been proposed. This involves the adoption of the following criteria: (a) a reproducible preclinical demonstration of safety and efficacy in multiple laboratories, (b) a reasonable degree of mechanistic understanding, and (3) validation in scaled-up, physiologically relevant large-animal models [Murry et al., 2005].

ECONOMIC AND ORGANISATIONAL ASPECTS

With the introduction of any new and novel medical therapy the concern comes up about clinical-effectiveness, as discussed above, as well as cost of therapy. Public and professional concern about the cost of medical care is increasingly rising, and, with resources being limited, this has brought about an increased emphasis on health economics and cost-effectiveness analysis for maintaining or introducing medical therapies.

A general underlying faith is that if cost-effectiveness analysis techniques were to become widely understood and accepted by the key decision makers in the health care sector, important health benefits or cost savings might be realised [Weinstein et al., 1977]; more value can be obtained for the money spent. It is important to consider that the application of economics to medical practice does not necessarily mean that less should or can be spent, but rather that the use of resources might be more efficient [Eisenberg, 1989]. In determining the cost-effectiveness of a new therapy, both scientific ('what is

good and bad in the available science’) and social (‘what is good for society’) value judgments will have to be made in the appraisal thereof.

For the introduction of new health technologies, the general, high-level strategy to be followed by a company in order to demonstrate cost-effectiveness in any case involves answering the following three primary questions:

- Does the new therapy address an unmet clinical need?
- How does the new therapy impact the total available health care budget? (usually on a national basis)
 - Not only will new health technologies typically cost more, in addition, with better health outcomes people may live longer, inherently increasing the economic burden on society.
- Does there exist a willingness to pay for the new therapy?
 - This often incorporates a strong social value judgment, more specifically the aspect of equality in the distribution of health care resources. How to choose between treating a child and an 80+-year old; or how not to disadvantage people who are not in regular paid employment when taking differential productivity at work into consideration?

The answer to the first question involves bringing in prevalence data, associated mortality and morbidity figures, and consequent determination of the economic burden in a particular market.

The second question is answered by performing a cost-effectiveness analysis. A cost-effectiveness analysis determines the costs of a therapy in relation to the obtained clinical outcome. Here, a new therapy is typically compared with current practice. In most instances new clinical management strategies provide better health outcomes than current standard practice but they also do cost more. The result obtained is then the ‘price’ of the improvement in outcome that is purchased by switching from current practice to the new therapy (usually in ‘Euro per life year gained’ or ‘Euro per quality-adjusted life year gained’). If the said price is low enough, the new therapy is considered cost-effective.

Cost-effectiveness of a new therapy is more often than not determined by health economic modeling. These health economic models are populated with data from clinical trials (new and old) as well as with input based on expert opinions. Needless to say, the cost-effectiveness outcome shall still be critically reviewed:

- Are the relevant clinical management strategies evaluated?
 - The determination of the incremental cost-effectiveness ratio is very sensitive. Hence, the choice of which strategies to evaluate strongly

drives the calculation and the conclusion of an incremental cost-effectiveness ratio.

- How good are the effectiveness data?
 - What information is used for determining cost-effectiveness? Ideally, the data should come from randomised trials.
- Do the effectiveness data reflect how the clinical management strategy will be used in the real world?
 - The generalisability of the effectiveness data will be carefully considered. Do the trial results pertain to the population and setting in which the clinical management strategy is likely to be applied?
- Where do the cost data come from?
 - Was resource use modelled, or was it measured in real practice?

It will be obvious that at the current stage of cardiac cell therapy many of the above questions cannot be answered as yet. What is more, given the fact that cardiac cell therapy currently is used as an adjunct to standard interventional or surgical revascularisation practices, it can be disputed whether any effectiveness modelling is relevant at the moment. Much depends on how the therapy will evolve. Will it become a stand-alone therapy or will it be part of a combination therapy?

In the latter case, the effectiveness modelling will be more complex:

- Which is the main contributor to the improved outcome? If standard revascularisation contributes most to the clinical benefit, how to make possible clinical benefit of cardiac cell therapy come to surface?
- If cardiac cell therapy improves the health outcome, when does this benefit become imminent; after 1 year, 2 years, 3 years, or even longer; is it a benefit with regard to mortality or to morbidity?

In the further development of cardiac cell therapy these key questions, which are just a few examples, will clearly have to be answered, primarily by means of performing appropriately designed further clinical trials.

CONCLUSIONS

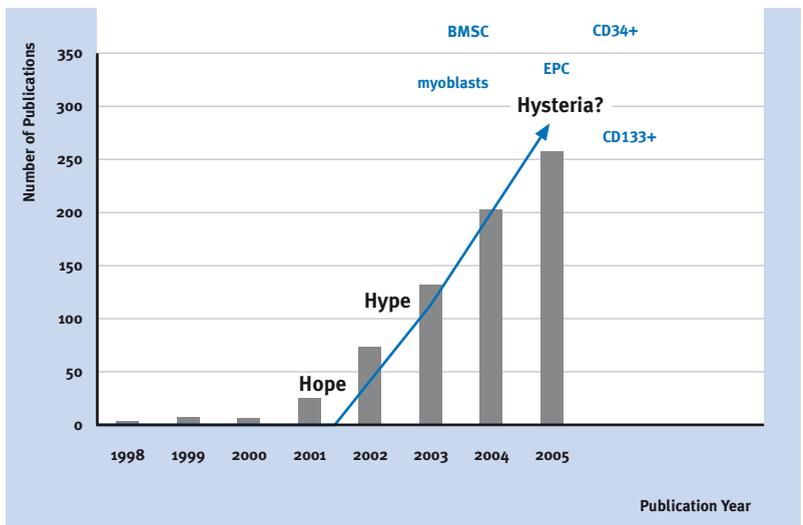
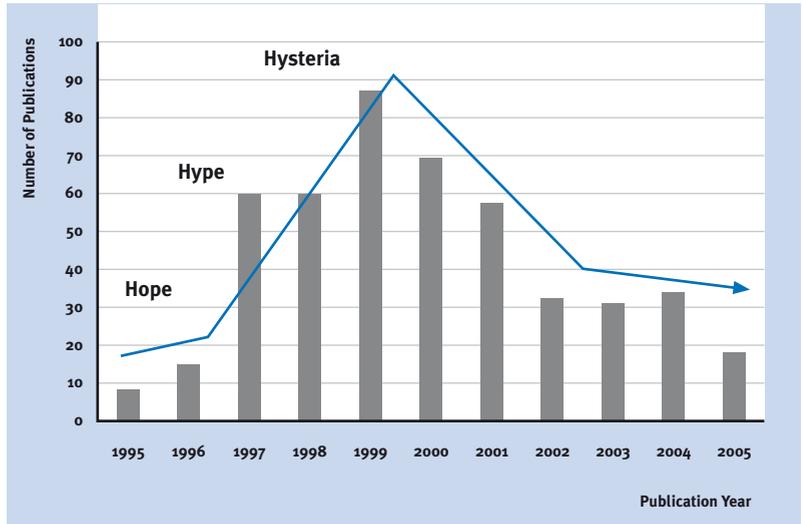
In recent years, cardiac cell therapy has appeared to take the clinical field by storm and the general belief is that cell therapy holds much promise. Early clinical results have confirmed this, but the outcome of recent randomised studies may temper the enthusiasm, however [Murry et al., 2005].

Without a doubt, the expectations that are generally held with regard to the clinical benefits cardiac cell therapy can bring, are far from being met today. The clinical and scientific community will in particular have to take care they

Figure 3

A comparison of annual publication intensity between 'transmyocardial laser revascularisation' (top) and 'cardiac cell therapy' (bottom). Are we (again) witnessing a case of hope, hype and hysteria?³

The enthusiasm regarding this novel procedure emerged quickly, as to be seen, for instance, by the number of publications on transmyocardial laser revascularisation. However, the enthusiasm was quickly tempered when results of well-controlled, large randomised clinical studies demonstrated the non-superiority of this procedure in comparison to control groups [Horvath, 2002; Stone et al., 2002].



2 Angina (*angina pectoris* — Latin for squeezing of the chest) is the chest discomfort that occurs when the blood oxygen supply to an area of the heart muscle does not meet the demand.

3 Publication intensity was determined using Entrez PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) using the following search criteria: 'transmyocardial laser revascularisation' and 'stem cell' OR 'stem cells' OR 'progenitor cell' OR 'progenitor cells' OR 'bone marrow cell' OR 'bone marrow cells') AND ('cardiac' OR 'heart') AND ('ischemia' OR 'infarct' OR 'regeneration' OR 'angiogenesis' OR 'neovascularisation' OR 'neovascularisation', respectively.

do not end up in a mode of 'hype and hysteria', as seen in the not too distant past with other newly introduced medical therapies, such as but not limited to transmyocardial laser revascularisation. Transmyocardial laser revascularisation is a procedure by which a physician uses a laser to perforate the heart muscle to relieve the pain of severe angina².

Similar emotional dynamics may be at play vis-à-vis cardiac cell therapy. The clinical and scientific community immediately and unreservedly embraced the technology, particularly triggered by the initial positive results coming from small, non-randomised clinical pilot trials. Is history repeating itself?

This section started off with a fictional press release on the fact that a case

of heart failure, very unusual at that time, had been reported. We have asked ourselves whether that might be a realistic possibility?

In our opinion, this question can be answered with a careful and conservative 'yes'. If the scientific and clinical community set the eradication of heart failure as the goal, it can undisputedly make cardiac cell therapy a promising instrument. The development of that instrument still requires significant learning, and much can go wrong before cardiac cell therapy is a viable treatment instrument. It is very important to recognise, however, that it should be considered that on the way toward developing cell therapy as a therapeutic instrument, it may well be that at the end of the day it will not be cell therapy as we know it today, but a first or even second order derivative therapy that provides the solution. As per Les Brown: "*Shoot for the moon, even if you miss, you'll land amongst the stars...*" This requires that the scientific community holds an open mind-set; that it is willing to learn, also from failures. History has shown that emotional dynamics do play a non-trivial role in the emergence of novel therapies. Hence, successful fostering of cardiac cell therapy necessitates steadfast and effectively coordinated efforts of the scientific community at large. The long-term goal must be maintained in order to not be frustrated by short-term failures. This calls for a policy that provides such nurturing, for instance by establishing an appropriately balanced scheme of private public funding.

REFERENCES

- Aicher, A. et al. (2003). Assessment of the Tissue Distribution of Transplanted Human Endothelial Progenitor Cells by Radioactive Labeling. *Circulation* 107, 16, 2134-2139
- American Heart Association Annual Conference (2005). <http://scientificsessions.americanheart.org/portal/scientificsessions/ss/lbctnewsrelease1>. Press Release, Dallas
- BHF (2000). *Annual Report*. British Heart Foundation Health Promotion Research Group Publications
- Caplan, A.I. (2005). Review: Mesenchymal Stem Cells: Cell-Based Reconstructive Therapy in Orthopedics. *Tissue Engineering* 11, 7/8, 1198-1211
- Caplice, N.M., B.J. Gersh, J.R. Alegria (2005). Cell Therapy for Cardiovascular Disease: What Cells, what Diseases and for Whom? *Nature Clinical Practice Cardiovasc Med* 2, 1, 37-43
- Dib, N. et al. (2005). Safety and Feasibility of Autologous Myoblast Transplantation in Patients with Ischemic Cardiomyopathy: Four-Year Follow-up. *Circulation* 112, 12, 1748-1755

- Dimmeler, S., A.M. Zeiher, M.D. Schneider (2005). Unchain my Heart: The Scientific Foundations of Cardiac Repair. *J. Clin. Invest.*, 115, 572-583
- Dow, J. et al. (2005). Washout of Transplanted Cells from the Heart: A Potential New Hurdle for Cell Transplantation Therapy. *Cardiovascular Research* 67, 2, 301-307, Aug 1
- Eisenberg, J.M. (1989). Clinical Economics. A Guide to the Economic Analysis of Clinical Practices. *JAMA*, 262, 2879-2886
- Euro PRC (2004). *Mentice Sponsors Breakthrough Virtual Reality Medical Procedure*. News Release, 27 May. Mentice Medical Simulation AB. page 214
- European Science Foundation (2002). European Science Foundation Policy Briefing. Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas. <http://www.esf.org/publication/142/ESPB18.pdf>, August
- Heinonen, M., O. Oila, K. Nordstrom (2005). Current Issues in the Regulation of Human Tissue-Engineering Products in the European Union. *Tissue Engineering* 11, 11/12, 1905-1911
- Herreros, J. et al. (2003). Autologous Intramyocardial Injection of Cultured Skeletal Muscle-Derived Stem Cells in Patients with Non-Acute Myocardial Infarction. *European Heart Journal* 24, 22, 2012-2020
- Hodgson, D.M. et al. (2004). Stable Benefit of Embryonic Stem Cell Therapy in Myocardial Infarction. *American Journal of Physiology* 287, H471-79
- Horvath, K.A. (2002). Results of Prospective Randomised Controlled Trials of Transmyocardial Laser Revascularisation. *Heart Surg. Forum* 5, 1, 33-39; Discussion 39-40
- Huang, N.F. et al. (2005). Injectable Biopolymers Enhance Angiogenesis after Myocardial Infarction. *Tissue Engineering* 11, 11/12, 1860-1866
- Jain, K.K., A. Jain (2001). *PharmaBiotech Report*, September
- Janssens, S., et al. (2006). Autologous Bone Marrow-Derived Stem-Cell Transfer in Patients with ST-Segment Elevation Myocardial Infarction: Double-Blind, Randomised Controlled Trial. *Lancet*, 367, 113-121
- Kuethe, F. et al. (2004). Lack of Regeneration of Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans with Larger Anterior Myocardial Infarctions. *International Journal of Cardiology* 97, 123-127
- Laflamme, M.A., C.E. Murry (2005). Regenerating the Heart. *Nature Biotechnology* 23, 7
- March, K.L., B.H. Johnstone (2004). Cellular Approaches to Tissue Repair in Cardiovascular Disease: The More We Know, The More There Is to Learn. *American Journal of Physiology, Heart and Circulatory Physiology* 287, H458-H463
- Menard, C. et al. (2005). Transplantation of Cardiac-Committed Mouse Embryonic Stem Cells to Infarcted Sheep Myocardium: A Preclinical Study. *Lancet* 366, 1005-12

- Menasche, P. (2004). Cellular Transplantation: Hurdles Remaining before Widespread Clinical Use. *Curr. Opin. Cardiol.* 19, 2, 154-161
- Murry, C.E., L.J. Field, P. Menasche (2005). Cell-Based Cardiac Repair: Reflections at the 10-Year Point. *Circulation* 112, 3174-3183
- Parliamentary Office of Science and Technology (2004). <http://www.parliament.uk/documents/upload/POSTpn221.pdf>. *Regulating Stem Cell Therapies* 221, June
- Perin, E.C. et al. (2004). Improved Exercise Capacity and Ischemia 6 and 12 months after Transendocardial Injection of Autologous Bone Marrow Mononuclear Cells for Ischemic Cardiomyopathy. *Circulation* 110, 11 Suppl 1, I1213-8, Sep 14
- Price, M.J. et al. (2005). Intravenous Mesenchymal Stem Cell Therapy Early after Reperfused Acute Myocardial Infarction Improves Left Ventricular Function and Alters Electrophysiologic Properties. *Int. J. Cardiol.*, Oct 21
- Reinecke, H. et al. (1999). Survival, Integration, and Differentiation of Cardiomyocyte Grafts: A Study in Normal and Injured Rat Hearts. *Circulation* 100, 2, 193-202, July 13
- Remme, W.J., K. Swedberg (2001). The Task Force for the Diagnosis and Treatment of Chronic Heart Failure. European Society of Cardiology, Guidelines for the Diagnosis and Treatment of Chronic Heart Failure. *European Heart Journal* 22, 17, 1527-60
- Shake, J.G. et al. (2002). Mesenchymal Stem Cell Implantation in a Swine Myocardial Infarct Model: Engraftment and Functional Effects. *Ann. Thorac. Surg.* 73, 1919-1926
- Souza, L.C., K.A. de Carvalho, C. Rebelatto et al. (2004). Combined Transplantation of Skeletal Myoblasts and Mesenchymal Cells (Cocultivation) In Ventricular Dysfunction after Myocardial Infarction. *Arquivos Brasileiros de Cardiologia* 83, 294-299
- Stone, G.W., P.S. Teirstein, R. Rubenstein et al. (2002). A Prospective, Multicenter, Randomised Trial of Percutaneous Transmyocardial Laser Revascularisation in Patients with Nonrecanalizable Chronic Total Occlusions. *J. Am. Coll. Cardiol.* 39, 10, 1581-1587
- Sugarman, J., E.G. Reisener, J. Kurtzberg (1995). Ethical Aspects of Banking Placental Blood for Transplantation. *JAMA* 274, 22, 1783-5
- Sugarman, J. et al. (1997). Ethical Issues in Umbilical Cord Blood Banking. Working Group on Ethical Issues in Umbilical Cord Blood Banking. *JAMA* 278, 11, 938-43
- Tambara, K. et al. (2005). Administration of Control-Released Hepatocyte Growth Factor Enhances the Efficacy of Skeletal Myoblast Transplantation in Rat Infarcted Hearts by greatly Increasing both Quantity and Quality of the Graft. *Circulation* 112, Suppl 1, I-129-I-134

- Taylor, D.A. (2004). Cell-Based Myocardial Repair: How Should We Proceed? *Int. Journal of Cardio* 95, Suppl. S, 8-12
- The Advisory Board Company (2004). *Future of Cardiac Surgery: Strategic Forecast and Investment Blueprint*
- Weinstein, M.C., W.B. Stasson (1977). Foundations of Cost-Effectiveness Analysis for Health and Medical Practice. *N. Engl. J. Med.* 296, 716-721
- Wollert, K.C. et al. (2004). Intracoronary Autologous Bone-Marrow Cell Transfer after Myocardial Infarction: The BOOST Randomised Controlled Clinical Trial. *Lancet* 364, 141-148
- Wollert, K.C., H. Drexler (2005). Clinical Applications of Stem Cells for the Heart. *Circ. Res.* 96, 151-163
- Yoon, Y.S. et al. (2004). Unexpected Severe Calcification after Transplantation of Bone Marrow Cells in Acute Myocardial Infarct. *Circulation* 109, 25, 3154-3157
- Zhao, R.C., L. Liao, Q. Han (2004). Mechanisms of and Perspectives on the Mesenchymal Stem Cell in Immunotherapy. *J. Lab. Clin. Med.* 143, 284-291

WEBSITES

- <http://stemcells.nih.gov/info/basics>
- www.chestpainperspectives.com

Tissue Models

*Carlijn Bouten*¹

INTRODUCTION

The hypes and hopes of tissue engineering and associated efforts of researchers to succeed in this area have resulted in many attempts to produce living tissue and organs outside the human body. These include the creation of skin, cartilage, bone, tendon, skeletal muscles, heart muscle, blood vessels, heart valves and bladder tissue, in which the degree of success is mainly evaluated on the basis of structural similarities with native or 'the original' human tissue. Despite their envisioned and highly recommended potential as tissue replacements inside the human body, many of these types of tissue still only function outside the human body and have not passed the stage of laboratory prototype or small-scale implantation studies in animals. Thus, the broad-scale clinical application of tissue-engineered products lies far ahead and, apart from commercial and regulatory problems, very much depends on scientific progress [Lysaght et al., 2004].

¹ Eindhoven University of Technology, Eindhoven, the Netherlands.

Notwithstanding these drawbacks, a decade of intensive and interdisciplinary research, converging knowledge from biology, material science, bioengineering and medicine, has brought scientific and technological progress in the field of regenerative medicine. In line with all this, a more immediate and directly assessable application of tissue engineering has been the creation of three-dimensional (3-D) laboratory models of tissues and organs. Even in those areas where clinically relevant tissues are decades away, the tissues that are currently being made provide powerful ‘living’ biological models. These 3-D models are far more realistic than existing two-dimensional (2-D) cell culture models and can be used to study or test a specific aspect of interest at tissue level with a higher level of experimental control and with less ethical considerations than animal models. Tissue model systems find their application in studying normal and pathological tissue functioning and the associated testing of potential therapies [Baar, 2005]. In addition, they represent useful tools for the development of technologies for regenerative medicine and early diagnosis and tissue screening [Rodriguez et al., 2003].

TISSUE MODELS — NEW DIMENSIONS OF TISSUE ENGINEERING

In its most fundamental paradigm, tissue engineering entails the seeding of living cells, harvested from a donor, on a pre-shaped biodegradable support material, or scaffold, of a synthetic or natural origin. This cell-scaffold construct is generally cultured in a so-called bioreactor under conditions that favour cell expansion, tissue growth and tissue functioning [Vacanti et al., 1999]. This includes the application of biological (e.g. hormones) and/or biophysical stimuli (e.g. forces, electric pulses) relevant for tissue development and functioning. The scaffold provides initial anchorage and support for the cells, until they have produced and reorganised their own environment, also referred to as the extracellular matrix, to form a tissue. Ideally, tissue formation and scaffold degradation should go hand in hand to ensure and maintain the mechanical stability of the tissue.

In the whole process of tissue formation the cells play a central role: They act as sensors for applied stimuli and respond to them by changing their own function and environment. The source of cells for the creation of a given tissue is therefore of utmost importance. Differentiated or undifferentiated cells have been used for tissue engineering purposes. Differentiated cells are specialised cells with a limited potential for renewal. Undifferentiated cells are less specialised (progenitor cells) or not specialised (stem cells) and have a larger renewal capacity. Given the right environmental stimuli, they may give rise to one or more specific cell types (see also the paragraph of Hendriks ‘Choice of cell type’).

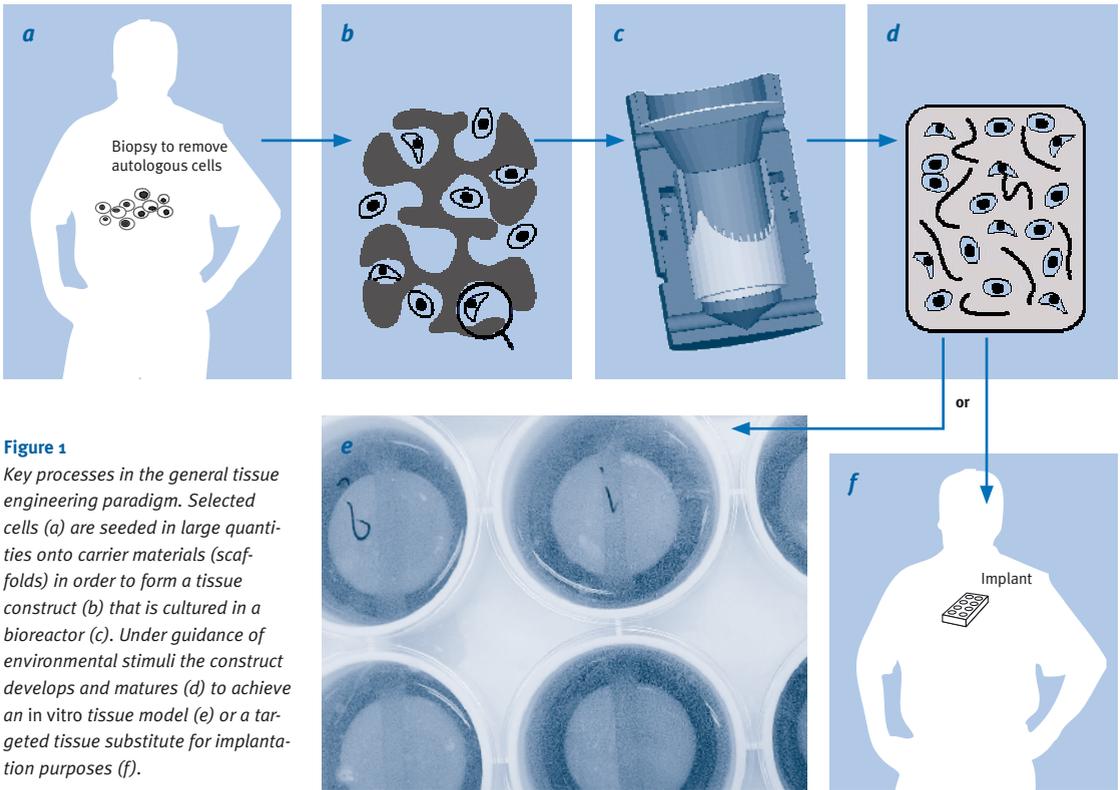


Figure 1
 Key processes in the general tissue engineering paradigm. Selected cells (a) are seeded in large quantities onto carrier materials (scaffolds) in order to form a tissue construct (b) that is cultured in a bioreactor (c). Under guidance of environmental stimuli the construct develops and matures (d) to achieve an in vitro tissue model (e) or a targeted tissue substitute for implantation purposes (f).

When creating tissue for implantation purposes, the target cells should preferably originate from the recipient so as to create an autologous tissue substitute that minimises the risk of immune rejection. This substitute is allowed to grow and develop in vitro, that is in the laboratory, depending on the degree of maturation required to ensure in vivo survival (in the body of the recipient) later on. Subsequent implantation and in vivo remodelling is intended to recapitulate normal tissue architecture and function with time. When the implantation step is omitted, the created tissue might function as a tissue model. The key processes in the general tissue engineering strategy are illustrated in Figure 1.

One of the most attractive promises of creating ‘living’ tissue replacements is their potential for repair, adaptation and growth; the latter being of specific relevance for paediatric patients. However, there are a number of obstacles to overcome before we can put this promise into clinical practice. For example, a morphological similarity of engineered tissue with native tissue does not ensure in vivo functioning and long-term survival. The mechanical strength of the replacement may differ from that required in the native body, resulting in a functional mismatch or failure either directly after implantation or later in time. In heart valve tissue engineering, for instance, current tissue evaluations mainly concentrate on extracellular matrix contents and morphological

similarities with native heart valves, whereas in vivo functionality of the valves merely depends on matrix organisation and most likely does not require a morphological resemblance with the native counterpart. In vivo functioning is also patient specific and age-dependent, requiring specific (e.g. age-dependent) guidelines for the engineered tissue replacement to be made. Target properties and target functions of engineered tissues are therefore the subject of many scientific debates and stress the need for functional evaluation techniques that can be applied in vitro as well as in vivo to follow tissue maturation and incorporation inside the body.

While these and other limitations currently prevent large-scale growth of clinically relevant tissues for use in regenerative medicine, the tissues that are being produced at the moment provide model systems for:

- understanding tissue formation, physiological functioning, malfunctioning and disease;
- test-beds in the development and evaluation of new medical devices and products;
- the development and testing of novel technologies for regenerative medicine.

The three-dimensional architecture of the engineered model tissues offers major benefits in this respect, as it mimics complex tissue interactions and physiology. While it is acknowledged that the models only provide a simplified representation of what occurs in the intact body, they produce a great deal of initial information with a degree of control that would never be possible in human or animal experiments. In addition, tissue models can be produced in relatively large quantities with reasonable reproducibility and at relatively low costs, offering the advantage of high-number, statistically relevant investigations. The risks of producing and investigating the tissues are minimal, while regulatory and ethical aspects only apply when human embryonic stem cells or genetically modified cells are used.

Another advantage over existing biological models is that each of the key processes of the tissue engineering described above (see Figure 1) can be intentionally modified to design on-demand model systems. For example, disease-specific cells (e.g. cancer cells) can be chosen, or cells can be ‘instrumented’ or transfected to track cell behaviour or migration through the tissue. Scaffolds can be engineered to release biologically active molecules to stimulate cell differentiation and tissue maturation. As living extracorporeal systems, the engineered tissue models allow spatial control and often real-time monitoring of various phenomena of interest, such as cell differentiation, molecular signalling, gene expression, extracellular matrix remodelling and

tissue viability on nanoscopic, microscopic and mesoscopic length scales. As a consequence the engineered model systems could accelerate research on disease pathways and the development of new therapies for regenerative medicine, potentially eliminating the need for transplants altogether [Griffith et al., 2002].

TISSUE MODELS OF PHYSIOLOGY AND PATHOPHYSIOLOGY

Growing and composing tissues outside the human body provides essential understanding of tissue growth and development and the right conditions for cell survival, extracellular matrix production and tissue functioning. Although in general only successful attempts reach the published literature, our failures in the lab provide invaluable insight in abnormal and pathological tissue development and functioning. In addition, the response of ‘healthy’ engineered tissue to a damaging or pathogenic stimulus can be monitored so as to gain knowledge of disease pathways.

The goal of any model is to have distinct experimental or predictive advantages while remaining as close as possible to the physiological reality. For example, tissues that have a predominantly biomechanical function, such as muscle, bone or cardiovascular tissues, should be represented by tissue models that have this specific function. Surrogate measures of mechanical functioning are then required to link in vitro experiments to the physiological function. In models of cardiovascular tissues, collagen synthesis and remodelling are correlated to functional changes, whereas functionality is assessed from tissue stiffness and ultimate tensile strain [Mol et al., 2003]. In skeletal muscle, protein-to-DNA ratio and tissue organisation are used to note tissue growth and differentiation and these in turn are correlated to force production and contractile properties of the tissue [Dennis et al., 2000]. Using these measures, it is possible to investigate the effects of altered chemical, biological or mechanical stimuli on the physiological functioning of the tissue. Obviously, the use of 3-D tissue models, instead of more simplistic 2-D cell culture models, is a prerequisite here.

Over the past years, various tissue-engineered models of (patho)physiological tissue function were presented, including models of bone growth and cartilage differentiation, extracellular matrix remodelling in heart valves, models of wound healing and wound treatment and bronchial mucosa models to study the pathophysiology of asthma.

To give an example, [Bursac et al., 1999] developed a tissue-engineered model of cardiac (heart muscle) tissue for electrophysiological studies. Electric pulse

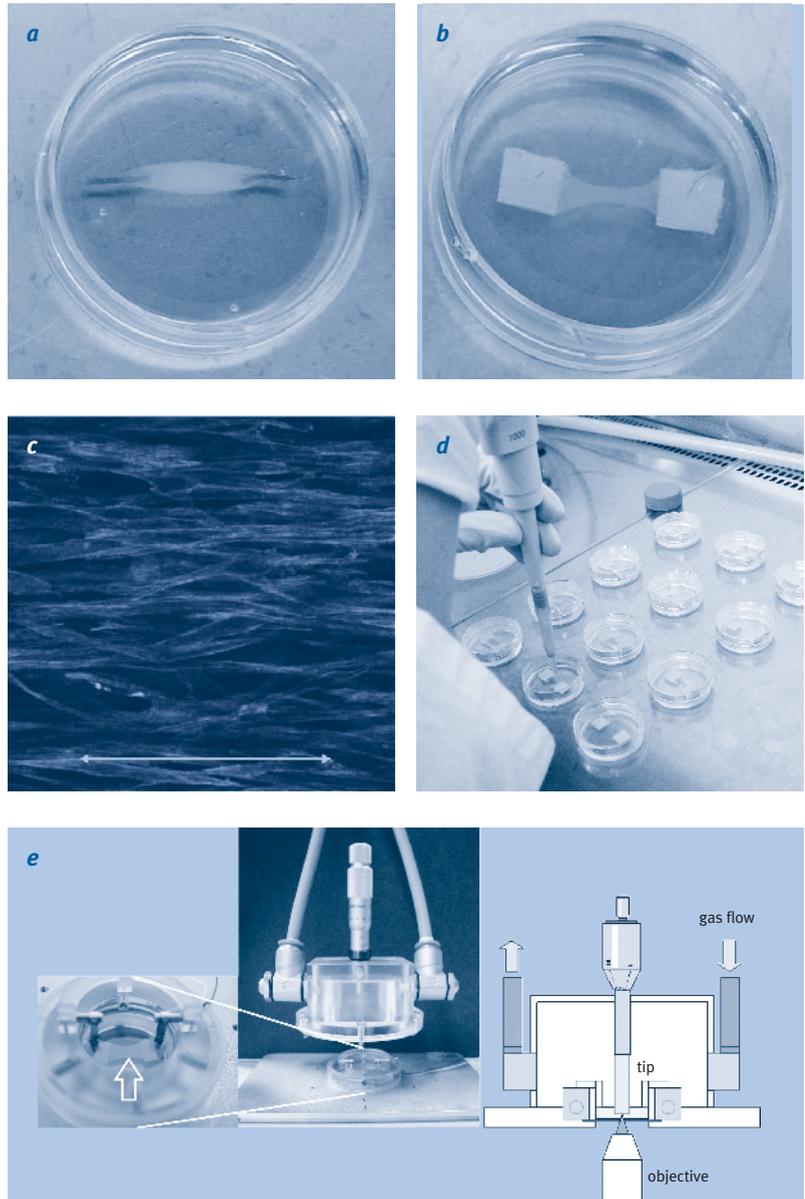
propagation is one of the dominant features of cardiac tissue and essential for a proper functioning of the heart. In the study cardiac cells from neonatal rats were cultured on 2-mm thick polymer scaffolds to form cardiac muscle equivalents. After 7 days, the protein-to-DNA ratio and 3-D tissue organisation in the cultured cardiac tissues resembled that of 'real' neonatal heart tissue. The electrophysiological properties, measured after electrical stimulation, were also specific for those of heart tissue. Later studies with the model concentrated on improvement of mass transport and metabolism in the tissue to grow thicker tissues relevant for future implantation studies [Radisic et al., 2004], whereas other research groups have used mechanical stimuli, such as cyclic stretching of the tissue, to improve the function of their engineered heart tissues [Zimmermann et al., 2002]. While it is clear that electrical stimulation, mechanical functioning and mass transport all contribute to heart tissue development, the respective models allow systematic investigation of their relative contribution to tissue growth and physiology under highly controlled conditions.

In another example, tissue-engineered models of skeletal muscle were used for studying disease pathways in mechanically induced muscle breakdown [Bouten et al., 2003]. Skeletal muscle tissue is highly susceptible to sustained compression, eventually leading to tissue breakdown in the form of deep pressure ulcers. However, the pathways whereby tissue compression leads to tissue damage are not completely understood. Because it is impossible to examine all pathways and predisposing factors involved in *in vivo* muscle tissue, *in vitro* tissue models were employed. In a first model, muscle tissue was created by a gelation process in which mouse muscle cells were mixed with a solution containing collagen and then pipetted into disk-shaped moulds [Breuls et al., 2003a]. The resulting disk-shaped tissues showed spontaneous contraction after 8 days of culture and conveniently fitted under the indenters of a compression device in a high-throughput fashion. This device could be mounted inside an incubation chamber onto the stage of an inverted microscope to monitor cell damage at different levels of tissue compression. For monitoring purposes, a viable fluorescent probe was developed to quantify cell damage in space and time [Breuls et al., 2003b]. An inverse relationship between the magnitude and duration of tissue compression and the onset of cell death was established, comparable to that described in animal models [Stekelenburg et al., 2005].

In a second model system, muscle architecture was optimised to achieve parallel aligned muscle fibers in a natural configuration [Gawlitza et al., 2005]. To that end, suture material or Velcro strips were used as artificial tendons for muscle anchorage. The muscle cell/collagen mixture was molded between and

Figure 2

Engineered muscle models (length ~2 cm) consisting of C2C12 cells in collagen/Matrigel scaffolds using suture material (A) or Velcro (B) as artificial tendons. Tissue stresses due to contraction of the tissue between the anchorage points cause the muscle cells to align along the main stress axis (arrow) into the natural muscle architecture (C). Such models can be produced in large quantities (D) to perform high-throughput studies, whereas the in vitro set-up allows mechanistic studies in loading devices under guidance and control of a microscope (E). With the shown device tissue compression and oxygen supply can be manipulated.



onto these anchoring points and allowed to gelate. Due to remodelling and shrinkage of the gel between the anchorage points, the internal tension in the constructs increased, causing the muscle cells to align. A new loading device was developed to investigate the relative contribution of deformation and decreased oxygen and nutrient transport in the causation of muscle cell death (see Figure 2). Newly developed viable fluorescent probes and associated real-time quantification methods were used to discriminate between acute and programmed cell death.

The above models are reproducible and can be easily produced in large quantities so as to favour high-throughput studies. Further studies concentrate on humanised models and the development of conductive scaffold materials for electrical stimulation of the model tissues to mimic voluntary muscle contraction [Popescu et al., 2005]. In addition the release of detectible molecules by the muscle cells upon compression is studied as a guideline for the development of diagnostic tools for early detection and possible prevention of deep pressure ulcers.

These and similar studies illustrate the potential of tissue models to systematically investigate normal and pathological tissue functioning. It should be mentioned, however, that the development of even very simplistic models and related surrogate markers requires considerable time, research efforts and sophisticated technology, which also stresses the long road to go before these tissues can actually be used as tissue replacements inside the human body.

TISSUE MODELS AS TEST-BEDS FOR MEDICAL PRODUCTS

New approaches to clinical problems, such as therapeutic treatments, medical devices or drugs, require extensive testing and risk assessment before the new medical product can be clinically applied and put on the market. Regulatory regimens for risk management give strict prescriptions of the required tests and targets the new product should comply with. These procedures often take years, running in follow-up stages to obtain the best possible estimate of safety, efficacy and side effects of the product. These stages include the use of animal models prior to small-scale clinical testing in humans, to evaluate the product under physiological conditions in living organisms for extended periods of time. However, animal studies are expensive and also restricted by national and international guidelines. In addition, disease pathways and response to treatment can differ between animals and humans, which limits the extrapolation of experimental animal data to human beings.

Subsequently, the testing in humans in clinical trials is cumbersome as there is little societal tolerance to possible harmful side effects. Nevertheless, these trials require large populations in order to provide statistically 'safe' measures of treatment efficacy and potential risks. Therefore, clinical trials are often complex and expensive, slowing down the translation of knowledge and implementation of new products to the clinic.

The use of in vitro model systems in addition to in vivo tests may aid in the process of risk assessment and strengthen the outcome of treatment evalua-

tions. When performed prior to animal testing, the initial information obtained will guide more efficient testing in the animal. More importantly, in vitro models can be humanised, that is incorporating human cells with properties of interest, facilitating more efficient clinical trials. The most reductionist in vitro models useful for medical product testing are those based on cultured cells. Cell models offer high-throughput screening environments at low cost and with precise control of the microenvironment. The latter feature facilitates mechanistic studies and allows for the minimisation of potential confounders, making the cell studies attractive for rapid screening and the discovery of new drugs [White, 2000]. It should be remembered, however, that 2-D cell models are non-physiologic and show little resemblance to the in vivo 3-D multicellular environment where cells are surrounded and embedded in an extracellular matrix. Engineered tissue models do have these properties and also offer the potential of reproducible disease-specific screening environments.

These advantages have been recognised by research groups developing e.g. cancer therapy models [O'Connor, 1999], engineered liver models to evaluate the efficacy of anti-hepatitis agents [Griffith, 2002] and engineered skin for toxicity and pharmacological studies [Ponec, 2002]. Engineered skin, such as the epidermal skin equivalents Epiderm (MatTek Corporation), Episkin (Episkin SNC) and SkinEthic (Laboratoire SkinEthic), has already become commercially available as test-bed for skin irritation studies. Other companies have entered the market of tissue-engineered models for therapy development. VaxDesign², a US company, has left the traditional approach of vaccine development through generating attenuated or inactivated pathogens as the vaccine itself and testing them in animal models. Instead, the company focuses on a tissue-engineered immune system for rapid vaccine development. An in vitro human vaccination site (e.g. tissue-engineered skin or mucosa equivalent) that includes blood and lymphatic endothelia, as well as various immune cells that are important for evaluating inflammatory reactions, is used as an immunophysiological model to rapidly test the vaccines. A miniaturised bioreactor for the model tissue culture, incorporated in a microfluidic vaccination device, the size of a coin, is now available for the rapid screening of vaccines and immunotherapies, potentially speeding up the cycle time and quality of vaccine development.

From this example it is clear that the development and application of high-throughput tissue models go hand in hand with developments in other areas of technology, such as microfluidics and nanotechnology, which are not directly related to medicine and health care. This convergence of technologies enables the design of miniaturised test-beds for tissue screening and the so-called 'labs-on-a-chip' that can be manufactured in stock. It is expected that

2 www.vaxdesign.com

with the commercial availability of such systems tissue models will soon be an attractive alternative for initial medical and pharmaceutical product testing.

TISSUE MODELS FOR TECHNOLOGY DEVELOPMENT

Despite the problems of introducing tissue engineering products to the market, or maybe we should say because of these problems, a growing number of research programs now concentrate on the complementary technologies that should enable the successful and large-scale production of biological tissue equivalents and subsequent clinical implementation to regenerate damaged tissue structures and organs in the human body. The development of production technologies goes along with the creation of tissues in the laboratory and is a prerequisite for the refinement and optimisation of three-dimensional tissue culture. At the same time, these tissue cultures provide a 'model' environment for the development and evaluation of implementation technologies that support future clinical application.

PRODUCTION TECHNOLOGIES

Tissue engineering itself has triggered the evolution of many production technologies, but technologies from related areas, such as stem cell technologies, molecular biology, biomaterials, or in vitro fertilisation, also contribute to the production of engineered tissues. Production technologies can be related to each of the individual key factors in the tissue engineering paradigm, namely the cells, the scaffold, bioreactors and tissue construct development and maturation (see Figure 1).

With respect to scaffolds, technological developments focus on the scaffold material as well as on material processing, where the use of a particular material or processing technique depends on design parameters such as the targeted tissue morphology, the desired degradation rate of the material, interconnected porosity, dimensions of pores for cells or microvasculature, mechanical properties, etc. Processing techniques include for instance electrospinning, printing, sponge and foam manufacturing, surface modification, micro-milling, salt leaching, and micro-sphere leaching. Scaffold materials can be broadly divided into synthetic or natural materials, with a rapidly emerging third category of semi-synthetic materials. Adaptation of (commercially available) materials already approved by regulatory authorities have advantages, because the safety and toxicity profiles of the materials in humans have already been defined, but there is also a need for the design of new materials that meet specific performance criteria in regenerative medicine (e.g. cell-material interactions, controllable degradation properties).

Developments in this area lean heavily on advances in (bio)material sciences and polymer sciences. But the most important changes come from the convergence of basic polymer science with molecular cell biology in the design of new, so-called bioactive, materials that carry out sophisticated signalling functions [Lutolf et al., 2005]. These materials may, for instance, trigger cellular differentiation or the production of extracellular matrix components. Such new materials can be easily tested in combination with various cell types and cell seeding techniques in a model set-up in the laboratory, where material performance can be followed closely. In this setting, related issues like sterilisation or biocompatibility of the materials can also be evaluated.

Bioreactors essentially provide the optimal environmental conditions of cultured tissues. They can be simple culture flasks that provide the necessary nutrients or sophisticated feed-back controlled systems that regulate culture conditions in response to measured tissue characteristics [Ratcliffe et al., 2002]. The culture conditions may include biological, chemical and or physical triggers depending on the targeted tissue structure and physiological function. Cardiac and skeletal muscle tissues, for example, require electrical and mechanical triggers for optimal tissue development, whereas cartilage development depends on repetitive tissue compression in combination with the right nutrients and growth factors [Seidel et al., 2004]. Model tissues can be employed here to obtain a better understanding of the effects of individual triggers and to define the optimal conditioning protocols in terms of trigger frequency, duration, magnitude, etc. that can be incorporated in the design of bioreactors for these specific tissues. Computer simulations of tissue metabolism, growth and differentiation can be helpful in this respect as they aid in the understanding and prediction of tissue responses to external stimuli, thereby steering the experiments and reducing the number of experiments [Sengers et al., 2005].

The ultimate goal of bioreactor technology is to grow 3-D tissues at a large scale, with targeted and reproducible properties and with minimal handling, in order to reduce the risk of contamination and damage. Bioreactor design, however, is complex and still at the early stages of its development. Intimate collaboration between biologists and engineers is required to design effective, yet scalable devices and to ensure that aspects like growth conditions, harvesting time, storage and sterility are all fully considered and incorporated in the design. Although some companies and institutions like NASA start to carefully introduce bioreactors on the market (e.g. <http://www.enduratec.com/>; <http://www.nasatech.com/>), these products are mainly intended for scientific purposes.

Tissue growth, development and maturation are highly dependent on culture conditions and available triggers and cannot be seen independently from bioreactor design. Measurement of tissue properties and maturation should ideally be incorporated in the bioreactor design and conditioning protocols but is currently mainly performed on harvested model tissues outside a bioreactor set-up. Measures range from the detection of markers or molecules signalling tissue growth or differentiation, microscopic inspection of cells and tissue structure, and functional performance. Preferably, these parameters should be measured in real-time and in a non-destructive way. Hence, vital and magnetic resonance imaging (MRI) techniques enabling the assessment of tissue structure and performance during culture are being developed. In addition, research programs are underway to follow specific signalling molecules in real-time using the principles of molecular imaging. The growing field of molecular imaging converges modern tools of molecular and cellular biology with state-of-the-art technologies for non-invasive imaging, such as MRI and computer tomography (CT) and positron emission tomography (PET) scanning [Herschman, 2003]. The goals are to develop technologies and assays for non-invasive in vivo investigation of molecular cellular events in normal and pathological processes. These approaches should help to lead to better methods for early diagnosis and management of diseases. Tissue models are very helpful in the development and evaluation of the molecular imaging methods and assays. For instance, incorporation of reporter molecules in scaffold biomaterials or signal amplification techniques for MRI can be effectively tested in vitro on tissue-engineered models before translating them to the in vivo situation.

CLINICAL IMPLEMENTATION TECHNOLOGIES

The aforementioned testing of molecular imaging methods in tissue models is an illustrative example of the application of tissue models in the development of technologies that support the clinical implementation of regenerative medicine approaches, such as tissue engineering or stem cell treatments.

Additional implementation technologies associated with tissue models are those related to the design of molecular markers and biosensors for normal and pathological processes that may eventually be used in the human body. These, as well as the imaging techniques, also aid in the upcoming shift from curative to preventive medicine where vital and early diagnosis is crucial. For other implementation technologies, such as implantation techniques (injection, percutaneous placement) or minimally invasive surgery, living tissue models are less useful. These should initially be developed and tested in combination with physical or animal models.

FUTURE EXPECTATIONS

One of the main requirements for regenerative medicine to become successful is a detailed understanding and insight in tissue formation, tissue repair, tissue functioning, and tissue adaptation. At the same time, the ongoing progress in science and technology should allow for the production and clinical application of regenerative medicine approaches. Model systems, whether used for technology development, the study of physiological processes or product testing, will help advance this process. In vitro 3-D model systems will increase the rate of drug testing, improve the likelihood that a new drug formulation will be successful in human clinical trials and facilitate the gathering of data that will be helpful in optimising drug formulations. The end result will be a reduction on the costs associated with drug development and a safer application of newly designed drugs in humans.

Further, in vitro 3-D model systems offer a profound opportunity to engineer clinically applicable tissues and organs, based on improved understanding of the functional relationship between different cell types and signalling cascades involved in cellular differentiation. The promise of such an approach is that tissue as well as organ substitutes become available, which are built on physiological principles and will be accepted by the human body as their natural counterpart.

Before this can take place, however, two distinct sets of limitations need to be addressed. The first set relates to the gain of knowledge required for a proper translation of model systems into clinical implants. So far, researchers have been quite successful in creating tissue structures like skin, heart valves and cartilage. Because of their limited thickness and perfusion rate, these tissues are less reliant on adequate perfusion and nutritional support. For an increased tissue size, however, continuous tissue perfusion or vascularisation is essential. Thus R&D is being performed to engineer blood vessels or to stimulate blood vessel growth (angiogenesis) through the administration of angiogenic growth factors. Other areas of study include the differentiation and transdifferentiation of donor stem cells to simultaneously produce all of the cells required to form a complete tissue and the creation of effective interfaces between the native tissue and the implant.

The second set of limitations relates to the translation of the knowledge obtained into applicable and effective clinical products. This requires the approval of tissue-engineered equivalents by regulatory authorities after the long-term integration in animal models and humans. It also requires answers to the question on how to produce tissue-engineered products on a commer-

cial and cost-competitive scale. Finally, it requires incorporation of the new products in existing clinical and insurance practices. Only when these aspects have been fully addressed, estimates of implementation times and potential market volumes will become realistic.

REFERENCES

- Baar, K. (2005). New Dimensions in Tissue Engineering: Possible Models for Human Physiology. *Exp. Physiol.* 90, 799-806, 263–275
- Bouten, C.V.C. et al. (2003). In Vitro Models to Study Compressive Strain-Induced Muscle Cell Damage. *Biorheology* 40, 1-3, 383-388
- Breuls, R.G.M. et al. (2003a). Compression Induced Cell Damage in Engineered Muscle Tissue: An in Vitro Model to Study Pressure Ulcer Aetiology. *Annals of Biomedical Engineering* 31, 11, 1357-1364
- Breuls, R.G.M. et al. (2003b). Monitoring Local Cell Viability in Engineered Tissues: A Fast, Quantitative, and Nondestructive Approach. *Tissue Engineering* 9, 2, 269-282
- Bursac, N. et al. (1999). Cardiac Muscle Tissue Engineering: Toward an in Vitro Model for Electrophysiological Studies. *American Journal of Physiology* 46, 2, H433
- Dennis, R.G., P.E. Kosnik (2000). Excitability and Isometric Contractile Properties of Mammalian Skeletal Muscle Constructs Engineered in Vitro. *In Vitro Cellular & Amp. Developmental Biology, Animal* 36, 5, 327-335
- Gawlitta, D. et al. (2005). Evaluation of a Continuous Quantification Method of Apoptosis and Necrosis in Tissue Cultures. *Cytotechnology* 46, 139-150
- Griffith, L.G., G. Naughton (2002). Tissue Engineering — Current Challenges and Expanding Opportunities. *Science* 295, 5557, 1009-1014
- Herschman, H.R. (2003). Viewpoints — Molecular Imaging: Looking at Problems, Seeing Solutions. *Science* 302, 5645, 605-610
- Lutolf, M.P., J.A. Hubbell (2005). Synthetic Biomaterials as Instructive Extracellular Microenvironments for Morphogenesis in Tissue Engineering. *Nature Biotechnology* 23, 1, 47-56
- Lysaght, M.J., A.L. Hazlehurst (2004). Tissue Engineering: The End of the Beginning. *Tissue Engineering* 10, 1-2, 309
- Mol, A. et al. (2003). The Relevance of Large Strains in Functional Tissue Engineering of Heart Valves. *The Thoracic and Cardiovascular Surgeon*, 51, 2, 78-83
- O'Connor, K.C. (1999). Three-Dimensional Cultures of Prostatic Cells: Tissue Models for the Development of Novel Anti-Cancer Therapies. *Pharmaceutical Research* 16, 4, 486-493
- Ponec, M. (2002). Skin Constructs for Replacement of Skin Tissues for in

- Vitro Testing. *Advanced Drug Delivery Reviews* 54, S (1 November), 19-30
- Popescu, D.C. et al. (2005). The Patterning and Alignment of Muscle Cells Using the Selective Adhesion of Poly(Oligoethylene Glycol Methyl Ether Methacrylate)-Based ABA Block Copolymers. *Advanced Materials* 17, 19, 2324-2328
 - Radisic, M. et al. (2004). Medium Perfusion Enables Engineering of Compact and Contractile Cardiac Tissue. *American Journal of Physiology, Heart and Circulatory Physiology* 55, 2, H507
 - Ratcliffe, A., L.E. Niklason (2002). Part IV — Tissue Generation — Bioreactors and Bioprocessing — Bioreactors and Bioprocessing for Tissue Engineering. *Annals of the New York Academy of Sciences* 961, 210-215
 - Rodriguez, H. et al. (2003). III Biomarkers for Tissue Engineered Products — 10 Oxidative DNA Damage Biomarkers Used in Tissue-Engineered Skin. *Advances in Experimental Medicine and Biology* 534, 129-136
 - Seidel, J.O. et al. (2004). Long-Term Culture of Tissue Engineered Cartilage in a Perfused Chamber with Mechanical Stimulation. *Biorheology* 41, 3-4, 445-458
 - Sengers, B.G. et al. (2005). Nutrient Utilization by Bovine Articular Chondrocytes: A Combined Experimental and Theoretical Approach. *Journal of Biomechanical Engineering* 127, 5, 758-766
 - Stekelenburg, A. et al. (2005). Compression-Induced Tissue Damage: Animal Models. In: Bader, D., et al. (eds). *Pressure Ulcer Research: Current and Future Perspectives*. Springer, 187-204
 - Vacanti, J.P., R. Langer (1999). Tissue Engineering: The Design and Fabrication of Living Replacement Devices for Surgical Reconstruction and Transplantation. *The Lancet* SI 32
 - White, R.E. (2000). High-Throughput Screening in Drug Metabolism and Pharmacokinetic Support of Drug Discovery. *Annual Review of Pharmacology and Toxicology* 40, 133-157
 - Zimmermann, W.H. et al. (2002). Integrative Physiology — Tissue Engineering of a Differentiated Cardiac Muscle Construct. *Circulation Research* 90, 2, 223-230

From Laboratory to Practice: Learning about normative issues

Klasien Horstman¹

INTRODUCTION

Spinal fusion, tissue-engineered organs and cardiac cell therapy: three examples of technological innovations in the field of ‘regenerative medicine’. This chapter deals with ethical and social questions that are associated with the rise of regenerative medicine, such as: ‘How to decide that the time is ripe for clinical experiments?’ and ‘What will happen to our concept of old age when our body can be regenerated?’

In this article, I will identify four clusters of normative problems that should be part of a research programme on regenerative medicine. Besides describing these dilemmas, attention will be paid to different ethical approaches to deal with these dilemmas. Pointing to different ethical traditions and approaches serves to make clear that ethical and social issues cannot be simply solved. In a pluralistic society there are no simple answers to ethical questions that are associated with new technologies, because there are different ways to frame the dilemmas as well as the solutions. We might come to a consensus about some issues and we even might agree on specific national or international legal arrangements [Kent, 2006]. However, as the political scientist Trappenburg has demonstrated, legal rules with respect to medical ethical issues function to create specific temporary boundaries

¹ Universiteit Maastricht,
Maastricht, the Netherlands.

for public discussion rather than end the discussion, and new controversial questions might arise [Trappenburg, 1993]. So, the work on the ethical and social agenda of medical technologies will never be finished. Technical and ethical innovation are both continuous processes.

Following the idea of plurality when it comes to ethics, I will finish this article with a reflection on the implicit promises and expectations of the ‘organised interaction’ between technology and society. Is this idea perhaps too much connected with the hope that planned interaction will close the gap between technology and society and make technology development unproblematic and not controversial again? Is this idea too much connected with the hope that all normative dilemmas will be solved? I will deal with this question by introducing a theoretical frame that focuses, rather than on solving social and ethical dilemmas of regenerative medicine, on learning about these dilemmas. Instead of hoping to return to a situation of uncontroversial technological innovations and of unproblematic social trust, this implies acknowledging and stimulating the public-ethical character of technological developments. But I will start with a sketch of the normative dilemmas of regenerative medicine as they are presented in the field itself.

NORMATIVE ISSUES IN BOTH LABORATORY AND IN SOCIETY

At the start of the development of a field that might be called regenerative medicine, scientists working in that field underlined the future fruits of their field. “*Of course, the entire goal of tissue-engineering is to benefit mankind.*” [Patrick, 1998, 319]. However, they foresaw that this goal would have its complications, because many social and ethical issues were to play a role in the development of the field. Ratner argued in ‘Biomaterials Science’, for instance, that ethical dilemmas might have quite an impact on biomaterials science: “*Perhaps the final frontiers in biomaterials science will be in the area of ethics.*” [Ratner, 1996, 467]. And in ‘Frontiers of Tissue Engineering’, Patrick, Mikos and McIntire pointed out the relevance of dealing with ethical issues as well: “*... tissue-engineering will not become a valuable clinical solution unless it is accepted by society.*” [Patrick, 1998, 312]. These pioneers of the field implicitly pointed at the relevance of a normative agenda for tissue engineering. In this article, I will make such an agenda. I will assume that technology and ethics have to work together to stimulate learning processes in both fields and to make them both ‘better’. The three examples of regenerative medicine that are presented in this book — spinal fusion, tissue-engineered organs and cardiac cell therapy — provide a good opportunity for drawing up a new normative agenda for regenerative medicine.

So as to identify specific normative questions in regenerative medicine, I will follow the innovative trajectory from laboratory to clinical practice and daily life from philosophical and ethical perspectives. Although this method is a little artificial, it provides the opportunity to do justice to the fact that, because these technologies are in the making, normative issues are in the making as well. Not every ethical issue is equally urgent, and whereas some issues have been defined quite well, others are only vaguely described or only arise when the implications of the technology become more obvious. Ethical questions with respect to the choice of cells, for instance, are more concrete and pressing than questions with respect to the integration of these therapies in health insurance. So, by following this trajectory, it is possible to identify actual and concrete dilemmas as well as issues that will play a role in the future.

By following the trajectory from laboratory into society, four clusters of normative problems of regenerative medicine are distinguished:

- normative issues with respect to the meaning of the human body;
- normative issues that have to do with the step from the laboratory to clinical experiments;
- normative issues that play a role when regenerative medicine will be introduced in regular health care;
- normative issues with respect to the promise of prevention.

The reason to discuss these normative issues is to make clear that, when research in regenerative medicine is stimulated, the study of these issues — all equally relevant — should be stimulated as well. In the introduction of this book, the relevance of an optimal selection environment for technological innovations is stressed. Systematically paying attention to ethical and social issues can be seen as an important contribution to such an optimal environment! The successful development and implementation of regenerative medicine requires that we face the ethical issues it entails and that we find a way to deal with these. We will therefore start with reviewing some issues concerning the body.

BODY-TECHNOLOGY RELATIONS: BODY-THING OR LIVED BODY

A first cluster of normative questions that arise in all three cases has to do with the relation between regenerative medicine and the body. With respect to this issue, it is primarily necessary to reflect on the promise of regenerative medicine that ‘the body will heal itself’. This promise implies that researchers only ‘help the body to heal itself’ by ‘mimicking nature’. In other words, the interventions of regenerative medicine are implicitly presented as non-inter-

ventions, and the technological character of regenerative medicine as well as the human decisions that play a role in this process are understated. By using metaphors like ‘mimicking nature’, regenerative medicine presents itself as a rather innocent practice and evades questions with respect to the responsibility for the real interventions of regenerative medicine [Derksen, 2005]. So, the first task is to identify the normative character of regenerative medicine by making a critical analysis of the self-image of this field and of the metaphors that play a role in staging the field. Instead of taking metaphors like ‘mimicking nature’ or ‘helping nature’ for granted, we should ask ourselves how regenerative medicine actually intervenes in the human body.

Which interventions in bodies, for instance, are implied in the three cases of this book? Spinal fusion, a therapy for lower back pain, implies the injection of growth factors to stimulate autogenous bone. Tissue engineering organs requires the implantation of cells — autologous or allogenic, embryonic or adult — as well as scaffolds and triggers so as to stimulate these cells in order to develop in a certain way. And in the case of cardiac cell therapy, cells are injected so as to create new cardiac muscle tissue or to increase the flow of blood in the injured cardiac muscle. It will be clear that, instead of letting the body ‘heal itself’, cells and bodies have to be technically manipulated to perform that role. We can distinguish several normative questions regarding these technological interventions in human bodies.

Some normative questions with respect to the relation between body and technology have to do with the body materials used in regenerative medicine to get the body ‘to heal itself’. And although embryonic stem cells do not play a major role in developing spinal fusion, tissue-engineered organs and cardiac cell therapy, in the broader field of regenerative medicine the opportunity to use embryonic stem cells does play a role! This possibility is still very controversial. First, this has to do with the moral position of an embryo [Henon, 2003]. In many countries, embryonic cells are considered as the beginning of human life, as intrinsically valuable, and therefore these cells should not be used in an instrumental way. Balancing the respect for embryonic cells as human life on the one hand and the expected value of these cells for scientific research and improving human health on the other hand results in different normative positions with respect to the actual use of embryonic cells. While some argue that the value of embryonic cells for developing therapies and improving the health of patients should prevail [De Wert, 2003], others argue that embryonic cells should not be used instrumentally, however great the expected benefits might be [Jochemsen, 2004]. These different normative positions are reflected in different national regulatory regimes as well. While some countries, such as England, develop a rather liberal policy, policy processes in

countries like the Netherlands and Germany show more reserve with respect to research on embryos [Kater, 2005; Gottweis, 2002].

Another important issue with respect to the use of embryonic cells does not focus on the moral position of the embryo but on the pain it costs women to produce these cells and the value these cells might represent to them. Embryonic cells derived from so-called rest embryos from IVF procedures might have an emotional value for the women and their partners because these cells could have been developed into their children. Even when one does not principally argue for the intrinsic moral value of the embryo, one might question the use of embryonic cells, because these cells mean something to actual persons in every day life, and these persons might find it difficult to live with the idea of these cells being used as 'research material'. However, now that researchers have defined the shortage of embryonic cells as a major problem and have proposed the donation of ova by women for research as a solution to this problem, another controversial issue is born [De Wert, 2003]. In this case, healthy women have to undergo hormone treatment so that several ova-statistics mentioned — vary from 10 to more than 50 — can be extracted at one time. However, the hormonal treatment as well as the extraction are both laborious and risky procedures and by definition serious interventions in a healthy body. With respect to this issue, balancing the benefits for science and health care and the pain it costs women to donate embryonic cells or ova results in different normative positions as well. While some conclude that it is reasonable to opt for ova-donation, others are more reserved [Huijjer, 2004].

Although ethical problems with respect to the use of embryonic stem cells attract much attention among philosophers, ethicists, engineers, scientists and the public, the use of other cells in regenerative medicine is debated as well. For when the focus is on adult stem cells, the question arises whether to work with autologous or allogenic cells. While most professionals agree that working with autologous cells minimises risks like the rejection of tissue, growing these cells takes quite some time, and it might be more practical — especially in acute situations — to use allogenic cells to develop 'of the shelf tissue'. This last opportunity is also considered beneficial from an economic perspective: It would allow the development of regenerative medicine as a market for mass products. Apart from the risks of using allogenic cells, this strategy stimulates ethical questions about the 'ownership' of the cells. How should we evaluate the opportunity to donate cells or tissue for altruistic or commercial motives to family, friends or tissue banks? Moreover, the use of allogenic cells stimulates the question whether the body should be considered 'a thing' to be repaired with strange elements when it seems necessary or a

‘lived body’ that embodies a ‘self’, an ‘identity’ or a ‘person’? When the latter is preferred, we have to study how regenerating the body with ‘strange’ ingredients affects ‘the lived body’.

In debates about body materials to be used in regenerative medicine, we can distinguish various styles of normative reasoning. On the one hand, there is a liberal, legalistic style that does not address the issue of the meaning of the human body but deals with most ethical issues in terms of ‘autonomous choice’ and ‘informed consent’, ethical principles that are legally embedded and supported. This style implies that when the risks of donating or receiving body materials are considered proportional — and professionals often express quite different opinions about the proportionality of emotional and physical risks that are at stake! — individuals should decide for themselves whether they are prepared to donate or to receive body material. Lately, this individualistic ethical style has been criticised.

Some authors argue that ‘autonomous choice’ implies that public ethical dilemmas are turned into the dilemmas of an individual: The individual has to choose and is left on his own with the concrete worries and experiences of making a choice for donating or receiving body materials and in dealing with the effects of the choice [Ten Have, 1998]. Another kind of comment on this individualism often heard in debates about organ donation is that the argument of autonomy is obstructing the system of organ donation and health care for people who are seriously ill [Den Hartogh, 2003]. In line with this argument it is proposed that — instead of referring to autonomous choice — we might think about the idea of a moral duty to donate or to participate in fair exchanges of body materials. Other authors criticise this individualist approach by pointing out the fact that body materials to be used for public purposes should be dealt with in a public way: By arranging public governance of biobanks and tissue banks, there will be more public space to deal with the ethical issues of dealing with body materials [Swierstra, 2004].

There are, however, philosophical traditions that, rather than focussing on the procedures of decision-making, do address the meaning of the body in concrete technological practices. Inspired by historical and anthropological studies of for instance blood donation and organ transplantation [Lock, 2002] this tradition reflects on the relation between body, identity and personhood. This tradition studies what it means to treat human body parts as ‘material’, as ‘property’ or as ‘merchandise’ and how these concepts of the body relate to the body as ‘a lived body’. From this perspective, the focus will be less on the autonomous choice of individuals to donate body material and more on the question whether it is right to ask a person to donate body materials for

altruistic or commercial reasons. For instance, is it reasonable to ask women to use their bodies in an instrumental way? In this context it is easy to evade the issue by pointing to the fact that we have become used to practices like blood donation and arguing that we will become used to the donation of all kinds of other body materials as well. However, this line of reasoning ignores the fact that it took many decades to let blood donation develop into a culturally accepted practice [Schneider, 1983]. From the fact that other — apparently similar — body technologies have become part of health care, we should not conclude that we have to accept specific regenerative technologies as well.

One interesting author in this tradition is the philosopher Donna Dickenson. Whereas some authors use the concept of ‘ownership’ of the body to argue for the freedom to sell body materials [Wilkinson, 2000; Resnik, 2002], Dickenson has criticised the concept of ‘ownership’ of the body as a justification of ‘the autonomous choice’ with regard to donating or selling body materials [Dickenson, 1997]. She recently developed the idea of a ‘bundle of rights’ with respect to property. Instead of a monolithic and digital concept of ownership (yes/no, 100% or 0%, all rights/no rights), she distinguished between different rights, such as physical possession, use, management, to be secured by being taken by others, to alienate, by gift or by sale, to capitalise its value, etcetera [Dickenson, 2006]. Such a layered concept of ownership provides the opportunity to take the different kinds of rights into account when justifying the donation or sales of body materials. Following this line of thought, ethical research in regenerative medicine should address the question which conceptions of the body are — implicitly or explicitly — presupposed and stimulated by regenerative medicine. Does regenerative medicine stimulate the commodification, commercialisation, fragmentation and disciplining of bodies to an extent we have not seen before?

When it comes to body-technology relations in regenerative medicine, other normative questions have to do with the limits to intervening in nature. Although the term ‘regenerative medicine’ supposes that ‘natural body processes’ are both the goal and the criterion for the interventions pursuant to this technology, there is no such thing as a ‘natural body’ that dictates which interventions are legitimate. We therefore need public debates about the goals and ambitions of regenerative medicine. Should regenerative medicine develop as a therapeutic enterprise, or should it aim at enhancing the physical condition of an individual? How should regenerative medicine relate to our actual notions of ‘normal body processes’ like ‘normal aging’ or ‘normal healing’? Will norms change in response to developments in regenerative medicine? Or do developments in regenerative medicine have to adapt to existing norms and values? How does regenerative medicine address cultural norms such

as the expression of youth and fitness? Will cardiac cell therapy be used to increase the 'natural' sportive performance, and will tissue engineering be used to cure sport injuries much faster than 'natural' healing processes? With respect to genetics these issues have been put on the agenda [Van Hilvoorde, 2005] but the ethics of regenerative medicine will have to address these questions as well.

To conclude, regenerative medicine generates important questions about the meaning of the human body, forcing us to find ways to deal with human bodies in a decent way.

STARTING CLINICAL EXPERIMENTS: NEW STANDARDS, NEW RESPONSIBILITIES

From the cases of spinal fusion, tissue engineering organs and cardiac cell therapy we can conclude that a second cluster of normative questions concerns decisions to go from the laboratory to clinical experiments. Although there are professional guidelines to deal with the step from laboratory to clinical experiments, these guidelines play their guiding roles best in established practices with a more or less established paradigm, such as drug research. In these practices, some level of consensus about standards has developed with regard to evaluation models, animal experiments and other laboratory tests and the assessment of risks of clinical experiments. Some of these standards have obtained a legal basis.

It is characteristic for a newly developing interdisciplinary field like regenerative medicine that although it very urgently needs guidelines to reduce the uncertainties, these guidelines do not exist. Like the Baron of Munchhausen, regenerative medicine has to draw itself out of the marsh of so many uncertainties. The actual research culture — international, multidisciplinary, public-private networks — complicates this process even more. That is why the decision to start clinical experiments in the course of the development trajectory of regenerative technologies requires the development of so-called benchmarks that reflect the evolving norms and criteria. From an ethical perspective, it is necessary to study how these norms are developed and whether the norms developed are right. Which stakeholders (researchers, clinicians, industry, patient organisations, medical ethical committees) and disciplines (medicine, engineering) influence this process? What are the arguments and perspectives discussed? Which compromises are negotiated between different stakeholders? And how can the outcome of this process — the norms — be accounted for?

One specific issue that has to be discussed in the context of clinical trials is the importance of different kinds of evidence — laboratory studies, modelling and animal studies and clinical experiments — in regenerative medicine. For instance, the function of animal studies as a safety pal presupposes that interventions in animals can to a certain extent predict the effects of interventions in human bodies, but the translation of results of experiments on animal models to the human body is not trivial. In pharmaceutical research the various kinds of evidence needed to make such a translation have become more or less standardised. Although such standards did become legally embedded in the 1960s and 1970s, they had to be highly differentiated so as to reflect the needs of specific research fields. In pharmaceutical research for HIV this standard has changed under the influence of patient organisations. So although some level of standardisation exists, pharmaceutical research practice is no monolithic situation. With respect to other kinds of medical technologies — surgery for instance — the level of standardisation is even less. This also applies to regenerative medicine. Therefore, the question arises how to compile evidence so as to be able to start clinical experiments. For regenerative medicine, this requires explicit reflection on the question whether research methods and research ethics developed in the context of pharmaceutical research are suitable for research on regenerative medicine or whether they should be adjusted in specific ways. Whereas patients in general should be protected against eager researchers and risky trials and animals should be protected from unnecessary experiments as well, for some patients the development of successful therapies should not be delayed longer than necessary. It might be part of the ethical agenda of regenerative medicine to think through the ethics of clinical trials for this specific field and to find ways to deal with such trade-offs.

To deal with the normative dilemmas of clinical trials characteristic of a newly emerging scientific field in health care, roughly two approaches can be distinguished: the protection paradigm and the participation paradigm. The protection paradigm was developed in the second half of the 20th century and aims to protect patients and healthy research subjects against researchers. To that end, the central principle is the right of patients/human beings to autonomously decide on their participation in a trial. In support of the patients right to autonomously decide about the pros and cons of participation in a trial, researchers are held to provide adequate information to patients. Thus, autonomy and informed consent are the cornerstones of the protection paradigm. However, this protection paradigm was recently criticised for several reasons. Firstly, the legal frame of the protection paradigm and the successful institutionalisation of this paradigm in medical ethical research committees have been accompanied by many administrative procedures. Whereas research-

ers complain that this bureaucracy hinders their work, ethicists complain that the focus on fulfilling administrative needs implies neglect of the real ethical issues at stake. Some even speak of ‘empty ethics’ [Corrigan, 2003]. Secondly, the protection paradigm is criticised because it assumes a rather hierarchic relation between researchers and patients as subjects and objects: Researchers are considered to be experts, while patients are considered to be dependent on them for information. Moreover, patients and healthy research subjects are given very passive roles in trials: They are allowed to consent as well as to quit the trials, but they are not supposed to play more active roles in the trials. In other words, the protection paradigm defines the voice of a research subject as insignificant. The paradigm stresses the protection against researchers and not the empowerment of patients/research subjects.

In response to this critique, the participation paradigm is nowadays being developed [Willems, 2005; Epstein, 2004]. This paradigm assumes a more equal relation between researchers and research subjects and addresses the fact that many — not all! — patients are becoming experts with respect to their own disorders and that researchers depend on them for relevant information about the course of the trial. Sharing their bodily experiences during and after a trial, when the risks and benefits in the long run have to be monitored, can be very valuable to researchers. Because the concept ‘evidence’ in the phrase evidence-based medicine has been one-sidedly interpreted as statistical evidence, researchers might nowadays think that they only need to rely on statistics to evaluate new medical technologies. However, it can be considered an ethical responsibility to look further than statistics, to keep an open eye for other kinds of evidence and to keep in touch with the experiences of patients dealing with these technologies in day-to-day life [Goldenberg, 2005]. From this perspective, research subjects should not only be given the opportunity for a silent consent and a silent exit but also an invitation to share their bodily experiences and opinions during and after the trials. The participation paradigm also provides the opportunity to argue that, from the angle of diversity, all groups in society not only have a right to be protected but also a right to be included and represented in trials (the elderly, children, ethnic groups), so that the results of scientific research will benefit different groups. Although still in its infancy, the participation paradigm appears to provide more clues to depart from the concept of an ‘average body’ and do justice to particular bodily experiences of individuals than the protection paradigm.

The ethical agenda of regenerative medicine involves studying the step from laboratory to clinical experiment and developing new standards from both perspectives. One important question is how the responsibilities of researchers and research institutions to protect patients might be combined with

their responsibilities to stimulate voice, participation and empowerment of patients/citizens and their responsibilities with respect to exclusion and inclusion. But besides this analysis of the responsibilities of researchers, insight is needed in the experiences of patients and research subjects (patient organisations) that participate in these research practices.

FROM EXPERIMENT TO STANDARD TREATMENT: CULTURAL ACCEPTANCE, INSURABILITY AND SOLIDARITY

A third cluster of normative issues in regenerative medicine concerns the integration of treatments in health care and health insurance. When clinical trials result in a positive evaluation of a therapy and the therapy is considered safe and effective, it still has to be introduced in general health care. Acceptance of a new therapy not only depends on efficacy and safety, but also on cultural, social and economic factors: Therapies are not launched in a vacuum but in a context where other therapies might be available as well and where various criteria determine the value of a therapy. Even when there appears to be a strong 'need' for a new and apparently better therapy, for such a therapy to be successfully introduced into the existing cultural and socio-economic context of the health care system it has to find a fit with, for instance, cultural norms or economic criteria for insurability. To that end, the new therapy will have to compete with other therapeutical options.

From a patient perspective, the pros and cons of therapies are not so obvious: In spite of the evidence about the efficacy of a new therapy, patients might prefer — for different reasons — other strategies to deal with their problems. When patients for instance do not like foreign objects to be inserted into their bodies, they might prefer other therapies than regenerative therapies. Apart from that, the differences in professional culture between the various medical specialties can result in conflicting opinions about the indications to prescribe a therapy [Berg, 1998]. Whereas some physicians would like to prescribe a new therapy like cardiac cell therapy at a rather early stage, others are more reluctant and would prefer to wait longer. Some would propose to limit such a therapy to patients with, for instance, 'serious' heart defects whereas others would prescribe it for a much broader group of patients. Some would focus on the benefits of cardiac cell therapy for the individual patient whereas others would give priority to the 'health of the population' and expect more from public health initiatives to change the lifestyle of the population. Some professionals and patients will prefer spinal fusion, others prefer a less invasive, behavioural therapy to control the pain. In other words, when discussing whether or not to accept a new therapy, health care becomes a normative

arena in which different cultural norms play a role. Therefore, the introduction of regenerative medicine in health care requires more work to be done than just demonstrating that it ‘works’. In addition, to be accepted in a cultural and normative sense, the added value of a novel therapy has as compared to other existing therapies has to be recognised by the different stakeholders. There are many examples of technologies and devices that may be considered as major improvements from the perspective of medical professionals and researchers, but not from a patient’s perspective. A well-known example is the refusal to use cochlear implants by a large part of the deaf community, as deaf persons prefer their existing identity and culture based on the use of sign language to the use of this device [Blume, 2001].

Apart from the issue of cultural acceptance, a new therapy has to be insurable. Few patients are able to pay for medical treatment themselves, and it applies to most patients that in order to get regenerative medical treatment it has to be part of general health care, through insurance such as in for instance the Netherlands or Germany or as part of a state health care system like that in the United Kingdom.

But how are therapies evaluated and selected as they are introduced in general health care? In the first place, there is a rationalistic approach [Timmermans, 2003]. This approach was developed in the last decades as a reaction to the rising costs of health care, the growing claims of competing professional groups and patient groups and the diminishing public trust in public institutions. The rationalistic approach argues that the introduction of new therapies should be evidence based, not only on conventional evidence about efficacy and safety, but also on cost-effectiveness. In this approach, ‘evidence’ is considered to be an objective criterion on which a decision can be based about the inclusion and exclusion of treatments in health care and about the indications to provide these treatments. Despite the fact that in the practice of health insurance ‘evidence’ about the efficacy and cost-effectiveness is often only one of the criteria underlying the decision whether or not to insure a new treatment, in several countries this rationalistic strategy is presented as an ideal way to decide on what to include in health care packages.

This rationalistic approach was criticised in different ways. The fundamental point of critique is that in the arena of health care there is no neutral point of view that legitimates difficult public policy decisions and that presenting some specific strategy as neutral and objective implies hiding the politics of that strategy [Porter, 1995]. Apart from this fundamental argument, the rationalistic strategy has its practical limitations as well. Firstly, there is the issue of therapies for rare diseases. In this case, patient groups are too small

to determine the cost-effectiveness. Although it seems unreasonable to deny patients a therapy because of this, the rationalistic strategy does not provide an answer to this dilemma. Secondly, the measurement and interpretation of ‘efficacy’ and ‘quality of life’ as an ingredient of efficacy is not trivial. Many debates about the cost-effectiveness of specific diagnostic or therapeutic procedures relate to this issue [Horstman, 2004]. With respect to spinal fusion or cardiac cell therapy, the question arises whether the subjective experiences of patients, such as pain or tightness, have to play a role in determining the efficacy of these therapies, and if so, how these experiences have to be disclosed. Thirdly, the rationalistic ideal of evidence-based care does not take resource restrictions into account. Therefore, it cannot provide the instruments to decide about the relevance of different kinds of care when the budgets become stricter and not all claims can be rewarded: Do we wish to pay for tissue-engineered organs for the elderly when low-tech day care of the elderly is still a problem? Therefore ‘objective evidence’ can only be successfully used to decide on the inclusion of new therapies in health care in situations of consensus. In case of controversial decisions this approach shows its limits. For then the normative assumptions of the notion ‘evidence’ will become apparent and will therefore be disputed.

Another way to deal with questions regarding the inclusion and exclusion of new therapies in health care instead of a rationalistic strategy is the political normative approach [Stone, 1997]. Such an approach explicitly acknowledges that health care is a political-normative enterprise and that the introduction of new therapies in health care should be dealt with in terms of justice and solidarity. It is obvious that insights in the efficacy and costs of therapies are important as well, but they will have to play their roles within the context of a political-normative approach. This means that the rise of new therapies requires a public deliberation about the solidarity between various patient groups, various risk groups or various generations. Who deserves our solidarity most, and why? Should we limit solidarity to people who are in need, to people who behave responsibly after therapy, to those who are not to be blamed for their disorders? Should we invest in cardiac cell therapy or in public health programmes to decrease cardiovascular diseases? Should we argue for spinal fusion in health insurance or for behavioural pain therapies, or maybe for both? Should we limit tissue-engineered solutions to serious or even fatal organ problems or use these to prevent all kinds of damage? Many different stakeholders — medical scientists, clinicians, patient groups, industry, insurance companies, politicians etc. — will contribute to the debates about these questions.

Regenerative medicine will probably change the range of available therapies considerably. The normative agenda of regenerative medicine implies a study

of the insurability of regenerative medicine in the contexts of financial scarcity, competing technologies and cultural preferences. This implies studying the actual political and social processes with respect to the integration of regenerative medicine in health care and considering the way to publicly account for these processes and for the outcome of these processes.

REGENERATING HEALTHY PERSONS: PREVENTING ILLNESS OR MAKING RISKS?

Although the cases presented in this book are all presented as therapies, regenerative medicine fits the general trend in medicine of focusing more and more on a-symptomatic, healthy persons. They can opt for new tissue or new organs before they are ill, and cardiac cell therapy can be performed when they still feel well and have no complaints. Regenerative medicine might in fact not only contribute to the idea of ‘preventing diseases’ but also to the idea of ‘preventing old age’. This implies that regenerative medicine, like so many other medical technologies, contributes to an imperialistic preventive health culture: A culture that strengthens the ideal of human control and denies the contingencies and vulnerabilities of human life. In such a culture, diseases will become considered as symbols of ‘failed prevention’ and of ‘lack of control’ and one might be punished because of it [Lupton, 1995].

The preventive approach in medicine and health care was developed in the 20th century in public health and epidemiology. During the 20th century, preventive medicine emerged as a low-tech approach public health but toward the end of the twentieth century, with the Human Genome Project, preventive medicine received a major high-tech impulse. In many medical specialties, predictive tests are now developed to identify genetic risks. Although most of these risks are characterised as complex and multifactorial, predicting these risks does stimulate preventive measures, such as lifestyle advice, preventive diets, preventive medication, regular check-ups [De Vries, forthcoming]. The recent developments of molecular imaging, bionanotechnology, ambient technology etc. only reinforce this trend toward design of medical technologies for a-symptomatic individuals. This trend will probably not only change the character health care but it could also considerably modify the basic concepts of health and disease and the ideas about being responsible for one’s own health. In fact, in such a situation every healthy person will become not-yet-ill and will be deemed responsible to remain so.

However, preventive medicine is accompanied by many ethical dilemmas. There is the issue of ‘knowing or not knowing’ the risks: Some prefer to live in

‘the here and now’ instead of anticipating some future health, but in a preventive health culture it is quite difficult not to be confronted with ‘risks’. Another question is whether it is right to intervene in someone’s life and body when there is no actual problem. Not every risk will become an actual problem, and people might become unnecessarily worried. How can we balance the opportunity to diminish health risks on the one hand with the threat of producing unnecessary insecurities and worries on the other hand [Tijmstra, 2004]? Since to most the idea of ‘living a good life’ is not the same as ‘living without a risk’, we may wonder whether preventive medicine is opposed to our ideas of ‘living a good life’ and how preventive medicine can become part of the idea of ‘a good life’ [Horstman, 2005].

Regenerative medicine, although primarily presented as a field addressing actual health complaints, will fit this trend of preventive medicine. For when spinal fusion, tissue-engineered organs and cardiac cell therapy ‘work’, the question will arise when to apply these therapies. And the promise of the field is that, instead of waiting until the damage has been done and there are complaints, it might be more useful to intervene at a much earlier stage. This implies that regenerative medicine will stimulate the use of predictive technologies, such as molecular imaging and ambient technologies and might become part of the organisation of screening programmes. Although this sounds rather futuristic, regenerative medicine will certainly stimulate early diagnosis so as to make early interventions possible, which means that healthy persons become persons ‘at risk’. Moreover, when the boundaries between preventing, helping and improving, between prevention, therapy and enhancement, become blurred, one may wonder where regenerative medicine will be effected in about 25 years: in the general physician’s surgery, in hospital or in fitness centres.

The development of regenerative medicine into preventive medicine implies that many ethical issues concerning preventive medicine in general, have also to be discussed in the context of regenerative medicine. When we take the idea serious that ‘the body heals itself’, we might wonder how to assess whether a little ‘damage’ will develop into a serious disease or will ‘heal itself’? How to assess the body’s own capacity to regenerate without the aid of regenerative technology? When does this capacity decrease, and how should processes of ‘normal aging’ be evaluated in this respect? And how to deal with the risk that regenerative medicine will produce ‘damage’, ‘pathology’ and ‘risks’ instead of curing real complaints? Just like research in genomics that is accompanied by normative analyses of genetic technologies, the field of regenerative medicine should address the ethical implications of developing a risk-oriented approach.

The introduction of regenerative therapies in health care might result in a shift of the point of intervention in the disease spectrum: From cure toward prevention and maybe even enhancement. Such a shift can be evaluated in different ways. A liberal ethical approach conceptualises health care as a market. The liberal approach implies that people should be offered the technologies available (when evaluated effective and safe) and that they should decide for themselves whether to use it. Individuals are assumed to be able to make autonomous choices about the technological opportunities offered to them, and therefore much should be done to adequately inform them, so that they will be really able to make the right individual choices. In this approach, patients and citizens are seen as consumers who should be able to freely move on the market of health care technologies. In contrast, a public ethical approach conceptualises health care as a public realm in which new cultural definitions of 'health', 'risk', 'responsibility' and 'autonomy' are developed that should be the object of a public debate. This approach pays closer attention to the cumulative cultural effects of the many individual choices, such as the ongoing medicalisation of normal daily life [Mol, 1989]. While the liberal ethical approach fits the idea of patients as consumers, the public ethical approach is critical toward trends like consumerism in health, for this does no justice to the fact that health is not a product but to some extent a fate that is beyond individual control. Even though health care might be directed more and more to healthy, a-symptomatic persons, this should not imply that individuals are to be conceptualised as being in control. Mol argues for a 'logic of care' in health care instead of a 'logic of choice', to stress that health care should be a domain where patients are allowed to show their complaints, inabilities and lack of control and will be taken care of.

FROM SOLVING TO LEARNING

Innovations in regenerative medicine will have to deal with four major normative issues: the ethics of body material, the ethics of clinical experiments, the ethics of insurability and the ethics of prevention. These four ethical issues have to be put on the research agenda of regenerative medicine. We should now go one step further and discuss the idea I introduced at the beginning of this article, that we should not focus on 'solving' these issues but on 'learning' about these issues. What do I mean by that?

The political scientist Dijstelbloem has pointed out the fact that current western democratic societies are confronted with many knowledge-intensive public issues, such as climate change and genetic modified food, which do not belong to one discipline or one institutional domain [Dijstelbloem, 2004].

Because these issues are full of factual and normative insecurities, are highly unpredictable and 'out of control', he calls them unidentified political objects: UPOs. UPOs are unpredictable in the sense that the interpretation of the relevant issues is not stabilised, that it is uncertain who is responsible for addressing the relevant issues (professionals, local/national/international governments, industry, citizens, NGOs etc.) and we have to find out how they are to be addressed. It is characteristic that many UPOs are taken up by so-called hybrid forums that develop a niche somewhere between traditional institutions, organise new assemblages of stakeholders and develop new repertoires to address these issues. In the words of Van Dijstelbloem, regenerative medicine can be considered as a UPO. Regenerative medicine is very much 'in the making', full of public and professional uncertainties, and there are no established institutional actors or repertoires to deal with these uncertainties.

How to deal with UPOs? Faced with new technical practices where a large number of public normative issues have to be addressed but where plurality reigns, the first reaction is often to shortcut plurality and to call for rules and guidelines to control the uncertainties and to 'solve' the normative dilemmas at hand. However, rules assume a certain consensus and that is exactly what is lacking. Apart from that, not every situation is suitable for routines, rules and the rituals that arise from the call for control. This in particular applies to contexts where innovations occur: Innovative trajectories in global, public-private and multidisciplinary networks by definition imply uncertainties, vague boundaries and surprises. Instead of striving for strict regulation and for restricting normative plurality, in this sort of situations the attention should go first and foremost to the question how the plurality can be organised and how the competencies needed for gradually taking reasonable decisions are obtained and distributed. Philosophers in the pragmatist tradition argue for the acceptance of lack of control and for refraining from 'solving' an issue. From a pragmatic philosophical perspective, we should focus on the question how learning processes can be organised. In order to work out his idea, I will introduce the theory of the sociologist-economist Alfred Hirschman.

According to Hirschman, learning processes are stimulated when institutions or networks obtain feedback from 'clients', 'patients' or 'citizens' [Hirschman, 1970]. Hirschman distinguishes two main feedback mechanisms: 'exit' and 'voice'. When persons turn elsewhere for better products or services, they give feedback by making use of the 'exit' option. When persons articulate their experiences and opinions in order to stimulate the improvement of the quality of products and services, they make use of the 'voice' option. Although these two types of feedback are often identified with, respectively, private and pub-

lic institutions, with markets or with public monopolies, Hirschman argues for the importance of ‘voice’ for learning processes in public and private institutions. For ‘exit’ does not teach much: The product is rejected or refused without telling why. ‘Voice’ on the other hand implies that the public tell what they like or do not like about a product. ‘Voice’ offers the opportunity to do justice to the subtle and complex character of experiences with new products. According to Hirschman, ‘voice’ is especially a valuable feedback mechanism for learning about the quality of complex goods, such as child care, education, medical technologies or health care. In the case of such complex goods, it is not evident what ‘quality’ means. Individuals express different views on quality, and in discussing these views the ideas about quality might change. Especially when we deal with relatively new complex goods that are in the process of being developed, ‘voice’ is a major feedback mechanism, for it has to be discovered what the production of ‘good practice’ means. ‘Voice’ is therefore particularly suitable for those situations that *“can be defined as ignorance and uncertainty, shared by consumers and producers, about the manner of procuring a desired good or service, and in fact, about their precise nature. ... For a number of such goods and services, doubts are periodically reborn in the light of new experience. ... In such situations, then, the use of ‘voice’ rather than ‘exit’ is to be expected and recommended.”* [Hirschman, 1982, 221]. ‘Voice’, in contrast to ‘exit’, is informative. The *“contribution of ‘voice’ can clearly be of the greatest importance, simply because the information it supplies is rich and detailed as compared to the bareness and blankness of silent ‘exit’.”* [Hirschman, 1982, 220]. And especially in this kind of developing practices voice does not only mean the expression of clear-cut and ready-made arguments and opinions but also inviting the public to articulate the tacit, careful, uncertain aspects of ‘voice’, the so-called ‘hesitant voice’ [Benschop, 2003]. While clear-cut opinions are often well known and in this sense of minor importance for normative learning, ‘hesitant voice’ often implies that new and surprising insights and experiences will be made public, and that is what public learning processes are about — about making things public that were not public before [Latour, 2005; De Vries, 2004]. This line of argument applies very well to regenerative technology. In Hirschman’s words, the developing technological practice of regenerative medicine can be considered a complex good, in which most persons involved do not know what ‘the product’ will look like and in which no standards for ‘best practice’ are available as yet. Some major normative issues have to be dealt with, but it is not clear how. That is why the technological and normative learning processes in regenerative medicine can be characterised as ‘voice-prone’: This developing practice very much needs ‘voice’ from professionals and non-professionals in order to learn about actual experiences and to stimulate the development of normative frames.

However, when this developing technological practice of regenerative medicine is organised like a market, these normative learning processes will be impeded. When the innovation trajectory of regenerative medicine is organised following the idea that the technology will be offered to society and that the public can autonomously choose whether to make use of it or not, there will be only an 'exit' option. This way of organising feedback about regenerative medicine will not provide the necessary insight in the way the public feels about this technology and therefore does not provide clues to improve this practice. It will be obvious that the four main normative issues of regenerative medicine are not issues that can be simply solved. The only way to enable the public — professionals as well as non-professionals — to learn about these ethical issues, to improve the selection environment of regenerative medicine and to attune technology to society, is to organise 'voice'. The organisation of 'voice' should therefore be stimulated as an integral part of research and innovation programs in regenerative medicine. That way, the ethical issues at stake can be further articulated and a way forward has to be found by the actors involved. Organisations and institutions involved in regenerative medicine — be these universities, industries, government, patients' organisations or insurance companies — should also invest in organising 'voice' with regard to the ethics of body materials, the ethics of clinical trials, the ethics of insurability and the ethics of prevention. Technological and normative innovations can go together, but only when we do not forget to invest in the feedback mechanisms that make normative innovations possible.

Stimulating 'voice' is presented as a way to mediate between technology and society, but it is not the same as 'closing the gap' between technology and society. Organising 'voice' is not a guarantee for social trust in technology, on the contrary, the science historian Simon Schaffer has argued that there is not much difference between the issue of trust in the era of the scientific revolution and the current worries about trust in science and technology [Schaffer, 2005]. In the 17th century, a broad spectrum of mediating technologies was developed to deal with the lack of public trust in science: The public demonstration of an experiment, the detailed written representation of an experiment, the drawing. These techniques made it possible to convince the authorities to provide more scientific freedom and to continue research. However, the same mediating techniques constituted a new public of more or less laypersons discussing science and technology and asking new questions: The increase of trust and the increase of new public debate went hand in hand. We can thus conclude that the need for mediating between technology and society is no recent phenomenon but has been part of the development of technology for quite a long time. But we can conclude as well that we should not be naive about 'closing gaps' and 'producing trust'. Trust and distrust, the

freedom to act and ask critical questions go hand in hand. ‘Voice’ makes normative learning possible about complex goods like regenerative technology, but is also helps to stimulate plurality and to keep the discussion going.

To conclude: Innovations in regenerative medicine are confronted with four major ethical issues: the ethics of body materials, the ethics of clinical trials, the ethics of insurability and the ethics of prevention. Successfully stimulating regenerative medicine requires 1. that these public issues are studied, and 2. that ‘voice’ is organised among professionals and non-professionals so as to stimulate normative learning by being continuously in touch with the practical experiences with these issues.

REFERENCES

- Benschop, R., K. Horstman, R. Vos (2003). Voice beyond Choice. Hesitant Voice in Public Debates about Genetics in Health Care. *Health Care Analysis* 11 (2), 141-150
- Berg, M., A. Mol (1998). *Differences in Medicine. Unravelling Practices, Techniques, and Bodies*. Duke University Press, Durham
- Blume, S.S. (1997). The Rhetoric and Counter Rhetoric of a ‘Bionic’ Technology. *Science, Technology and Human Values* (22), 31-56
- Corrigan, O. (2003). Empty Ethics: the Problem with Informed Consent. *Sociology of Health and Illness* 25, 7, 768-785
- Derksen, M.H.G. (2005). *Negotiating the Body in Tissue Engineering*. Presentation XIX European Conference on the Philosophy of Medicine and Health Care, Barcelona
- Dickenson, D. (1997). *Property, Women and Politics: Subjects or Objects?* Cambridge University Press, Cambridge
- Dickenson, D. (2006). *Lichaam en eigendom*. Amsterdam, Boom
- Dijstelbloem, H., C.J.M. Schuyt, G. de Vries (2004). Dewey en de nieuwe politieke kwesties in de samenleving. In: E.R. Engelen, S. Dhian Ho (red.). *De staat van de democratie*
- *Democratie voorbij de staat*. Amsterdam University Press, Amsterdam, 113-134
- Epstein, S. (2004). Bodily Differences and Collective Identities: Representation, Generalisability, and the Politics of Gender and Race in Biomedical Research in de United States. *Body and Society* 10 (2). Special Issue: Bodies on Trial, 183-204
- Goldenberg, M.J. (2005). On Evidence and Evidence-Based Medicine: Lessons from the Philosophy of Science. *Social Science and Medicine*
- Gottweis, H. (2002). Stem Cell Policies in the United States and Germany: between Bioethics and Regulation. *Policy Studies Journal* 30 (4) 444-469

- Hartogh, G. den (2003). *Gift of bijdrage. Over morele aspecten van orgaan-donatie*. Rathenau Instituut, Den Haag
- Have, H.A.M.J. ten, J.V.M. Lelie (eds.) (1998). *Ownership of the Human Body: Philosophical Considerations on the Use of the Human Body and its Parts in Health Care*. Kluwer Academic Publishers, Dordrecht
- Henon, P.R. (2003) Human Embryonic or Adult Stem Cells: an Overview on Ethics and Perspectives for Tissue Engineering. *Advances in Experimental Medicine and Biology* 534, 27-45
- Hilvoorde, I. van, B. Pasveer (2005). *Beter dan goed. Over genetica en de toekomst van de topsport*. Veen Magazines, Diemen
- Hirschman, A.O. (1970). Exit, Voice, and Loyalty — Responses to Decline in Firms Organisations, and States. Harvard University Press, Cambridge Mass. In: A.O. Hirschman (1982). *Shifting Involvements — Private Interest and Public Action*. Princeton, University Press, Princeton
- Horstman, K., R. Houtepen (2005). *Worstelen met gezond leven. Ethiek in de preventie van hart- en vaatziekten*. Het Spinhuis, Amsterdam
- Horstman, K. (forthcoming). Lifestyle, Genes and Cholesterol. A New Arena of Struggle about Responsibility and Solidarity. In: G. de Vries, K. Horstman. *Genetics from Laboratory to Society*. Palgrave Macmillan (Health Technology Series), Basingstoke
- Huijjer, M., K. Horstman (2004). *Factor XX. Vrouwen, eicellen en genen*. Boom, Amsterdam
- Jochemsen, H., E. Garcia, R. Harris (2004). *Human Stem Cells. Source of Hope and Controversy*. Lindeboom Institute/Business Ethics Center of Jerusalem, Ede/Jerusalem
- Kater, L. M. Kirejczyk (2005). Kennis, beloften en de ontwikkeling van ethisch beleid. In: *Kennisvragen in de polder*. Jaarboek Kennissamenleving. Amsterdam, Aksant. 55-70
- Kent, J., A. Faulkner, I. Geesink, D. FitzPatrick (2006). Towards Governance of Human Tissue Engineered Technologies in Europe: Framing the Case for a New Regulatory Regime. *Technological Forecasting & Social Change* 73, 41-60
- Latour, B., P. Weibel (eds.) (2005). *Making Things Public. Atmospheres of Democracy*. MIT Press, Cambridge Mass/ ZKM Karlsruhe
- Lock, M. (2002). *Twice Dead: Organ Transplants and the Reinvention of Death*. University of California Press
- Lupton, D. (1995). *The Imperative of Health. Public Health and the Regulated Body*. Sage, London
- Patrick, C.W. jr., A.G. Mikos, L.V. McIntire (1998). *Frontiers in Tissue Engineering*. Pergamon, Oxford
- Porter, T. (1995). *Trust in Numbers: the Pursuit of Objectivity in Science and Public Life*. Princeton University Press, Princeton

- Ratner, B.D. (ed.) (1996). *Biomaterials Science. An introduction to Materials in Medicine*. Elsevier Academic Press, San Diego
- Resnik, D.B. (2002). The Commercialisation of Human Stem Cells: Ethical and Political Issues. *Health Care Analysis* 10, 127-154
- Schaffer, S. (2005). Public Experiments. In: B. Latour, P. Weibel. *Making Things Public. Atmospheres of Democracy*. MIT Press, Cambridge Mass/ ZKM Karlsruhe
- Stone, D. (1997). *Policy Paradox: the Art of Political Decision-Making*. Norton, New York
- Swierstra, T. (2004). Een tumor is ook een collectief bezit. Het afstaan van lichaamsmateriaal ten behoeve van DNAS banken. *Krisis. Tijdschrift voor empirische filosofie* 5, nr. 4, 36-54
- Tijmstra, T. (2004). *Humane genetica en samenleving. Bouwstenen voor een ander debat*. RMO Advies 29, Den Haag
- Timmermans, S., M. Berg (2003). *The Gold Standard. The Challenge of Evidence Based Medicine and Standardisation in Health Care*. Temple University Press, Philadelphia
- Trappenburg, M. (1993). *Soorten van gelijk. Medisch-ethische discussies in Nederland*. Tjeenk Willink, Zwolle
- Vries, G. de, K. Horstman (forthcoming). Learning from the Work that Links Laboratory to Society. In: G. de Vries, K. Horstman (eds). *Genetics from Laboratory to Society*. Palgrave/Macmillan, Basingstoke
- Wert, G. de, C. Mummery (2003). Human Embryonic Stem Cells: Research, Ethics and Policy. *Human Reproduction* 18, 4, 672-682
- Wilkinson, S. (2000). Commodification Arguments for the Legal Prohibition of Organ Sale. *Health Care Analysis* 8, 189-201
- Willems, D., T. Swierstra (2005). Ethics and Diversity in Clinical Research. In: N. Wieringa et al. (eds.) *Diversity Among Patients in Medical Practice: Challenges and Implications for Clinical Research*. Amsterdam, Universiteit van Amsterdam. 111-128

Discussion and Conclusions

John Jansen¹, Maurits Doorn²

In this case study, we have discussed regenerative medicine, an emerging field of medical research with the objective to develop therapies that make use of the capacities of the human body to repair itself. This is in contrast with conventional medical approaches that treat tissue-related conditions through removal of the damaged tissue or by replacing it through transplantation or implantation. The essence of regenerative medicine is that it attempts to recreate the original tissue function by triggering the regenerative capacity of native tissue.

The treatment of defective tissues has been one of the key issues in medical practice and research for centuries. Although effective therapies were developed in the course of the twentieth century using implants or organ transplantation, such therapies do have disadvantages. For example, organ transplantation is associated with rejection and implants are prone to failure. Regenerative medicine promises solutions for these problems.

¹ Radboud University Nijmegen, Nijmegen, the Netherlands.

² STT, Den Haag, the Netherlands.

This promise of regenerative medicine is based on the convergence of developments in several fields of technological development in the last decades of the twentieth century. Advances in life sciences and in biotechnology provided a better insight into physiological processes of tissue development as the biochemical, and cellular processes were better understood. At the same time, in materials science, it was discovered through experimentation with synthetic materials used for the manufacturing of implants that some synthetic materials have bioactive properties. These properties result in the formation of a chemical bond between tissue and implant. The combination of results in these fields opened up a space to explore new possibilities. The key shift was that if synthetic materials can evoke a physiological healing response, such materials can also be used to trigger physiological processes underlying the regeneration of native tissue.

The tissue-engineering paradigm that emerged in the 1990s was the first attempt to explore the possibilities in this field. This was the beginning of a period of optimism. It was suggested that in the near future a generic production technology for the in vitro production of human tissues and organs (a 'body-shop') could be developed. The central idea guiding the development of tissue-engineered products was to regenerate tissues and organs outside the patient's body, preferably using the patient's own cells. However, this turned out to be an unrealistic promise.

Some tissue-engineered products have been introduced in clinical practice, in particular tissues like cartilage, skin and bone that are considered 'simple' compared to entire organs. However, in general these products were not able to meet expectations. With the advantage of hindsight, the underlying ideas of the tissue-engineering paradigm were an example of mono-dimensional thinking. Obviously, 'scientific' and 'technological' complexities were underestimated, and the uptake of these technological novelties in the real-life context of the medical sector was more problematic than expected. The chances to come up with a generic manufacturing strategy for tissues and organs were overestimated. Manufacturing tissue-engineered transplants was much more complex and time-consuming than expected, and transplants could not be provided off the shelf to physicians and surgeons. In addition, contradictory results were reported regarding the clinical efficacy of the launched products.

It is obvious that promises made with regard to tissue-engineering programmes were too daring. For a newly emerging field of research, the articulation of expectations and promises is a necessary step in agenda setting and resource mobilisation. Such a process can give direction to the field and help to create a protected space where possibilities can be further explored.

In the case of tissue engineering, a focus on short-term results in combination with commercial pressure forced researchers to overstate expected outcomes. Such over-blown promises, made by researchers but heartily welcomed by policy-actors, financiers, industry and the media, resulted in a cycle of hype and disappointment. Ultimately, as actual developments were not able to meet expectations, this affected (and still affects) the field. It has resulted in loss of trust, both with the public and with financiers/sponsors. In addition, the unrealistic commitments made it difficult to flexibly deal with the contingencies and setbacks of the development process and to adapt to new insights on the way.

After this period of research within the tissue-engineering paradigm and the ensuing ‘crisis’, the field of regenerative medicine currently enters a new phase. Alternative lines of development are now explored toward the objective of tissue regeneration. These efforts partly use capabilities developed in the context of tissue engineering, such as the use of growth factors and scaffold materials, and combine these capabilities with recent results in genomics, proteomics and in particular stem cell research (‘cell-omics’).

Unlike the over-optimistic situation of the late 1990s, the ideas expressed today about future developments in the field of regenerative medicine seem to be less mono-dimensional. In view of this, multiple lines of technological development are being evaluated for multiple application areas and acknowledging the longer time-spans needed for introduction in medical practice. Contrary to earlier developments, the focus is not on the development of generic manufacturing capabilities for tissues and organs, but it is now recognised that each separate application has specific challenges, requiring a focused custom approach.

In this case study two examples of such development lines are discussed in detail. The chapter about spinal fusion discusses the use of biomolecular growth factors (BMPs) for spinal fusion (see the chapter of Delawi et al. ‘Spinal Fusion’). It presents the first successful experiments with BMPs in orthopaedic surgery as first steps toward a promising transition from an ‘age of reconstruction’ to an ‘age of regeneration’ in spinal surgery. The extensive research performed on BMPs in the last decade provided new insights into the regeneration mechanisms of cartilage and bone, opening up possibilities for the development of causal therapies. The effective application of such therapies will depend on the complementary development of minimally invasive surgical techniques and improved diagnostics. The chapter about cardiac cell therapy discusses whether cell therapy provides a viable approach to mend broken hearts (see the chapter of Fernandes et al. ‘Cardiac Cell Therapy’).

The results of early clinical trials have resulted in an immediate and unreserved acceptance by the scientific community, but recent studies tempered the enthusiasm. Possible regenerative therapies for the treatment of heart failure may well be different from the ones imagined today, but today's experiments may provide valuable first steps if the results are considered open-minded and critically, with a willingness to learn from successes as well as from failures. In particular regarding stem cells, a second or third order derivative may in the end turn out to be the successful approach for accomplishing the objective.

Furthermore, the development of regenerative techniques is also hampered by limitations in the use of laboratory animals and extensive clinical trials. As a consequence, improved model systems have to be designed for the translation of the available basic knowledge so that they can be used in clinical practice. The chapter about tissue models illustrates how the original idea of in vitro tissue manufacturing is now taken up to manufacture so-called 'living' biological models in an attempt to provide such an improved model system (see the chapter of Bouten 'Tissue Models'). The use of in vitro model systems in addition to in vivo tests can be very helpful in the reduction of risk and can result in a more efficient use of in vivo animal studies. Engineered 3-D models offer a physiologic environment which can include various cell types and also human cells. They also offer the potential of reproducible disease-specific screening environments.

The examples in the case study reflect that currently there is a greater awareness of the real-life intricacies and complexities that are encountered as these novel ideas and experimental therapies emerge in the reality of clinical practice and the broader context of the medical sector. It is not possible to sidestep the technological complexities, and it is necessary to explore relevant niche applications. As such, the development of regenerative therapies is not only a matter of science and technology, but these therapies will also be shaped by factors as diverse as health insurance systems, economics, regulation and social and ethical issues. In order to deal with this complexity, the development of regenerative medicine requires a step by step learning approach and a long-term commitment with respect to both technological and non-technological issues. If such an approach is not taken, there is still the risk of another round of hypes as in tissue engineering. For instance, the hype that recently emerged regarding the applications of stem cell therapies might have consequences for the broader field of regenerative medicine. The lack of an adequate regulatory environment and established working practices lead to scientifically inadequate experiments based on trial-and-error treatments of patients. The results of such studies are usually rarely studied in a systematic way and may sometimes even be ethically questionable.

Horstman (see the chapter of Horstman ‘From Laboratory to Practice’) also stresses the need for a step by step learning approach in her discussion of ethical issues in regenerative medicine. Following the development trajectory from laboratory to medical practice, she identifies four clusters of normative issues that emerge as regenerative therapies are in the making. These clusters of ethical dilemmas concern:

- the value of the human body;
- the step from the laboratory to clinical experiments;
- the introduction in regular health care;
- the promise of preventive medicine.

The ethical dilemmas encountered in these clusters are not easily solved, because there is no universal approach to these ethical dilemmas. Fernandez and Hendriks, for example, discuss that although regenerative therapies are developed today, it is not clear what the eventual regenerative therapy will look like, because there are no standards or ‘best practices’ as yet. It is therefore not possible to deal with the related ethical issues in advance. Horstman discusses some examples of ‘competitive’ approaches to the ethical dilemmas but concludes that these are incompatible and that therefore a pragmatic approach is necessary: Instead of focusing on solving ethical issues in advance, these issues have to be articulated and addressed in a learning process linked to the technological development process. Such an approach will not ‘close the gap’ between science and society, but it may help to find a socially acceptable way forward.

Important issues in the articulation of the expectations and promises of regenerative medicine are misunderstanding and lack of knowledge among both insiders and outsiders. For instance, whereas engineers can have difficulty in understanding clinical problems and requirements, clinicians do usually not have a sufficient insight into underlying scientific phenomena. Obviously, such cognitive problems can be a source of confusion and may lead to an inefficient use of means and money. At the same time, outsiders such as investors and granting foundations demand early valorisation, thus involving researchers in strategic and political games reflecting neither actual developments in science and technology nor the actual needs in medical practice. As a result promises and expectations can be created that are completely unrealistic and not feasible in the time-frames demanded by investors. That is why successful research programmes require a committed long-term involvement of all relevant partners. Multidisciplinary research teams also have to create coherence in their experimental programmes based on shared, realistic and medically relevant goals. An additional critical issue is the communication of the obtained knowledge to society. Especially in the area of regenerative medicine there has been

an obvious failure in this communication process resulting in an erroneous perception of this future technology. The lack of accurate and balanced information concerning the risks as well as the potentials of a new development can hamper its final implementation. A realistic public image can only be obtained by emphasizing the practical and life-improving societal benefits of regenerative medicine while at the same time painting a realistic picture of the risks.

On the basis of all efforts and results as obtained till now, it can be concluded that cell-based in vitro approaches do not seem practical in the near future for the development of regenerative therapies. On the other hand, in vitro techniques can be used as model systems for the development and testing of new drugs and therapies as well as provide more knowledge of physiological and pathological cellular processes.

The same seems to apply to cell therapy. Due to its complexity, the underlying mechanism and final activity of this method is yet poorly understood. For example, wound healing starts with the formation of a blood coagulum, which is followed by an inflammatory response. Growth factors and other cytokines are involved in this initial body reaction and initiate in a concerted action a cascade of processes that ends in the proliferation and differentiation of resident adult stem cells into dedicated cells that support the healing response. It is unknown how cell therapy can trigger, and is involved in, such a process.

Growth factor-induced tissue regeneration appears to be more feasible in clinical practice, because this entails a direct biochemical cell triggering similar to the application of drugs. In addition, growth factor-based tissue regeneration allows the manufacturing of directly available products (in stock and not on demand). However, a wide-spread market penetration will not occur before optimal scaffold materials become obtainable, which are easy to handle by clinicians and provide a standardised, predictable release pattern of the growth factors included. The final release profile of the growth factors is relevant in order to create systems that are affordable in clinics from the point of view of both cost and reimbursement (by health care insurance companies).

In the long term, it will perhaps be possible to develop a smart synthetic material that stimulates tissue regeneration by its intrinsic inductive properties, completely independent from the additional supplementation of growth factors and/or cells. Present information already supports the feasibility of such materials, which are based on a merger of nanotechnology and regenerative medicine. Additional knowledge of, for example, growth factors, cell signalling, stem cells, biomaterials and surface technology is required to determine the final added value of this recent development.

FUTURE PERSPECTIVES

TOWARD EARLY INTERVENTION

At the moment, regenerative medicine is emerging as a new approach to the diagnosis and treatment of medical diseases and disorders. What will be the ‘added value’ of this new approach when compared to existing therapies? Because large series of very expensive clinical trials will be required to provide evidence about the clinical efficacy of regenerative medicine, it is difficult to prove the benefits of new regenerative therapies when directly compared to existing therapies. To fully reap the benefits promised by regenerative medicine, a completely different approach may be required as compared to that of current medical treatment. One approach would be a shift toward the earlier stages in the disease spectrum, employing the potential of regenerative therapies to intervene earlier in a disease process than is possible with conventional therapies.

Tissue regeneration aims to support and expand the self-healing capacity of the human body. The underlying philosophy is that body tissues are able to completely regenerate when the underlying biomolecular and cellular processes are in balance. A serious disruption of this balance, e.g. by disease or trauma, causes the regenerative capacity of the body tissues to decline. It can therefore be assumed that for many degenerative diseases an early intervention can reverse or even prevent the degenerative process and allows the return to a balanced situation in which self-healing is possible. Thus, when the regeneration of a damaged tissue or organ is the preferred treatment option, the entry point of regenerative medicine can shift toward an earlier phase in the disease continuum. Regenerative medicine is perfectly suited to play a key role in such an approach. However, it has to be noticed that this is only possible when certain critical conditions are met. For example, early preventive treatment is closely associated with early diagnosis. That is why considerable improvements in the predictive value of current diagnostic methods have to be made in order to indeed allow such recognition of threatening tissue defects at an early stage and to prevent over-treatment. This is not only a matter of diagnostics but also raises ethical dilemmas, as healthy persons are confronted with risks of any future disease and medical intervention, although there is no actual problem (as yet). Besides, preventive medicine always includes the danger of increasing health care costs, a risk that becomes even greater in an ageing society. Finally, preventive medicine is only useful when patients are prepared to adapt their lifestyle and disease supporting behaviour.

DEDICATED RESEARCH PROGRAMMES

In the previous millennium, the principles of tissue engineering not only revolutionised our way of thinking about health care problems but also showed that we need a complex process of convergence between clinical disciplines and a wide variety of biological and engineering sciences. In this context, it has to be emphasised that such 'media attractive' developments can easily result in a hype with a peak of inflated expectations characterised by increased visibility but with a low grade of maturity. This in turn is frequently accompanied by the establishment of extensive research programmes with apparently well-defined end goals, suggesting that serious socio-economic benefits can be achieved within a very narrow time frame. In practice, such research programmes lack focus, because no clear choices have been made and a really unachievable aim has been set. The wide variety of sub-themes and sub-projects characteristic for such programmes often results in a lack of coherence, ineffective cooperation and disappointing productivity. In addition, the suggested early valorisation results in additional research programmes with a serious involvement of the industry. The companies, however, expect short-term results and products under pressure of their stake-holders. Subsequently, a closed circle is created that leads to overstretched expectations, followed by the characteristic trough of disillusionment that often follows the hype. In the end, all the participants become disappointed, and the interest in a development that in principle was promising, fades away.

In order to avoid this kind of hype-driven research and to establish an effective knowledge infrastructure and research climate, a long-term vision has to be developed. At the moment, the regular time frame for a research programme is 4-5 years, which, in the biomedical field, is too short to achieve and finalise the goals set. As a consequence, the structure of current research programmes results in short-term behaviour and the continuous creation of surrogate successes. In view of this, broad and dedicated research programmes have to be launched, which cover the multidimensionality of the field while retaining a strong cohesion. Such programmes should not only involve scientific research and technology developments but should also pay attention to contextual issues that arise as these technologies become embedded in society. Why such issues are not trivial has been discussed by Horstman with regard to the social and ethical issues, while regulatory, economic and other issues have been addressed in other chapters. A way forward can only be found if such non-technological issues are addressed simultaneously with scientific research and technology developments in a step by step learning process. Further, a critical part of research and development programmes which claim to provide health care solutions is to give balanced information and, when required, education about the implications and potential societal

benefits of these new technologies in health care.

Apart from dedicated programmes, the maintenance of open technology grants is required. They offer the possibility for the development of new knowledge in a free, less constraining 'armour'. In the end, this kind of research will prove to be the nurturing ground for a profitable knowledge industry.

Introduction

Fred van Roosmalen¹, Maurits Doorn²

A SMALL HISTORY OF MINIATURISATION

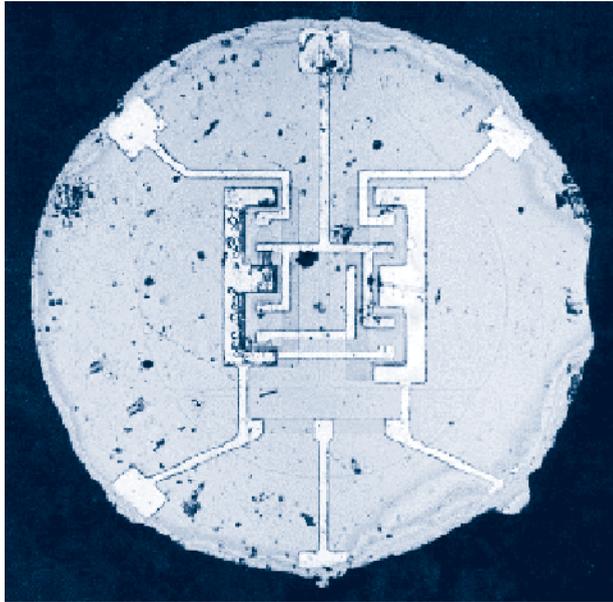
When the later Nobel prize Richard Feynman gave his talk ‘There’s Plenty of Room at the Bottom’ at the 1959 Caltech end-of-the-year event [Feynman, 1960], few people will have imagined that most of his predictions were to turn into reality before the end of the century. Feynman’s presentation was on ‘manipulating and controlling things on a small scale’ and the first question he asked his audience was ‘Why cannot we write the entire 24 volumes of the Encyclopedia Britannica on the head of a pin?’ After which he quickly demonstrated that a conventional half-tone reproduction on this scale would allow for some 1000 atoms per dot, a level of detail that is readily visible through an electron microscope. This argument does not say anything about practical execution, but that is not the point. Its strength is in the insight that many seemingly impossible questions on miniaturisation can be answered from realising that the Laws of Physics do not forbid it.

¹ Philips Semiconductors,
Eindhoven, the Netherlands.

² STT, Den Haag, the Netherlands.

Figure 1

First integrated circuit (IC) [Moore, 2003].



In that same year 1959, Texas Instruments' engineer Jack Kilby submitted a patent request called 'Miniaturised Electronic Circuits', on making resistors and capacitors in semiconductor technology together with transistors on one and the same silicon substrate. A concept which at that time existed only on the drawing table — Figure 1 shows the demonstrator realised one year later — but what became quickly known as the integrated circuit (IC).

Just a few years later, Intel co-founder Gordon Moore postulated a bold theorem that predicted exponential growth in IC complexity [Moore, 1965]. As years went by, it turned out that Moore was right, and the theorem became widely known as Moore's Law. Frequently and erroneously quoted as some force of Nature that doubles anything in high-tech, Moore's Law is an economic argument which states that the cost of delivering digital functions on silicon wafers — for example, storing one bit of information — can be halved every two years. It is this cost-down enabler that has allowed the electronics industry to expand with double-digit growth over most of its present lifetime.

Figure 2 shows Moore's prediction together with the evolution of dynamic random-access memory (DRAM), which has been the dominant stand-alone memory device for almost as long as the industry exists. The graph starts at $T=1$, marking Kilby's invention of an IC with one transistor. The eventual result was not as dramatic as in Moore's forecast, but the growth turned out to be exponential all-right, with the largest single circuits of today ($T > 1,000,000,000$) carrying as much transistors as there are people on Planet Earth.

Figure 2

Transistors per circuit; dotted line: Moore's original prediction, drawn line: DRAM actual [Moore, 2003].



Two technological developments have paved the way for Moore's Law: minimum pattern dimension (decreasing) and wafer size (increasing). In 1965, manufacturing relied on 25-mm substrate wafers; now it is 300 mm. At the same time, the smallest patterns on these wafers have been reduced from several times the size of a red blood cell (6-8 micrometre) to that of the common cold virus (20 nanometre).

Very soon after the demonstration of the single-wafer-IC from Figure 1, multiple circuits could be realised on one substrate. From that point on, finished wafers were diced into individual silicon chips, provided with contacts for soldering on a printed circuits board (PCB), then encased in plastic for ease of handling, which results in the all-too-familiar picture of the IC as a headless silver-legged bug with a company stamp on its back. Because of its place in the semiconductor manufacturing chain, the production of the circuit on the wafers is traditionally called front-end, while the flow starting with dicing is called back-end, also known as assembly and packaging.

Identifying and predicting the key parameters and main technical challenges in the industry has become a science in itself through the International Technology Roadmap for Semiconductors [ITRS]. Today, the ITRS is a global forum populated by semiconductor makers, equipment and material suppliers, institutes and universities. The information provided in its annual symposia plays a leading role in determining the world's semiconductor technology agenda.

FROM MICRO TO NANO

At the start of this millennium, the processes used by leading semiconductor manufacturers for the production of state-of-the-art high-density logic circuits crossed the official 100-nanometre border between 'micro' and 'nano'. Over the past few years, nanoelectronics has become the common denominator for a broad suite of technologies having in common that they are all based on or related to silicon semiconductor manufacturing in some way or another. Figure 3 shows that the semiconductor industry is the cornerstone of the high-tech economy already today, as it provides the essential hardware for electronic product and service innovation in growth markets such as automotive, avionics, consumer electronics, telecommunications, medical systems and manufacturing. More and more, innovation and value creation in these markets stems from nanoelectronics.

But nanoelectronics is more than nano alone; it encompasses a broad variety of functions and options doing more than 'just' digital computing. And this variety is still growing, requiring an increasing number of scientific disciplines, from the obvious electronic engineering and solid-state physics and chemistry, to (nano)mechanics, (nano)fluidics, and (nano)biology. While nanoelectronics is certainly not as broad as nanotechnology, it has rapidly expanded beyond its origin in 'simple' silicon semiconductor technology.

Nanoelectronics enables electronic systems by switching, storing, receiving, and transmitting electrical data and signals, by providing suitable connections to power sources, and by sensing and actuating non-electrical data for conversion into electrical information and vice-versa. Figure 4 shows a generic outline of an electronic system, indicating its 'brain' (compute) and the system's other 'body functions' (interact), the 'ears, eyes, arms, and legs'. It is obvious

Figure 3
Global high-tech market size [Future Horizons, 2005].

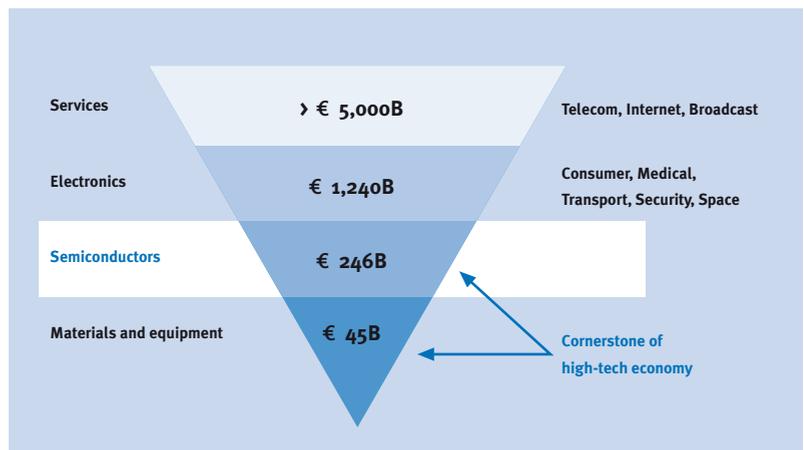
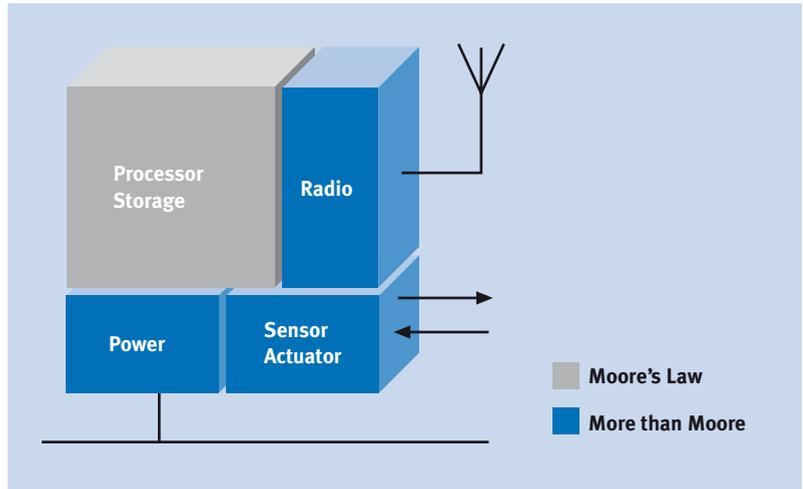


Figure 4
Generic electronic system outline.



that personal computing and internet access meet this description, but also a cell phone, a television set, and a CD or DVD player fit the outline. Physically larger but equally complicated electronic systems are automobiles and airplanes; at least 25% of the value of these products nowadays is in the electronics. Even less obvious systems that still meet the outline are pacemakers and smart cards (SIM, RFID), and household appliances such as dishwashers and shavers.

The pervasive presence of nanoelectronics is closely connected to the notion of ambient intelligence. The world of ambient intelligence has been defined as 'environments that are sensitive and responsive to the presence and needs of people, characterised by many invisible devices distributed throughout the environment, devices that know about their situational state, that can recognise individual users, tailor themselves to each user's needs, and anticipate each user's desires without conscious mediation' [Van Roosmalen, 2005], which is exactly what electronic systems as outlined in Figure 4 will do.

POLITICAL IMPACT

Because of the importance of nanoelectronics as a driver for innovation and economic growth, policy makers have become increasingly interested. Today, nanoelectronics is highly visible on global as well as national level. In Europe, a major step forward was the recent installation of ENIAC (European Nanoelectronics Initiative Advisory Council), the European Technology Platform (ETP) for nanoelectronics. ENIAC is an industry-led initiative bringing together leading industrial and academic groups with national and European bodies to establish and implement a coherent and integrated European

research and development strategy. The initiative has its roots in the EUREKA programme cluster MEDEA+, a transnational cooperation between industry and EC member and associated states.

On the national level, the Dutch Innovation Platform has outlined a strategy to improve innovation and growth by focusing on key areas that represent existing strengths and excellence. One of these key areas defined by the Platform is High Tech Systems and Materials. Plans are now being developed to enhance and stimulate the Dutch economy based on the vision that a world-class ecosystem must be created in the area of nanoelectronics and embedded systems, the two critical enablers for innovation in this key area. This ecosystem is expected to become a breeding ground with global visibility for major players because of its unique combination of strengths in the value chain and the proven track record for success of its industry. Critical mass is provided by having large industrial players foster SME and start-ups in emerging segments throughout the economic value chain, and by enabling research infrastructures in which industry stimulates innovation-focused scientific research and education, and vice-versa.

These developments underline the need for a thorough analysis of nanoelectronics, especially in the technology domains relevant for the Netherlands and its immediate environment. This analysis must show what opportunities are addressed by nanoelectronics, and what consequences that will have for society. Questions to be answered include whether the evolution of nanoelectronics is driven by application pull or by technology push, how roadmapping and forecasting must be done, and what the impact will be on system partitioning and the evolution of the overall value chain.

DISRUPTION AND CONVERGENCE

The possibility to combine a rapidly increasing number of digital functions on one IC has caused a virtual implosion of all systems requiring large amounts of electronic circuit overhead. Early computers that would easily fill multiple file cabinets with individual components collapsed into a single drawer, then a single PCB, and eventually, a single silicon chip. With size, also the cost came down at an even higher speed, while performance went up. For example, the cost of computing power expressed in mega-instructions per second (MIPS) is decreasing with a factor of 1000 per decade, a process which is already going on for at least half a century.

As a result, computing became affordable for non-military applications, then

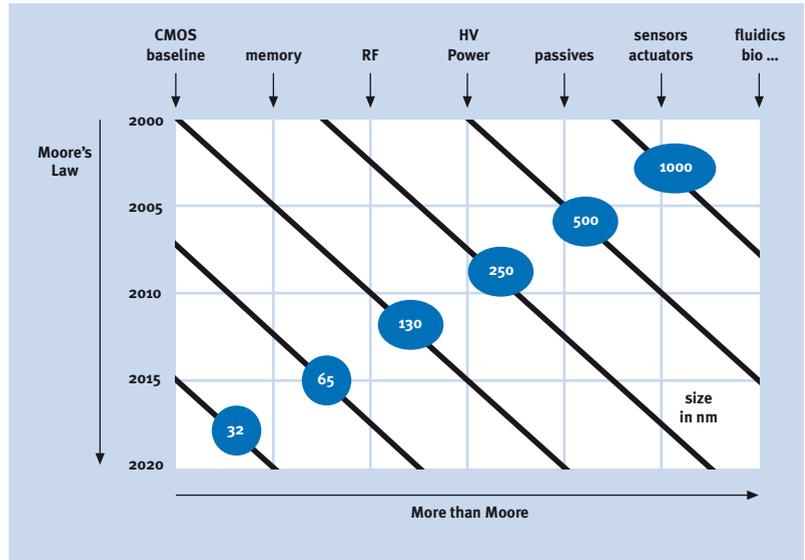
for individual office workers, and eventually for consumers. The step from a handful of mainframe systems to many millions of personal computers (PC) was a major disruption in the market, opening the way to new players and causing established names to disappear from the field entirely. A similar exponential growth curve resulting from technical miniaturisation is seen in hard disk drives (HDD). The cost for storing one megabyte of information is decreasing with the same factor of 1000 per decade; this, too, caused disruptions in subsequent product generations and in the position of the market leaders [Bower, 1995].

It should be noted that the disruptions indicated above mostly are in the electronic products and services. The underlying technologies supporting these disruptions are evolving on a much more continuous scale, in semiconductor circuits as well as in magnetic storage. Not just by improving the existing electronic products and services that constitute electronic systems, but extending these systems with new concepts and features. Through this ongoing cascading of old and new processes, nanoelectronics is an amalgamate of growing complexity that can truly be called a converging technology. One can say that nanoelectronics as a whole is disrupting rather than disruptive, as many of the individual new additions to the overall semiconductor manufacturing technology portfolio will have been a disruption for the equipment and material suppliers.

Moore's Law predicts the evolution of digital logic, the 'brain' of all electronic systems, by providing more transistors at the same overall price, thus increasing data storage capability and computing power. But a brain also needs intelligent interaction with its environment, as exemplified in Figure 4. Micro and nanoelectronics have made it possible to realise the necessary 'ears, eyes, arms and legs', using processes derived from the manufacturing of conventional transistors for digital logic. However, the device structures associated with these non-digital functions do not necessarily scale with minimum pattern dimensions. Radio communication, for example, relies on dimensions determined by the transmission frequency. Mains power circuits are limited by electrical breakdown fields. Sensors for non-electrical interactions often rely on mechanical phenomena through microelectromechanical switches (MEMS), such as the acceleration sensors triggering automotive airbags.

To meet the overall system cost-down drive, also the non-digital-logic features need to be miniaturised, but that evolution is along paths deviating from the 'simple' minimum pattern-size direction of Moore's Law. Together, the technologies enabling these features have become known as the 'More than Moore' group of processes. Figure 5 shows Moore's Law and the overall More than

Figure 5
Two-dimensional nanoelectronics
technology roadmap.



Moore miniaturisation trends in a single 2D diagram. The evolution of baseline CMOS, the common technology used in making digital logic, is depicted on the far left side of the graph, with the minimum pattern dimension associated with the latest technology node. The scale on the horizontal axis is the increasing technological deviation from baseline CMOS needed to accommodate the associated More than Moore functionality, ranging from memory processes being very close to baseline CMOS to the 3D sculpting for fluidics that is only remotely related.

Common denominator in all technologies is still size reduction at a rate similar to what follows from Moore's Law but with (much) larger absolute dimensions. Modern baseline CMOS, for example, is already well below 100 nm, while MEMS sensors have just entered the submicron domain. An interesting conclusion that can be deduced from this graph is that production infrastructure for digital logic becoming obsolete at the left side of the graph at some point in time may be re-used for devices in More than Moore technologies emerging from the right.

Finished semiconductor products look quite simple, and from that, packaging seems easy, with one product containing one silicon chip. This might have been true in the past but not any more. Today, functions that cannot be conveniently incorporated in one single wafer process in order to be combined in a System-on-Chip (SoC), are increasingly built together in a System-in-Package (SiP), combining multiple chips in a single outline, each chip with its own dedicated wafer process. The interior of such packaged products can be quite complicated, certainly if MEMS devices are involved. MEMS devices need

room to move; some even need a controlled atmosphere for proper operation. Combining multiple technologies in one SiP solution is also called heterogeneous integration.

Looking again into Figure 5, it will be clear that the left hand side of the graph is associated with SoC, with a single die and relatively simple packages, while the right hand side requires SiP with multiple die and more complicated packaging. One may say that SiP is to SoC what More than Moore is to Moore's Law, providing the system designer with again an extra dimension for creating new system opportunities.

A VIEW ON THE FUTURE

Forty years after its conception, Moore's Law is still showing the way for digital logic, but the overall pace is gradually slowing down. Medium-term ITRS predictions state that density doubling in the most advanced processes will decrease from once every two years to once every three years. This is believed to be caused by a combination of soaring investments for volume manufacturing in advanced CMOS and stagnating circuit performance resulting from running into physical limitations of advanced CMOS miniaturisation. To cope with the latter, investigations have started to identify alternative switching and interconnect structures 'beyond CMOS' that can replace today's conventional CMOS devices. 2013 has been mentioned as the first moment of incidence for these alternatives to baseline CMOS [Van Roosmalen, 2005].

Triggered by the gradual deceleration of the logic roadmap, the More than Moore and SiP clusters are gaining ground today, offering alternative ways to improve overall electronic system value. Multi-chip packaging, the essential technology enabler in SiP, has started growing rapidly from 2003 onward, which demonstrates that the technology has now gained market acceptance [IC Insights, 2006]. An interesting side effect of this evolution is the traction generated toward further integration into one package of non-logic functions that so far resided elsewhere in the electronic system or PCB.

A category in nanoelectronics strongly influenced by the drive to system integration is the family of MEMS devices. MEMS have 3D sculpting as common denominator, and are mostly based on processes derived from traditional semiconductor wafer manufacturing. MEMS commonly available in the market today are used for sensing pressure and acceleration in automotive applications but also in video projectors (moving mirror arrays) and inkjet printers (fluidic arrays). Traditionally, MEMS is a niche market, but some

devices are now finding inroads in emerging volume markets for consumers, such as feature phones. Recent market reports predict a growth for MEMS as much as twice as high as the total semiconductors market growth [Yole Développement, 2005].

In terms of dimensions, large-area electronics (LAE) is at the far side of the nanoelectronics technology spectrum. Based on processes from PCB manufacturing rather than from the silicon wafer industry, LAE offers alternative integration schemes that can be considered as extended packaging. Also here, the objective is to pull-in multiple external functions in one integrated product but on a still larger physical scale. Typically targeted areas are flexible circuits for RFID, flexible displays, and flexible lighting. In LAE, the obvious challenge lies in the essential combination of nano, micro and macro in one single design.

The value chain in nanoelectronics is very much segmented, with a limited number of highly specialised players in each segment. Throughout this value chain, deliverables are steadily pushed down from customer to supplier. For example, mobile phone makers increasingly request IC manufacturers to develop the complete hardware interior, keeping only the physical outline and the user software. Further down the chain, IC manufacturers ask suppliers of production equipment to develop and maintain the processes executed on their equipment. Obviously, even moderate concept changes in the IC manufacturers' technology can result in significant disruptions elsewhere in the value chain.

In the following chapters, a more detailed analysis is provided of the developments in nanoelectronics. First, expectations about the role of nanoelectronics in society will be further articulated. Nanoelectronics in combination with embedded systems technologies are presented as key enablers for materialising the promises of ambient intelligence. This is detailed further for the relevant application domains. The next chapter explains the innovation dynamics in the existing value chain for semiconductors, followed by two chapters providing an in-depth review of developments of More than Moore technologies enabling heterogeneous integration and polymer electronics as an enabler for new large-area electronics applications. The final chapter discusses how innovation in nanoelectronics can be promoted from the perspective of the SMEs, start-ups and other ventures pursuing opportunities outside the existing value chain. The case study is concluded by a general discussion in which recommendations will be formulated for the actors involved.

REFERENCES

- Bower, J.L., C.M. Christensen (1995). *Disruptive Technologies; Catching the Wave*. Harvard Business, January-February
- Feynman, R.P. (1960). There's Plenty of Room at the Bottom. *Engineering & Science*, Caltech, February
- Future Horizons (2005). *International Semiconductor Forecast Seminar 2005*, London
- IC Insights, Inc. (2006). *The McClean Report*. 9th Edition
- ITRS. *International Technology Roadmap for Semiconductors* (<http://public.itrs.net>)
- Moore, G.E. (1965). Cramming More Components onto Integrated Circuits. *Electronics* 38, April
- Moore, G.E. (2003). *No Exponential is Forever*. International Solid-State Circuits Conference 2003, San Francisco
- Roosmalen, A.J. van (ed). (2005). *ENIAC Strategic Research Agenda*, 1st Edition
- Yole Développement (2005). *The Ultimate Market Analysis for MEMS*. Lyon, France

Nanoelectronics and Society

Fred van Roosmalen¹, Maurits Doorn²

AMBIENT INTELLIGENCE

The concept of ambient intelligence provides a vision of the future where the emphasis is on user-friendliness, efficient and distributed services support, user-empowerment, and support for human interactions. People are surrounded by intelligent intuitive interfaces that are embedded in all kinds of objects and an environment that is capable of recognising and responding to the presence of different individuals in a seamless, unobtrusive and often invisible way. The vision of ambient intelligence assumes a shift in computing from desktop computers to a multiplicity of computing devices in our everyday lives whereby computing moves to the background and intelligent, ambient interfaces to the foreground. The keywords are systems and technologies that are sensitive, responsive, interconnected, contextualised, transparent and intelligent [Friedewald, 2003].

¹ Philips Semiconductors,
Eindhoven, the Netherlands.

² STT, Den Haag, the Netherlands.

Scanning and integrating these qualitative factors within a systematic road-mapping process is theoretically and practically difficult. The ‘human dimensions’ have rather to be addressed with qualitative and case-by-case studies complementing the identification and characterisation of the key functions. Still, people do not accept and use every innovative function that is technologically made possible and supplied. In the past, there have been many market failures (videotext, WAP) and unforeseen successes (SMS, camera cell phones). It is therefore difficult to foresee which applications in future ambient intelligence environments will provide the trigger for reaching a critical mass of users. Moreover, people use new technologies in ways that are very different from their intended uses by suppliers (e.g. the Internet). There is no typical, uniform user and use but rather a diversity of users and uses. Suppliers generally have difficulties in understanding the user market in a qualitative way. Successful innovation is the result of a specific socio-economic and technological constellation, i.e. the right product, on the right market, at the right time and in the right combination where specific requirements in terms of user needs, user-friendliness, price, attractive supply, standards, interoperability, and so are met. If they are not, the commercialisation will certainly fail. However, failed attempts may ultimately emerge as successful, perhaps in new guises, when the right conditions are in place.

Ambient intelligence is materialised into physical products and services through two main platforms of enabling technologies, i.e. nanoelectronics for the hardware part and embedded systems for the software part. For each of these platforms, pan-European public-private partnerships have been installed — ENIAC for nanoelectronics, ARTEMIS for embedded systems — and strategic research agendas are defined scanning developments up to 2020.³ The division between the two platforms is less clear than it might seem at first sight. With the growing complexity of the overall system, designing hardware increasingly needs to be aided by software, while flawless operation of software programs in advanced circuits has become impossible without taking into account fundamental hardware parameters. The European technology platform ENIAC has established a basic vocabulary for translating societal needs into potential future applications and technology requirements [Van Roosmalen, 2005a]. Outlines of the intelligent systems that are expected to emerge in each of these application domains are summarised below. The figures illustrating the domains show actual implementations being researched today.

³ <http://www.cordis.lu/ist/eniac/>
<http://www.cordis.lu/ist/artemis/>

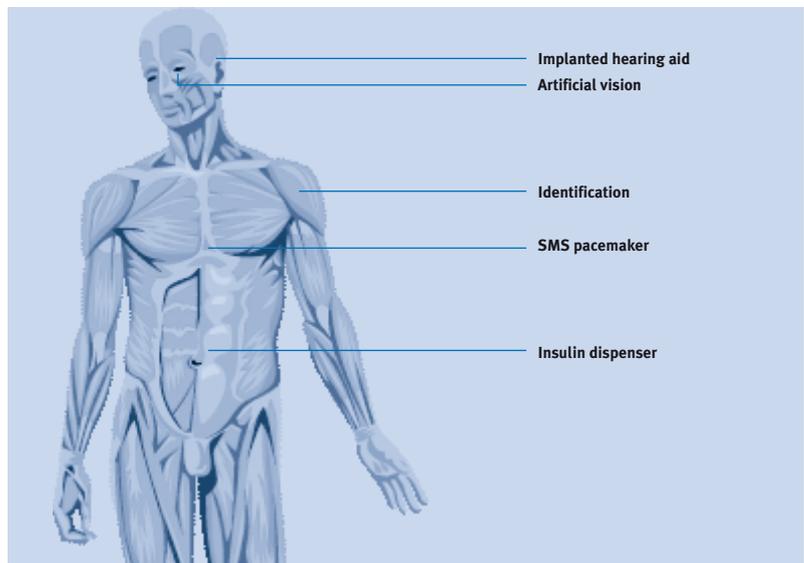
HEALTH

With the advent of nanotechnology, medicine will undergo a revolution. Fast, highly sensitive DNA/protein assays made possible by innovative new bio-sensors will allow many diseases to be diagnosed 'in vitro' from simple fluid samples (blood, saliva, urine etc.) even before sufferers complain of symptoms. Similar tests will identify those pre-disposed to certain diseases, allowing them to enter screening programs that will identify early onset of the disease. Conventional and molecular imaging, increasingly combined with therapy, will pinpoint and eradicate diseased tissue. Early diagnosis will lead to earlier treatment, and earlier treatment to better prognoses and after-care. By 'nipping disease in the bud' it will make many therapies either non-invasive or minimally invasive. And equipped with body-sensors that continuously monitor their state of health and report significant changes through tele-monitoring networks, patients will be able to return home sooner and enjoy a faster recovery. Nanomedicine will also revolutionise prosthetics, with bio-implants restoring sight to the blind and hearing to the deaf. Automated drug-delivery implants will prevent conditions such as epileptic fits.

For developers of the nanoelectronic based systems that will lie at the heart of many of these developments, it will pose many challenges, such as the bio-compatibility of the materials they use both for in vitro and in vivo applications, and the maximum thermal load that implanted devices can impose on the human body. In some cases, bio-sensors will have to achieve phenomenal sensitivities, equivalent to detecting the presence of a grain of salt in an Olympic swimming pool. Developing implants in bio-compatible packages will

Figure 1

Intelligence applied — silicon meets carbon [Van Roosmalen, 2005b].



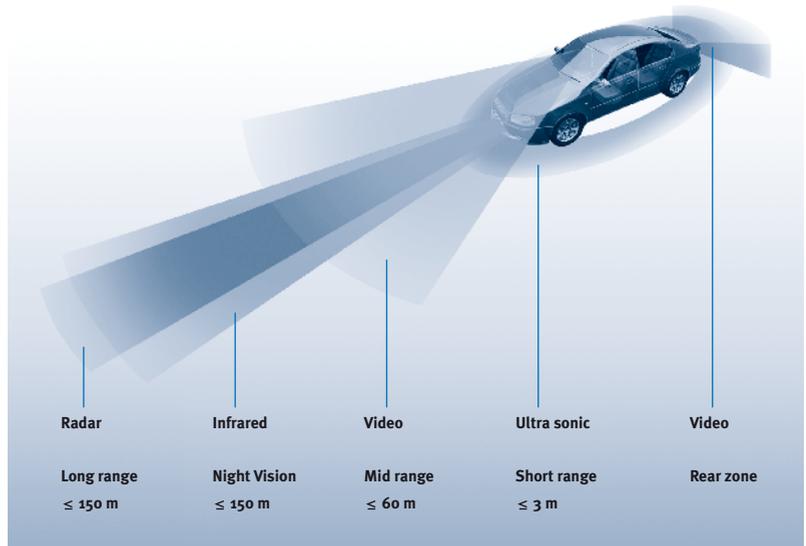
push System-in-Package (SiP) miniaturisation to the limits, while at the same time having to cope with the integration of devices such as biological sensors, nanoscale MEMS devices, optical devices, energy scavenging systems and RF interfaces. At the same time many of these highly complex heterogeneous systems will have to provide life-support system reliability.

MOBILITY AND TRANSPORT

As the volume of traffic on our roads continues to increase, there will be an increased demand for safety management systems that out-perform their drivers in terms of speed control and collision avoidance through drive-by-wire systems. At the same time there will be a need to transfer much more information to and from moving vehicles, not only for driver information, navigation and entertainment systems, but also for vehicle tracking and road toll applications. The world's limited oil and energy resources will stimulate the development of far more fuel-efficient vehicles as well as new alternative energy (battery or fuel-cell powered) vehicles. Nanoelectronics will be at the heart of many of these advances.

Electronic systems for automotive systems have to withstand very harsh environments, including high temperatures, humidity, vibration, fluid contamination and electro-magnetic compatibility. While these problems have largely been solved for conventional IC-style packaged devices, a whole new set of challenges will have to be faced, when these packages also contain integrated sensor, actuator, mechatronic or opto-electronic functions. Some systems,

Figure 2
Intelligence applied — safety cocoon [Van Roosmalen, 2005b].



such as collision avoidance radars and engine-assist/traction motor drives, will push the performance limits of current high-volume low-cost semiconductor solutions in terms of frequency capability or power/thermal handling. In addition the critical role in drive-by-wire systems will require extreme reliability, measured in parts per billion instead of today's parts per million. On top of this, the automotive industry imposes special constraints such as parts warranty for up to 20 years and compliance with EC directives.

SECURITY AND SAFETY

Statistics show that we live in a much safer world, yet there is still constant demand for increased safety and security in just about every aspect of our lives, driven by the principle that 'one death is one death too many'. It reflects itself in public demand for personal emergency and home security systems, and government led protection from crime and terrorism. Always, however, there is a need for personal protection without restriction of liberty, which means that safety and security systems need to be both reliable and easy to use. It is in this area that ambient intelligence's ability to recognise individuals and be responsive to their individual needs will be highly valuable. Nanoelectronics will provide the necessary sensors, computing power and reliability at cost levels that allow safety and security to be built into the fabric of our environment.

Safety and security systems can be divided into two groups. Firstly, low-cost personal emergency and home protection systems that are affordable for consumers. Secondly, high-performance high-efficiency systems for applications such as banking, identity card and safety critical systems. To make these systems unobtrusive enough so that we do not end up resenting them they must be small and easy to use. They therefore put high demands on miniaturisation. Yet their requirement to be highly reliable also means that they must be complex and multi-functional, so that they make decisions based not on a single parameter but on combinations of parameters (fingerprint, voice, iris pattern). This will involve the integration of a wide range of sensors, MEMS and opto-electronic devices. Such devices will also need to communicate reliably by wired and wireless networks, and they must be made tamper resistant and able to withstand environmental conditions that might affect their performance (radiation, chemical corrosion, shock).

COMMUNICATION

People are becoming used to having easy access to friends, relations and information services and more frustrated when that access is not available to them. Making information available anywhere at any time relies on connectivity and communications, increasingly via the use of wireless-based networks (cell phones, Wi-Fi networks) to meet the ‘anywhere’ requirement. In future, such communication systems must be even easier to use, even to the point where specific connectivity channels become irrelevant to the user. Information will simply tunnel itself to its destination by whatever communications channels are available. At the same time, the bandwidth of systems will increase dramatically to cope with the increasing amount of data that people want to move around (voice, pictures, video, file transfer) and they will become much more secure against eavesdroppers and hackers.

Nanoelectronics will be needed not only to meet the miniaturisation requirements of handheld portable communications devices. It will also be needed to allow much more functionality, in terms of the number of different communication channels, to be packed inside them. The ‘multi-band multi-mode’ devices that will enable this will be the key to decoupling communication from specific communication pipes, heralding a whole new era of seamless communications. At the same time, wireless communications channels will move to higher frequencies in order to increase data rates and maximise spectrum usage. This will require the increasing integration of RF MEMS and new RF architectures that allow circuitry to be re-used across many different RF channels and modulation schemes.

Figure 3

Intelligence applied — personal comfort [Van Roosmalen, 2005b].



As portable communications devices pack more functionality, low-power consumption will become an even more critical requirement. The need to keep devices active for long periods of time between battery re-charges or even autonomous in terms of energy supply, will require the integration of energy scavenging devices that pull and store power from the local environment. At the same time, affordability, reliability and environmental compatibility (disposability, re-cycling and re-use) will be other major drivers.

EDUCATION AND ENTERTAINMENT

Content for education and entertainment must not only be accessible anywhere and anytime. It must also be of the right quality and accessible in the right format. Access to similar information will be required in many different locations (at home, in the car, in the street, in hotels) and delivered through a variety of channels (terrestrial, satellite, cable, phone line, wireless, discs). Yet in each location the rendering device for that content, and people's expectations of it, will be different (for example, what is expected from a flat-panel TV set compared to a video-phone). Pre-recorded digital media, such as DVDs and HDTV, have increased people's expectations of video quality, yet this video quality will have to be delivered through existing networks.

The need to deliver high quality media through a range of different communications channels while maintaining the required quality will require new developments in multi-format encoder/decoders, data compression and transmission systems, with media senders (e.g. internet servers) automatically tailoring transmission to the capabilities of the rendering device on which the content will be experienced. Storage and distribution (CD, DVD, digital home networks) will need to be developed that are compatible with the digital rights management requirements of content providers.

Content generators will require new equipment (for example, HDTV studio equipment and lightweight portable HDTV cameras) to capture content and content providers will need advanced video compression and transmission schemes to distribute it. The demand for users to create their own content will also require significant advances in areas such as image capture (digital cameras, camcorders), image analysis and picture quality improvement at affordable consumer-product prices.

REFERENCES

- Friedewald, M., O. Da Costa (eds) (2003). *Science and Technology Roadmapping — Ambient Intelligence in Everyday Life*. JRC/IPTS — ESTO Study, June
- Roosmalen, A.J. van (ed.) (2005a). *ENIAC Strategic Research Agenda*, 1st Edition
- Roosmalen, A.J. van (2005b). *More than Moore — Directions in Nanoelectronics*. Micro System Technologies Conference 2005, Munich

Innovation from within the Existing Nanoelectronics Value Chain

Ivo Raaijmakers¹

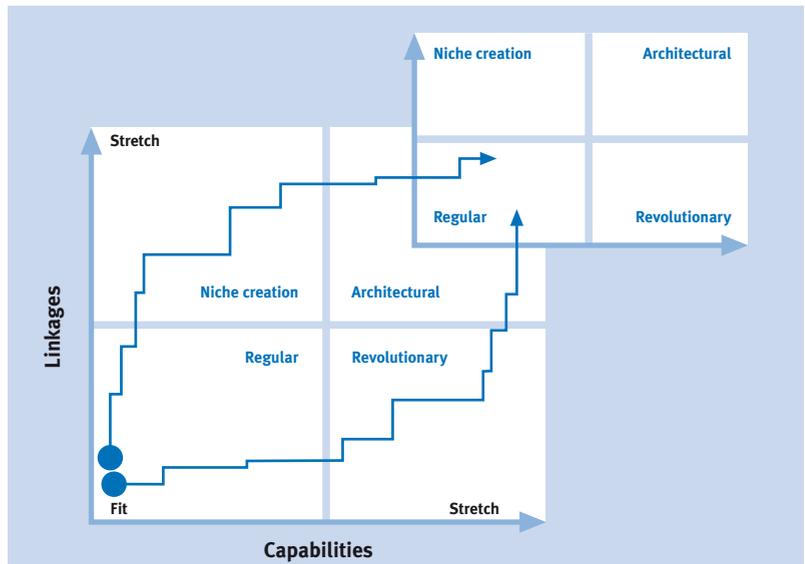
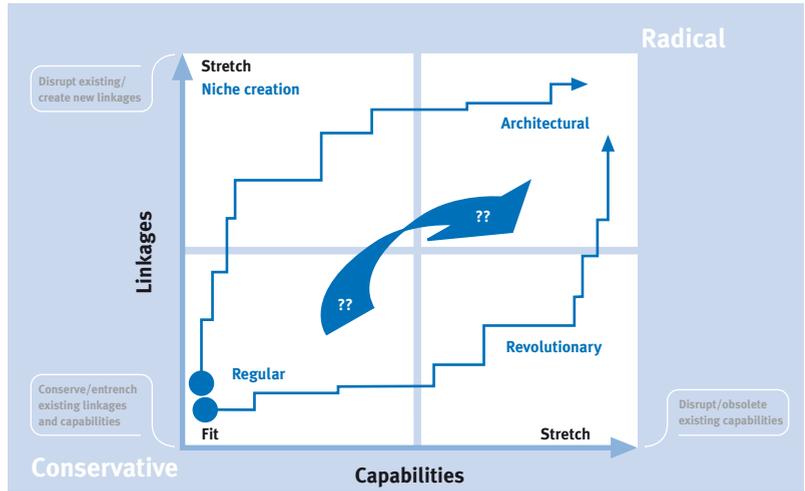
INTRODUCTION

In order to realise the nanoelectronics roadmaps, high-intensity, basic and applied R&D, efforts throughout the entire value chain are needed. Porter argues that all links in a value chain should be able to add value (or, equivalently, collect a profit) for the chain as a whole to be viable [Porter, 1985]. If not all participants in the value chain perceive that a certain innovation will add value, some participants may not sufficiently invest in R&D and may put the realisation of an innovation as a whole at risk. This means that understanding and dealing with problems in the nanoelectronics value chain are important for the creation of feasible innovation trajectories.

¹ ASM International NV, Bilthoven, the Netherlands.

Figure 1

Top: Abernathy and Clarke framework. Two paths of managing incremental innovation are shown. A disruptive innovation as shown by the curved arrow in the diagram is less likely. A sequence of small incremental steps as shown by the stepped solid lines can actually appear to be a disruptive or radical innovation in hindsight. Bottom: After a series of innovations, a new status quo can be reached. In this new status quo, a radically new architectural framework becomes established forming the basis for subsequent incremental innovation.



In the Abernathy and Clarke diagram, as discussed in detail in the article of Doorn et al. ‘Anticipating Converging Technologies’ (see paragraph ‘The Abernathy and Clark model and its generalisation’) innovations from the existing value chain start in the lower left quadrant. The established value chain will tend to conserve and utilise as much as possible the existing competences and linkages. Innovation is usually a superposition of small, lower risk steps along one of the axes in the diagram; see Figure 1 (top). After a sequence of such steps in the Abernathy and Clarke diagram, the resulting value chain and business model may be completely unlike the original situation (disruptively innovated, located in the upper right quadrant), but it has not become so by one single event but by unperceivable small steps. In retrospect, the value chain can be seen to have co-evolved with the technology/market innovations.

New baselines or architectural frameworks are established (see Figure 1, bottom), on which subsequent innovations will be superposed.

In this article, first today's value chain in the context of Moore's law and the problems within it will be described. Although we do not really deal with the direct implications of Moore's law in the present case study, this value chain analysis is included as a good frame of reference that we know quite well. After that, development trends in the other nanoelectronic domains will be described, and the problems that can exist when innovation is effected from within an established value chain.

It will be shown that in order to sustain innovation at any substantial speed, cooperation throughout the entire value chain is essential, for small and large companies alike. Along the way, this may lead to the emergence of new business models, including new intellectual property (IP) management models, intensified cooperative research models, and so on. Public action can significantly help in increasing the speed of new linkage creation in technologies (horizontal in Figure 1) and markets (vertical in Figure 1). This is essential for the realisation of the ambitious nanoelectronics roadmaps along a low risk trajectory from within the existing value chain.

THE ESTABLISHED VALUE CHAIN

Figure 2 schematically depicts the value chain in the electronics industry (terminology partly according to [Rieppo, 2005] with adaptations by the author). In analogy to food in food chains, a non-balanced distribution of profits along a value chain will eventually kill the chain or at least mutate it until the profits are balanced. The goal of each activity in a value chain should be to add value

Figure 2
Today's electronics value chain. This generic structure can also be used to analyze the (emerging) nanoelectronics value chain.



[Porter, 1985]. In order to optimise the incremental profit distribution along the value chain, participants have to be cognisant with the entire value chain and be able to cooperate both along and orthogonal to the value chain. This will become very important in the emerging nanoelectronics domains, as we will see later.

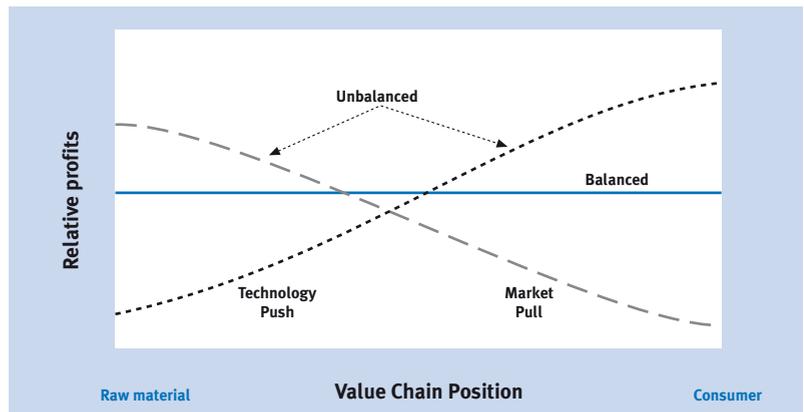
Two broad scenarios in the distribution of value production along a value chain can be considered: A 'Market Pull' scenario, where a market need stimulates the development of new products and a 'Technology Push' scenario where new technology offerings are abundant and are looking for adoption in products and markets. The effects of these scenarios on the value chain are important (see Figure 3). In a Technology Push scenario, the technology will have to be pushed up the value chain in order to generate demand. The abundant and diverse availability of technology will squeeze the profits at the bottom of the value chain. In a Market Pull scenario, shortages (of technology solutions) will drive down to the bottom of the value chain, focusing profits there and leaving fewer profits at the top. In a balanced push/pull situation, the profit distribution will be balanced along the chain. Such a situation may be the most fertile ground for a successful innovation. As we will see, this may a priori not be the case in nanoelectronics. Such an unbalance, in combination with the problems in the established value chain, puts the innovation in emerging nanoelectronics at risk.

VALUE CHAIN EVOLUTION

Moore's law predicts that the complexity of chips for digital logic will double every two years, whereas the price per complexity or price per function drops at about the same rate. This law has held for over 30 years and is the driving force that made a \$ 200 billion industry emerge, historically growing at a pace

Figure 3

Distribution of profits along a value chain. In a Technology Push scenario profits are squeezed at the supply side. In a Market Pull scenario, technology is in short supply and has a high value, thereby decreasing profits at the top of the value chain.



in the range of 15-20% per year, at least until 1995 [Rieppo, 2005; Hutcheson, 2004]. It should be understood that Moore's law is really more about the economics of the entire industry than it is about the technology itself.

But, in the last decade, the semiconductor industry no longer grew at double digit rates; expectations today are that the density doubling will decline from once every two years to once every three years. Around 1995, the semiconductor content in electronics reached saturation, and the semiconductor industry slowed down to a growth of about 6% [Rieppo, 2005; Hutcheson, 2004]. The slower growth will, and has already, pushed down R&D spending. This is a serious trend that affects certain parts of the value chain more severely than other parts. For example, the profitability of many equipment and material suppliers is marginal today, and for the first time in three decades, equipment suppliers seem to have decreased their total annual R&D expenses as a percentage of total annual revenue [Hutcheson, 2004].

It is important to assess the underlying reasons for this stagnation in growth. If it is a simple shortage of capital, an upward macroeconomic conjuncture trend would result in demand pick-up. This is not so likely considering the long duration of slower growth (1995-2005), apart from a few hype years. More likely, the electronics industry produces more technology than the market can handle (a Technology Push scenario). In that case, demand will structurally drop, and margins will fall/profitability will be squeezed, particularly at the bottom of the value chain where technology supply is abundant. See for example Figure 3, where this would correspond to a position in the bottom left corner.

One of the strategies employed by companies in such situations is to move up in the value chain in order to capture more added value. Equipment suppliers, for example, become more and more involved with customer process technology, and IC manufacturers move into the area of system integrators. The emergence of System-in-a-Package (SiP) draws away value from the printed circuit board and system assemblers and puts it with the integrated device manufacturers. These solutions for existing value chains can be formulated in the Abernathy and Clarke context: essentially, they are trajectories moving along the horizontal axis, moving from regular into revolutionary (see Figure 1). Frequently these moves will be followed by architectural changes driven by visionary innovations, such as 'ambient intelligence'.

Technical gap analysis [Reichl, 2005] shows that in order to realise the nano-electronics roadmap extreme miniaturisation of more reliable devices will be needed in combination with the ability for hetero-integration of widely different devices in one System-in-a-Package (from 1 cm³ single chip packages to

0.01 cm³ multiple chip packages in about 10 years). In addition, for mobile electronics, more efficient power generation and management are needed, and environmental adaptation and interfacing have to be improved, e.g. in cars and on or in the human body. All this should also be realised at acceptable costs to consumers. It is at present unknown how realistic it is that the cost targets for these complex miniature systems can be met. This is not new, as this cost issue has existed in microelectronics as well. But in addition to this cost issue, applications and products are becoming much more diverse and much more multidisciplinary. This implies that opportunities are spread thinly in a complex and broad value chain, possibly making the market strategy and business model greater challenges than the technology itself. The more fragmented value chain makes the cost issue more persistent and less straightforward to solve.

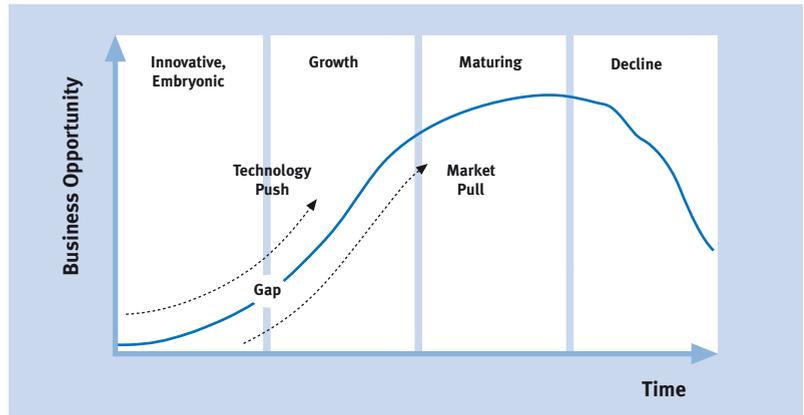
IS DISRUPTIVE INNOVATION POSSIBLE WITHIN AN ESTABLISHED VALUE CHAIN?

Large firms in particular face organisational difficulties when launching applications based on disruptive innovations and radically new technologies due to the cannibalisation of their own market and due to organisational inertia as a result of policies and procedures and a relatively short-term focus [Christensen, 1997]. Large entrenched firms listen to their existing customer base. They tend to aim their R&D at sustaining technologies designed to enhance their current offering making it better, faster, cheaper. The firms are entrenched on the right side of the — discontinuous — bell curve in Figure 4, i.e. in the growth and maturing business environment, see for example [Moore, 1991]. These firms are less likely to pursue disruptive technologies and to introduce discontinuous innovations that start in the embryonic or innovative part of the bell curve in Figure 4. Large firms have therefore to develop linkages with radical innovators and build bridges across the gap in Figure 4. If they do not do so, they may eventually face a significant sacrifice in their market place position or even failure. Indeed, the last decades showed several occasions where dominant large firms in the semiconductor industry failed to stay in top positions over time (e.g. Fairchild, National Semiconductor). Large firms will primarily use lower-risk Market Pull strategies to bridge the gap: it is better to be a fast second than a failing first [Markides et al., 2005].

Small high-technology firms are more responsive to the commercialisation of disruptive technologies [Christensen, 1997], but they are prone to have less (continuous) attention for business opportunities and strategies. Many com-

Figure 4

The technology generation/business development cycle depicted as a bell curve. There is a gap, discontinuity or chasm [Moore, 1991] between the innovative or embryonic part of the curve and the growth/maturing parts of the curve. This gap has traditionally been difficult to bridge.



panies that initiated a certain radical innovation in the market are not the companies that finally end up being the most successful in the market [Markides et al., 2005]. Small companies tend to focus more on the generally higher-risk Technology Push approach [Berry et al., 1998; Oakey, 2003] to bring technologies to the growth stage.

Not many companies are able to combine the skills needed to be successful in an innovative environment and in a growth or maturing business environment [Moore, 1991; Christensen, 1997; Markides et al., 2005].

Technologies labelled as potentially disruptive are most likely created or absorbed by firms when serious ‘movements’ are made regarding the firms’ differentiating competencies and capabilities, i.e. a significant move in the horizontal direction of the diagrams of Figure 1. However, established firms often fail to break open their tunnel vision of the future, to expand their mental models and reorganise their knowledge base to embrace the radical innovation. Only by drastically shifting the company’s existing knowledge assets (that provide the basis for a firm’s competitive capacities and sustainable advantages), large companies are able to see through the market and business implications of new radical technologies (i.e. a significant move along the vertical direction in the diagrams of Figure 1). In terms of [March, 1991], return on investment (ROI) alone is not a good performance indicator to drive changes that can lead to radical innovation. A firm needs to invest in exploitative and explorative mindsets without an easily identifiable ROI or deterministic net present value (NPV) and create fundamental changes in both its knowledge base and market linkages. Changing the way a company addresses the innovative business environment in Figure 4 minimises the distance between the two parts of the bell curve and will ensure that technologies have ample opportunities to tunnel across the gap, creating mainly horizontal moves in the diagram of Figure 1.

High technology is a phenomenon that is generally created and developed by cooperating organisations (small and large companies with or without their own research and development facilities, and large companies with their own incubator departments, high-technology start-ups, universities, governmental funded research organisations, customers, etc). When (clusters of) cooperating organisations do not have the abilities to co-develop or absorb new radical technologies that are critical for next generation applications, their long-term added value creation/wealth creation position is under threat. The creation of high-tech development ecosystems is essential for stimulating cooperation and driving radical innovation and architectural changes. Organisational openness toward actors not (typically) present in current cooperation activities is needed in order to sharpen awareness to disruptive innovative threats to the existing order. The organisational openness creates bridges across the discontinuity in the bell curve of Figure 4, resulting in horizontal and vertical moves in the diagram of Figure 1.

One method for generating moves along the vertical axis of Figure 1 is to change the business model. A business model describes the market, the value proposition, the position of the participant in the overall chain and the cost structure and profit potential of the participant. The role of the business model is important, especially in Technology Push scenarios [Astebro et al., 2005]. This article describes spin-offs of Xerox in such a scenario. Each spin-off was only successful after the business model had been significantly changed (note: Xerox itself had to change its own business model in order to be successful in the copier market, it was changed from capital buy to lease). One of the conclusions in the present article is that technology that makes little business sense in a market one way may have great potential when the business model is changed.

It is obvious that, in order for successful radical innovations to occur in an existing value chain or industry at a substantial intensity, major changes in organisational fundamentals may be necessary. These changes are not likely to take place without external force and significant management attention, as they are perceived to be high-risk moves. The most likely path to successfully innovate from within an existing value chain is by way of an incremental approach, carefully progressing by building new linkages in the market, the technology, or the products, i.e. primarily with little steps along one of the axes in the Abernathy and Clarke diagram (see Figure 1). Over time, this will also lead to radical innovations and architectural changes, at least when looking back from the new status quo.

THE PERSPECTIVE OF THE MATERIALS AND EQUIPMENT SUPPLIER

Traditionally, integrated device manufacturers (IDMs) have pushed risks down the value chain, chiefly to the suppliers of equipment and materials. Particularly during the 300 mm wafer size transition, this took place to a great extent, and the combination of these additionally assumed risks with the slower growth rate has left some of the suppliers of equipment and materials in a very bad shape. Today, this industry segment will therefore not enthusiastically pour money on post-2015 nanoelectronics technologies. However, the participation of this segment of the value chain in the innovation is dearly needed as much of the required process and material expertise in the industry resides in this segment. Innovation would be much less effective if the resources in this segment were to remain untapped.

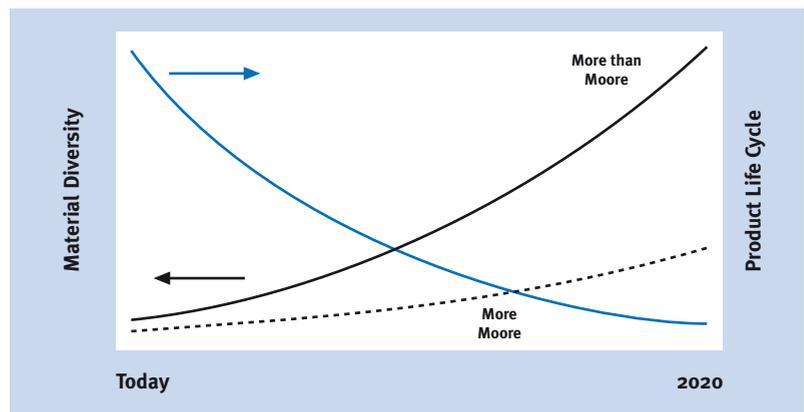
A second problem with this segment is related to the — earlier alluded to — increased differentiation in processes and materials needed for the nanoelectronics revolution and the expected very short product life cycle (see Figure 5 for a schematic representation of these effects). Can mass production ready equipment and materials ever be developed for these diverse, low-volume applications, while meeting the costs of ownership targets of the IDMs? How can this increased diversity be profitably managed?

There are a few possible answers to this question.

- *Change of technology management.* The equipment and material suppliers have to move to more efficient platform-based technology and knowledge management. From a well-defined platform-based product structure, a large amount of individual products with remarkably different functions can be generated. One example is the introduction of new technology platforms like Atomic Layer Deposition that can produce a large amount of different materials for a wide variety of nanostructures, and nano imprint lithography

Figure 5

Schematic representation of material diversity as a function of time in the More Moore and More than Moore segments. The coloured curve indicates the decrease in product life cycle in the More than Moore segment.



that can be used to cost-effectively generate nanostructures.

An alternative way to change technology management is described in the article of Eijkel et al. 'Architectural Innovations in Perspective'. In this article, several cases describe how companies manage to get through the disruptive innovation cycle by creating a highly entrepreneurial ecosystem and by communicating a consistent vision that creates the force to converge wild ideas into manageable innovations.

- *Cooperating more intensively along the value chain.* A model where the IDM contributes directly to and is actively involved in an equipment and material product development project (paid-for or shared development) is viable. This shares much of the upfront risk, deploys the special experience of the supplier and ensures an active cooperation between these two important links along the value chain. So as to make this model attractive for the IDM, a period of exclusivity is sometimes negotiated. In addition, the formation of consortia can help to redistribute the profits more uniformly along the chain. On the one hand, the government can play an active role in the formation of consortia, and consortia can on the other hand help the government to channel funding for a maximum innovative effect.
- *Cooperating more intensively throughout the value chain.* Up to a certain point, many of the applications may better be developed by small and medium enterprises (SMEs) outside the current, higher-cost semiconductor infrastructure. But SMEs do not generally have the infrastructure, the expertise and the IP base to successfully design, build or sustain mass production equipment for, or in an IDM environment. Therefore the question is then how an innovation will be taken from the prototype stage and scaled up to mass production equipment.

Cooperation is obviously important when decreasing the restraining forces that stand in the way of innovation. Symbiotic partnerships can be envisaged between a larger capital equipment supplier and several SMEs, with proper participation incentives for all parties in an intensively interactive ecosystem. The larger equipment supplier should have a collection of flexible and universally applicable technology platforms that can serve as jumping boards for the development of mass production equipment. The technology platforms ensure a quick adoption of the new technology developed by the SME. The ownership of IP and the flow of the resulting rights are a point of concern, and new models should be worked out protecting the IP position of the SME in its niche and continuing to positively reinforce the SME to create new technologies. Moreover, the fragmentation of experience and knowledge throughout a more complex and more diverse value chain should be managed. There are thousands of small nanoelectronics technology suppliers (and users), each of them of sub-critical mass and not able to implement adequate knowledge

management processes. Open innovation platforms, such as the Holst Centre and IMEC, can be a solution to this problem. An analogy to Silicon Valley in the late 1970s and early 1980s immediately crosses one's mind, where the close proximity of pioneers that could informally share knowledge, caused a US \$ 200 billion industry to emerge. Such an environment should be cultivated in order to have a chance of success in the Netherlands and in Europe. Reference is again made to the conclusions in the article of Eijkel et al. 'Architectural Innovations in Perspective', specifically those on ecosystems and stimulating entrepreneurship.

ROADS TOWARD SUCCESSFUL INNOVATION

From a strict economic viewpoint, it is rewarding to commercialise an invention if the discounted net profits exceed the discounted net costs [Chesbrough et al., 2002]. The authors of this reference continue to prove that not only perceived profits are important, but that perceived technological opportunity is equally important. This means an unbalanced Technology Push scenario (see Figure 3) as analyzed from a strictly monetary sense will not necessarily lead to the failure of a value chain for a certain technology development. It just requires an early evaluation of technology opportunities in the market and a constant adaptation of the development so as to stay aligned with the developing market. Hence, the chance of success can be increased by an intensive cooperation along the entire value chain.

It has been shown in the foregoing that lower down the supply chain, where the margins get smaller, a disproportionate part of the risk is borne. Consortia can help in redistributing the development cost for nanoelectronics. There is an obvious need for partnerships in both the electronic (chips) sector and the application sector. These partnerships should actively reach out to SMEs, which can stimulate a large part of innovation due to the different cost structures.

In its current paradigm of decreased growth rates and profitability, the industry cannot pour a lot of money into products or an infrastructure coming to fruition only ten or more years ahead. The situation is entirely other than that of the microelectronics revolution in the 1970s and 1980s, where money was available due to the high industry growth rates. Although technology predicts fantastic capabilities, in order to realise these economically across the nanoelectronics industry, expectations should be communicated for a much larger public funding percentage. A structure has to be build that brings the innovation from smaller, more agile SMEs to larger corporate structures. For example, the Holst Centre will request 60% public/40% private, even in 2009.

These levels of funding may indeed be what is necessary to realise the Lisbon target of making Europe the world's most competitive knowledge economy. It appears that in Asia (notably South Korea) and in the USA such communicated visions are quite effective in creating driving forces, so that incremental innovations converge to support the vision.

In such a 'public' world, it will be increasingly difficult to secure and protect IP rights. Especially the IP position of SMEs has to be better protected. New IP ownership and exploitation schemes may have to be devised to secure the long-term viability of innovating SMEs in the nanoelectronics value chain.

Last but not least, there is no managed innovation without a communicated vision. This is true for public authorities and industrial partners alike. The vision should describe the desired architectural changes in the upper right hand quadrant as in the Abernathy and Clark diagram (Figure 1). As pointed out in the previous sections, an established value chain will not likely embrace these innovations because the risk is too high, but it will innovate in small steps. By providing and strongly communicating a vision, these steps can be made to converge and the value chain and technology base can co-evolve in a profitable way to produce the new architectures required in application road-maps. Public authorities can therefore best direct funding toward the establishment of new links, as this will accelerate sustainable innovations.

SUMMARY AND CONCLUSION

Cooperation along and orthogonal to the value chain is of the utmost importance. Any public funding program should emphasise this aspect.

Only with increased public funding can nanoelectronics be developed as a commercially attractive discipline. This may be essentially different for the More Moore and More than Moore segments. The public sector should join as a full partner and assist in creating linkages in market and technology, creating and concentrating high-tech ecosystems and securing Europe's IP leadership by adapting legislation where needed.

The most likely scenario may be that today's electronics and semiconductor SMEs will push the technology that develops the niche markets much like semiconductor technology did in the 1970s and early 1980s, and that along these revolutionary and niche pathways many new, potentially large players will follow to capture the value of what in hindsight will turn out to be a radical innovation.

REFERENCES

- Astebro, T., K. Dahlin (2005). Opportunity Knocks. *Research Policy* 34, 1404-1418
- Berry, M.M.J., J.H. Taggart (1998). Combining Technology and Corporate Strategy in Small High Tech Firms. *Research Policy* 26, 883-895
- Chesbrough, H., R. Rosenbloom (2002). The Role of the Business Model in Capturing Value from Innovation: Evidence from Xerox Corporation's Technology Spin-Off Companies. *Industrial and Corporate Change* 11, 529-555
- Christensen, C. (1997). *The Innovators Dilemma*. Harvard Business School Press
- Hutcheson, D. (2004). *The Chip Insider*, November 4. VLSI Research Inc., Santa Clara, CA, USA
- March, J.G. (1991). Exploration and Exploitation in Organisational Learning. *Organisational Science* 2 (1), 71-87
- Markides, C.C., P.A. Geroski (2005). *Fast Second*. Wiley, San Francisco
- Moore, G.E. (1991). *Crossing the Chasm: Marketing and Selling Technology Products to Mainstream Customers*. Harper Business, New York
- Oakey, R.P. (2003). Technical Entrepreneurship in High Technology Small Firms: Some Observations on the Implications for Management. *Technovation* 23, 679-688
- Porter, Michael E. (1985). *Competitive Advantage*. The Free Press, New York
- Reichl, H. (2005). *Presented at ENIAC Stakeholders Meeting*, Sept 16, Grenoble, France. http://www.cordis.lu/ist/eniac/meeting_160905.htm, accessed 26 Sept
- Rieppo, P. (2005). *How to Respond to Changes in the Semiconductor Value Chain*. Publication Number Goo126802, May 13. Gartner, Stamford, U.S.A.

More than Moore and Heterogeneous Integration

*Chris van Hoof*¹

INTRODUCTION AND APPROACH

INTRODUCTION

In this chapter we will describe emerging technology in the More than Moore domain, in particular paying attention to heterogeneous integration.

Rather than providing an exhaustive overview of technological developments in More than Moore, we will discuss examples of specific devices: Above-IC-MEMS, Above-IC RF and 3D Integration. These examples will be discussed in-depth, both from the perspective of technological developments and from the perspective of the value chain. This will allow us to map trajectories for these technologies, retrospectively or anticipatorily, providing a deeper insight in the factors that shape the dynamics of technological development and innovation in this domain. Such insights in factors that shape trajectories can be useful to define the technology and business strategies in these emerging domains. Subsequent to these examples, we will discuss how the use of a combination of application and technology roadmaps can help to anticipatorily articulate trajectories in these emerging technology domains and so to better coordinate the activities of the actors involved. A technology roadmap for heterogeneous integration and an application roadmap for wireless autonomous sensors for health care applications will be used as examples.

.....
¹ IMEC vzw, Leuven, Belgium.

APPROACH: ABERNATHY AND CLARK POSITIONING MECHANISM FOR MORE THAN MOORE

The positioning of emerging More than Moore technologies in the Abernathy and Clark framework [Abernathy and Clark, 1985] is a relevant exercise. It permits the highlighting of their emergence and past evolutions as well as the indication of key (present and future) challenges. However, it is not simple. Apart from having a temporal dependence, the precise actual position depends on the perspective/definition of technology disruption and is therefore based on several assumptions.

- As a point of reference, we consider the More Moore domain as a key example of conservative innovation. The underlying ITRS (International Technology Roadmap for Semiconductors) roadmaps [ITRS, 2005] indicate the existence of technology drivers within this quadrant.
- Matured More than Moore applications are found in the quadrant of conservative innovation. Although they may have been architectural innovations, they now have a complete value chain. Examples are volume microsystems (e.g. accelerometers for airbag sensors, pressure sensors, inkjet printheads) that historically caused a technology disruption (see further).

This chapter concentrates on the dynamics of emerging applications in the More than Moore domain that could also rely on such existing value chains (More Moore-based or otherwise) in the future. It therefore concentrates on the conservative innovation quadrant and explorations to and from the adjacent quadrants. Current and emerging production processes for More Moore and, speaking more generally, silicon-based technology platforms are considered as the points of reference. The More than Moore emerging technologies are mapped in terms of their ‘relative departure’ from these platforms and their past, current, and future positions will be discussed.

The above assumptions and the focus on IC-centric technologies are meaningful: the emergence of new modules within IC foundries (standard CMOS and otherwise) is indeed either a way to strengthen existing competences or will at least lead to niche creation in the More than Moore application domain.

Can we categorise or quantify the relative ease or difficulty that future More than Moore applications will have to face? This brings us to the introduction of the term ‘technology disruption level’. Although it is not a quantity that can be measured or predicted in absolute terms, the introduction of new technologies may have to face smaller or larger hurdles depending on its relative ease of fitting into an existing technology platform, and the success of future/emerging technologies will therefore indeed depend on the level of technology disruption. A higher level of technology disruption will not imply failure but increases the challenges (risk, time, cost) for adopting it.

From an IC-centric perspective, a non-exhaustive list can be drawn up of factors that affect the technology disruption. The technology disruption level is related to the sum of the technological ‘complicators’ minus the sum of technology ‘facilitators’ (each with applicable weight factors). The table lists a number of known complicators and facilitators. In many cases, a complicator turns into a facilitator and vice-versa by negating or inverting each column.

Table 1
Technological facilitators and complicators for the introduction/integration in a silicon process environment.

Complicators	Facilitators
– amount of new materials	– silicon-based
– known contamination issues (need to radically change materials in order to avoid contamination)	– batch wafer-level processing demonstrated
– amount of new processes to be introduced	– process windows demonstrated on process step level
– amount of new tools that need to be introduced	– low-temperature processing compatible
– device/component size (cost factor)	– number of commercial foundries that can (or potentially can) handle materials/processes
– lithography and CD requirements	– number of R&D centres that could handle the process flow
– reliability (and testability) issues	– availability of design libraries
– undemonstrated yield (requires time + money)	– possibility to integrate in heterogeneous fashion
– specialty packaging/encapsulation	– understanding on several levels/correct modelling
–	– (multi-parameter)
–	–

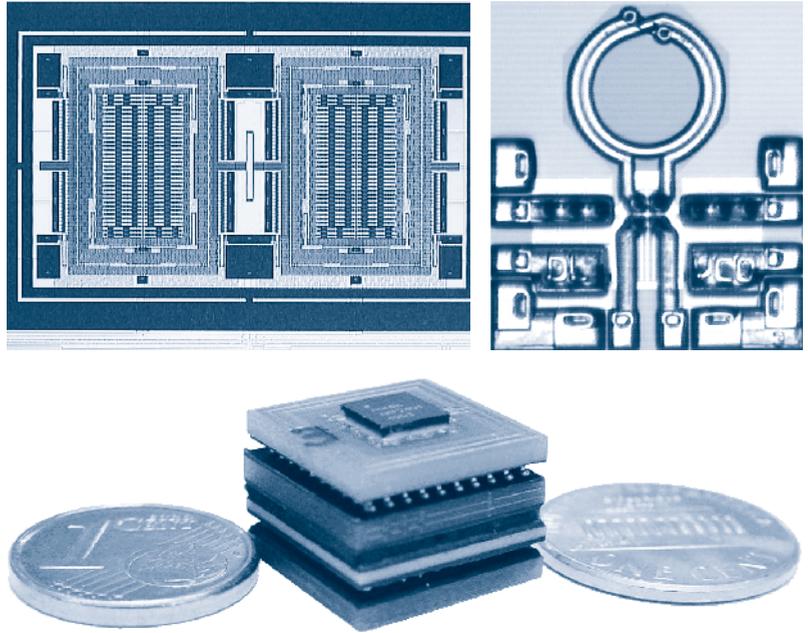
More than Moore functionalities that can be integrated ‘above’ or as part of what is called the back-end of the CMOS line cause less technology disruption than functionalities that require front-end CMOS modifications.

The above parameters can be applied to several More than Moore emerging technologies. We have selected three cases that consist of past and current R&D at IMEC. These examples — briefly described below — will be further explained in terms of their levels of technology disruption:

- Above-IC MEMS technology serves as an improved technology for an existing product in an existing market (accelerometers and gyroscopes for automotive application) (as well as in new markets). As such it is partly conservative (i.e. regular) innovation. In select cases, it could cause obsolescence of other (hybrid) MEMS, i.e. a revolutionary innovation.
- Above-IC RF work provides a new and improved technology. Its resulting miniaturisation and drastically reduced power consumption benefit existing products in existing markets. It is an example of regular innovation. It could be seen as making certain off-chip passives obsolete (revolutionary innova-

Figure 1

More than Moore examples: above-IC MEMS gyroscope (top left), above-IC RF tuneable oscillator (top right), 3D System-in-Package (SiP) for wireless autonomous sensing (bottom).



tion). RF-MEMS, on the other hand, makes use of a disruptive technology and could significantly impact the cell-phone and wireless technologies. As such, it is an example of revolutionary innovation.

- 3D integration as an example of Heterogeneous Integration — IC-centric packaging and integration technology that can be adopted by existing markets and products. It therefore mainly resides in the lower half of the Abernathy and Clark transilience map. The technology roadmaps presented further on in this chapter mainly address a horizontal evolution on the map.

ABOVE-IC MEMS

INTRODUCTION

Microsystems Technology, also called MEMS (for Micro-Electro-Mechanical Systems) has historically been a technology disruption with respect to standard silicon processing in terms of models, tools, materials, and processes. Early work involved piezo-actuators and FET accelerometers in the early sixties. Anisotropic deep silicon etching (pioneered in the late sixties) provided a breakthrough and enabled the development of a host of components (pressure sensors, accelerometers) in the seventies. Kurt Petersen's book 'Silicon as a Mechanical Material' [Petersen, 1982] became a landmark publication. In the eighties, surface micromachining technologies for polysilicon were developed and employed for the manufacturing of, for example, comb drive

actuators and accelerometers. In the late eighties, silicon wafer bonding (developed since the late 1960s) was an established baseline process for the batch fabrication of bulk micro-machined sensors, such as pressure sensors. From then on, microsystems were seen as adding value to the microelectronics industry and providing leverage to this industry. More elaborate overviews can be found in the references [Madou, 2002] and [Gad-el-Hak, 2001]. In the future, CMOS electronics wafers will be a commodity and the major added-value will come from the More than Moore system addition. In the early nineties, government agencies started large microsystems support programmes. In 1993, Texas Instruments presented its Digital Mirror Display now used in large parts of the display market. In 1994, Analog Devices announced the commercial introduction of surface micro-machined accelerometers now widely used as airbag sensors in the automobile industry. In that same period, the inkjet printhead nozzle became an enormous success and is now one of the most prevalent MEMS systems (see Figure 2).

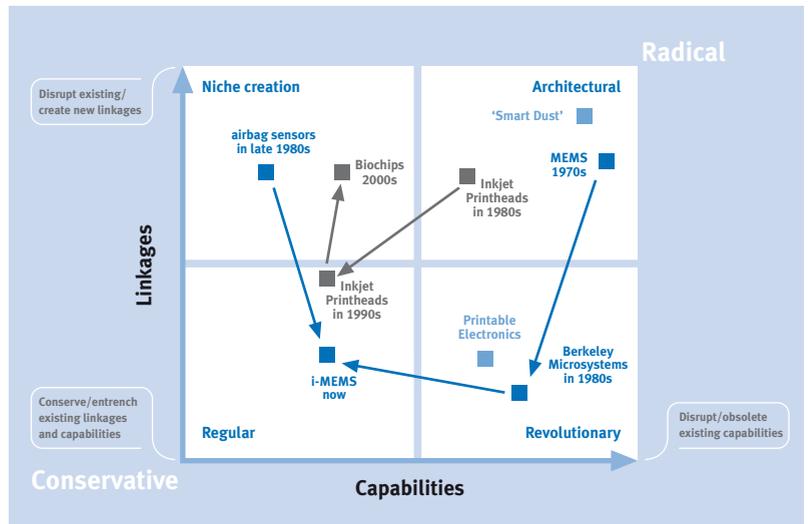
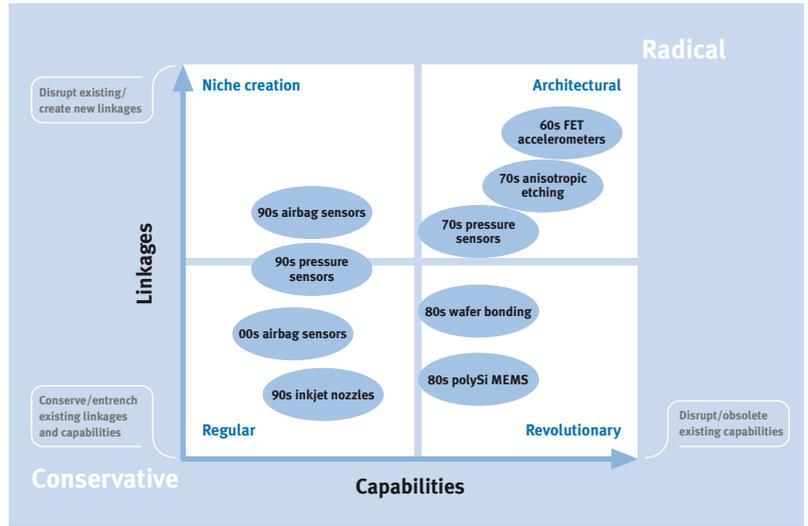
At the time of introduction, these technological novelties definitely contributed to revolutionary or architectural innovations depending on whether they addressed new markets or provided better solutions for existing markets. Even today, although the design of MEMS technologies has matured over the years, there is still no standardisation as, for example, in CMOS design and fabrication. That is why process development still has a low predictability. Despite this lower degree of standardisation and in view of the current existence of a very large MEMS market, dedicated tool manufacturers, MEMS foundries and a well-established value chain, MEMS is now considered to be a regular technology underlying conservative innovation.

Apart from selected volume applications such as inkjet nozzles, in many of the microsystems applications it has been the goal to boost the 'intelligence' of the systems by adding driving electronics, readout circuitry and signal processing on the same chip. Obvious benefits are a combination of functional integration, improvement of performance and reliability, miniaturisation, and cost reduction. We are on the brink of seeing a further integration coming of, for instance, wireless connectivity in such systems. MEMS resonators could be the revolutionary innovation replacing current ubiquitous quartz crystal oscillators.

At the moment, most 'intelligent' microsystems are hybrid assemblies consisting of multiple dies. The functional integration of MEMS and CMOS is not straightforward. First of all, there is no generic MEMS technology platform. Furthermore, it is necessary to combine essentially 3D structures (MEMS) with essentially 2D circuit technology. There are presently three approaches to achieve this integration: (i) processing MEMS first, integrated circuits last (a

Figure 2

Transilience map for selected historic microsystems examples. Breakthroughs are listed together with suitable Moore than Moore applications.



method pioneered by SANDIA), (ii) the integration of the MEMS process within the IC process flow (a method adopted by Analog Devices) (iii) processing IC first, MEMS last (a method pioneered by Berkeley — also called above-IC MEMS, and adopted by, among others, IMEC in Belgium). The last mentioned method implies the ability to modularly process and interconnect MEMS devices above (any) underlying circuitry, without the need for deeper know-how of the underlying circuit technology.

The above-IC method offers more freedom (in terms of materials) and more possibilities than the other two methods. Compared to methods (i) and (ii), the above-IC method conceptually causes the least amount of deviation from CMOS platform technology and could almost be considered as an add-on

to existing CMOS back-end technology competences. However, there is no (restrictive) need for a fixed CMOS foundry or a fixed CMOS process technology. The creation of increased device functionality (and hence the creation of increased value) does therefore not require an IDM² approach and can even be adopted in a fab-less manner. This allows for a more widely spread adoption. Post-CMOS bulk micromachining was the first demonstration of this kind. PolySiGe MEMS is a second example technology platform of this third kind. It features minimal disruption and can be fabricated above many CMOS technologies. Volume device applications are not critical since the development cost is lower than that of a CMOS-integrated MEMS process.

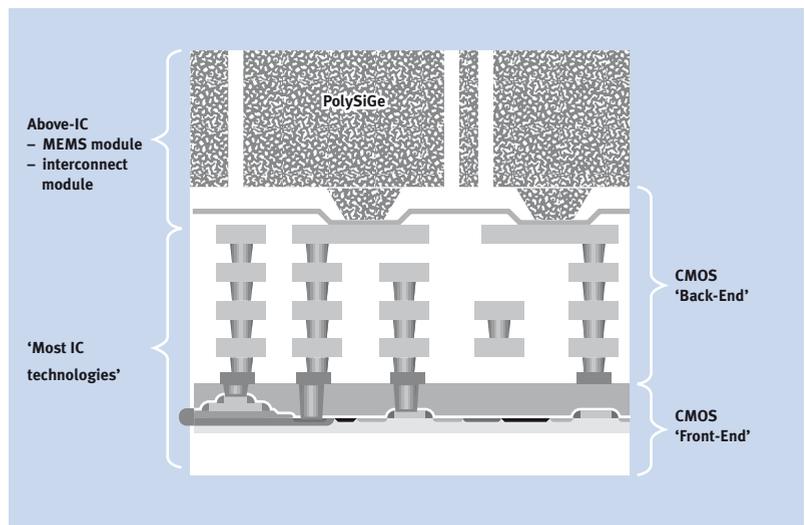
Mechanically speaking, polySiGe is an attractive alternative to poly Si, as it has similar properties. It is therefore very suitable for kinematic MEMS (accelerometers, gyroscopes, etc.) while the desired electrical and mechanical properties can be realised at a temperature suitable for post-processing MEMS on top of standard IC wafers with Al or even Cu on-chip interconnects.

PolySiGe started almost a decade ago at academia [Franke et al., 2003; Franke, 1999] and at IMEC [Sedky, 2005; Sedky, 1997]. The research initially focused on structural material and device characteristics and evolved to devices and integrated systems made possible by the monolithic polySiGe-MEMS-CMOS integration. Key devices fabricated while using this above-IC method are integrated accelerometers, gyroscopes, RF-resonators and optical MEMS devices.

DYNAMICS AND VALUE CHAIN

PolySiGe MEMS scores well on the aforementioned ‘semi-quantitative’ technology disruption level (facilitators-complicators) score. It is silicon-based,

Figure 3
Schematic representation of above-IC MEMS: a MEMS module processed above standard CMOS without any impact from or on the front-end and back-end of the CMOS platform.



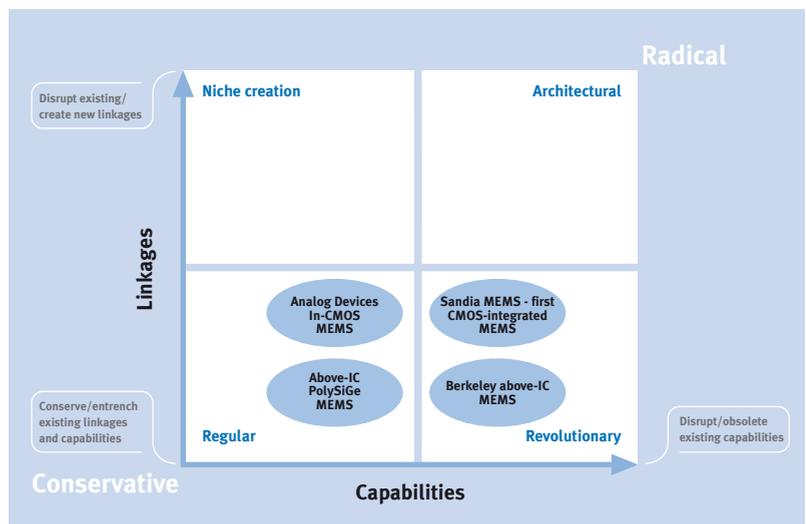
wafer-level technology. PolySiGe is available in most foundries offering a BiCMOS process and in many R&D centers investigating such a process. The cost increase due to the use of germanium is tolerable. Integration is by definition in a wafer-level fashion. As a consequence, nearly all facilitators are met, including the low temperature budget. No new materials and therefore no new contamination conditions apply. Remaining complicators concern the actual device production itself (the isolated process steps and modules) in a similar fashion as in evolutionary process scaling (with virtually no disruption).

PolySiGe above-IC MEMS could be considered a ‘sequential foundry mode’ of operation in the sense that it is realised by consecutive processing, after back-end CMOS technology. It can in principle be applied to any CMOS wafer. This MEMS add-on can take place in any suitable wafer processing facility and is not restricted to the CMOS foundry – it is not bound to a certain front-end/back-end of CMOS. As there is (in addition) an immediate link to equipment manufacturers that may be needed for MEMS-suitable tools, the value chain is not disrupted.

Such an approach is very different from the other CMOS-MEMS models, such as the dedicated CMOS-MEMS vertical integration adopted by captive MEMS companies. This approach works well if the large cost of a full and dedicated integration process can be written down over a large production volume.

Whereas the presented above-IC MEMS method certainly addresses merely a subset of all MEMS sensing or transducing device applications (bulk crystalline Silicon is an essential material for many hybrid MEMS device functional-

Figure 4
Transilience map for CMOS-MEMS integration.



ties), the presence of a well-established Si-fabrication value chain permits volume applications and ensures low costs. Successful future integrated MEMS technologies would therefore also benefit from meeting these constraints.

ABOVE-IC RF

INTRODUCTION

The ongoing revolution in wireless technologies results in a proliferation of new devices. Requirements become more demanding all the time: smaller size, lower weight, higher bandwidth and lower power consumption, and all this at ever-decreasing costs. As a consequence, the need for on-chip integration of mixed Digital-RF systems has become a reality. However, true System-on-Chip (SoC) integration remains a challenge, since the integration of many passive components (i.e. resistors, capacitors, inductors) and all the required active circuitry and optical devices are hard to integrate in a cost-effective way with sufficient quality or size on the same chip. That is why the System-in-Package (SiP) approach was developed. In this approach, the active devices may be integrated in one or two SoC devices, and the external passive devices and e.g. switch devices (such as RF MEMS) or resonators should be integrated in the SoC package, effectively realising an RF-System-in-a-Package, RF-SiP. A more elaborate technical review is provided in the references [Ulrich et al., 2003] and [Tilmans et al., 2003], and the sections below provide a summary perspective.

(a) Thin-film passives technology: SiP and heterogeneous SoC technology

An enabling technology for the realisation of these integrated resistors, inductors, and capacitors is a multilayer thin-film technology (Figure 5, left) used to realise these devices as well as the necessary electrical connectivity (interconnect) in a cost-effective wafer-level process. Technical details of this technology are provided in the reference [Carchon et al., 2005], and an example result is shown in Figure 6.

A characteristic feature of RF front-end integrated circuits is the relatively large area occupied by on-chip inductors. The large size of these inductors is a result of the physical limitations of scaling inductors while maintaining performance (the quality factor of the inductors decreases). Realising these inductors on such an RF-SiP substrate, as described above, is therefore not an option for higher frequency applications as the interconnect parasitics, even something as small as a flip-chip solder bump would completely degrade all performance improvement gained from using better off-chip inductors. When

manufacturing such passive components ‘above-IC’ (Figure 7), such a degradation is avoided. Because the inductor is further away from the lossy substrate and because thicker metal layers can be used, the quality of the inductor is higher. This leads to less power consumption for a given performance, or a better performance for a given power consumption.

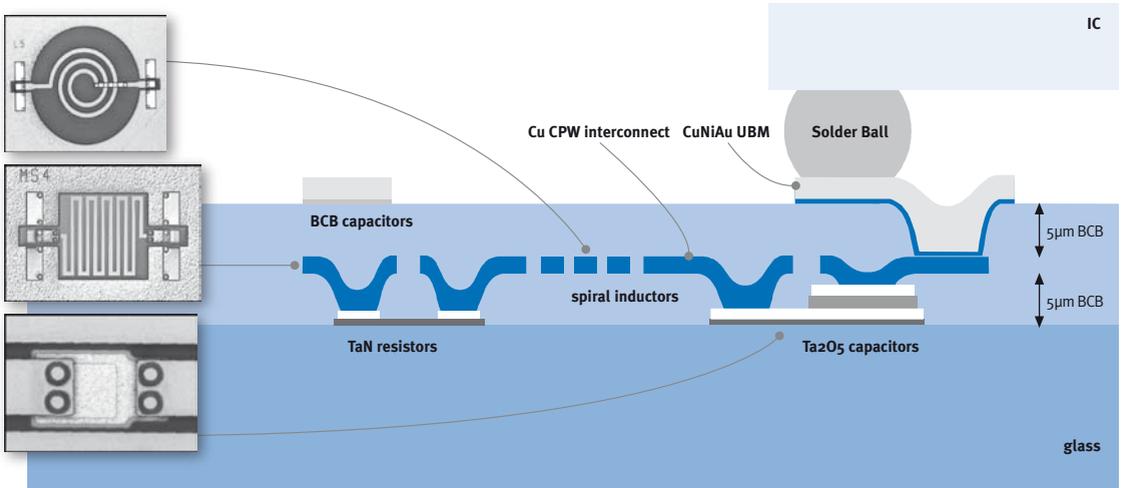


Figure 5 (top)
Schematic cross-section of the multi-layer thin-film technology platform.

Figure 6 (right)
One RF-SiP example, a 7x7 mm² Bluetooth RF module with integrated passives and solder ball connections.

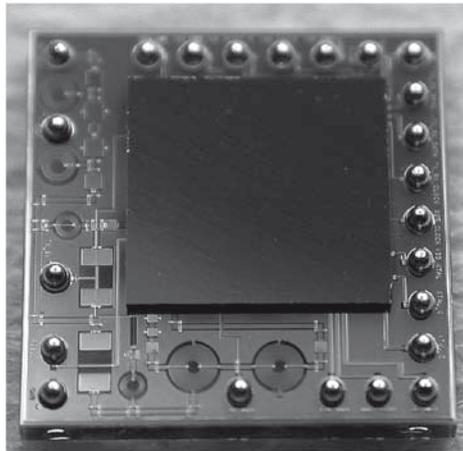
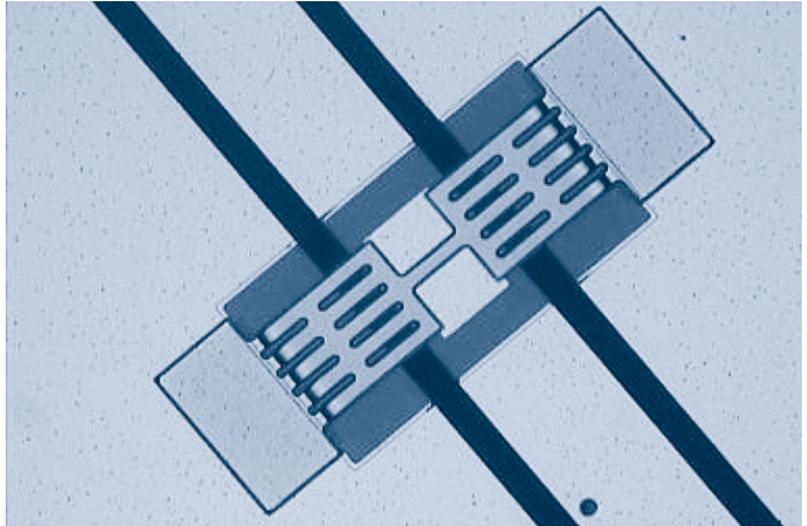


Figure 7
Above-IC inductor (left) and cross-section electron microscope image of the inductor-built-up (right) showing on the bottom the ‘above-IC’ principle: CMOS back-end metallisation stack (thin lines at bottom of the figure) and the 10 µm above-IC Cu (mushroom-like structure on top).



Figure 8

Picture of an unpackaged RF-MEMS switch.



(b) The future: RF-MEMS devices

To meet the required specifications of future mobile RF systems, it will be highly advantageous to expand the fixed passives technology with variable passives such as switches and variable capacitors. RF-MEMS devices can play a role here.

RF-MEMS switches have two stable states just like semiconductor RF switches. However, switching between the two states is achieved through the mechanical displacement of a freely movable structural part. This displacement is induced via a micro-actuator, generally based on electrostatic or piezoelectric actuation. Key benefits are a higher isolation, a lower loss over a wide frequency range, extremely low stand-by power consumption and the excellent linearity. An example is shown in Figure 8.

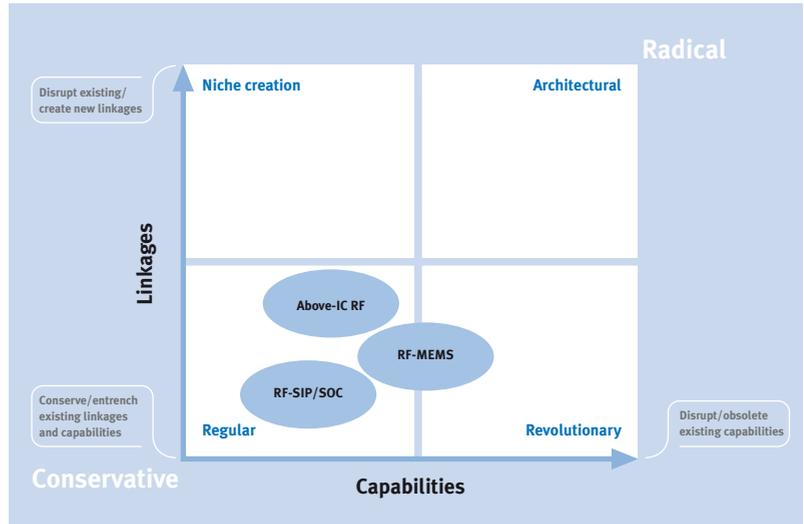
In the IMEC examples provided above, the required technology to build these devices is very closely related to the multilayer thin-film technology: RF-MEMS device processing predominantly uses the same materials, tools and processes as the multilayer thin-film and above-IC RF technology.

TECHNOLOGY FORECASTING USING THE ABERNATHY AND CLARK PERSPECTIVE

This above-IC post-processing process — although not standard CMOS — is compatible with both Cu and Al back-end interconnect processes of advanced CMOS. It therefore also causes low to very low technology disruption (Figure 9). In essence, it is a silicon-based, wafer-level technology, and the materials (Cu, BCB) are established materials (particularly Cu). Remaining complicators are the actual device fabrication itself (the isolated process steps and modules),

Figure 9

Transilience map for RF integration. The restrictive use of back-end compatible process modules forms a conservative innovation example. RF-MEMS comes in many flavours and historically caused architectural innovation. Emerging successes stem from using modules with little or no technology disruption.



in a similar fashion as in evolutionary process scaling (with virtually no disruption).

By limiting the RF-MEMS technology choices to materials and processes fitting within thin-film processing lines and CMOS above-IC, the level of technology disruption is further reduced or altogether avoided (Figure 9). While this puts more constraints on making such devices work at all or work reliably, the benefits in terms of a complete value chain are obvious. RF-MEMS will also play an important role in above-CMOS integration because of their compatibility with the thin-film passives. Ultimately, the CMOS platform will carry different built-up technologies, depending on the application and the system requirements.

Future RF systems will require ever higher integration densities, lower costs, operating at higher frequencies (bandwidth) and lower power levels. The concepts for above-IC high Q passives are therefore only the first step of a steady evolution. Other emerging devices are disk resonators (for intermediate frequency applications) and (film) bulk acoustic resonators ((F)BARs). Other More than Moore applications can be exploited in similar ways.

3D-INTEGRATION

INTRODUCTION: VARIOUS TECHNOLOGIES AND THEIR POSITIONING

Today, electronic interconnection and packaging is mainly performed in a planar, 2D design style. Further miniaturisation and functional and performance

enhancement of electronic systems requires the use of 3D interconnection schemes. Key technologies for realising true 3D interconnect schemes are the realisation of vertical rather than just lateral electrical connections, either through the Si-die or through the multilayer interconnect in which the silicon die is embedded. This form of heterogeneous integration is seen as one of the major enablers of More than Moore applications.

Different applications require different complexities of 3D-interconnectivity and this leads to various technology platforms. In an attempt to categorise these technologies, it is possible to start from the technology platform ('factory-type') used to create the 3D interconnect structures. Three major technology platforms for 3D integration are identified, based on the underlying infrastructure:

- 3D-SiP: System-in-Package (SiP) using Packaging infrastructure.
- 3D-WLP: Wafer-Level Packaging (WLP) Si-technology infrastructure; post CMOS fabrication.
- 3D-SIC: Stacked-IC technology; IC-foundry infrastructure; post front-end and before back-end.

In the following subsections, a very brief summary of these technologies and their applications will be given. Technical reviews are provided in the references [Beyne, 2004; Garrou, 2005; Karnezos, 2004].

3D-SiP

The 3D-SiP technology encompasses the packages with wire-bond die-stacks, but also involves package-on-package 3D stacks. It is currently the most mature technology and used in high-volume production. A relatively low packaging density is obtained.

A particularly interesting application area for 3D-SiP is the realisation of distributed, fully autonomous systems for realising so-called 'ambient intelligence' systems. These are sometimes referred to as smart-dust, e-grains or e-cubes. As shown in Figure 10, such systems can be divided into several subsystems: the radio (antenna, rf-front-end), the main application (processor, sensors, actuators) and the power management (regulation, storage, generation). Each of these functions can be realised as a SiP-subsystem. These may be very small (a few cubic mm to a few cubic cm), permitting its realisation using wafer-level processing technologies. These 2D-subsystems can be stacked on top of each other, realising a dense 3D-SiP system. Figure 10a shows such a conceptual 'e-cube' module with a volume of only 1 cm³. Figure 10b compares a real embodiment of the e-cube with standard technology.

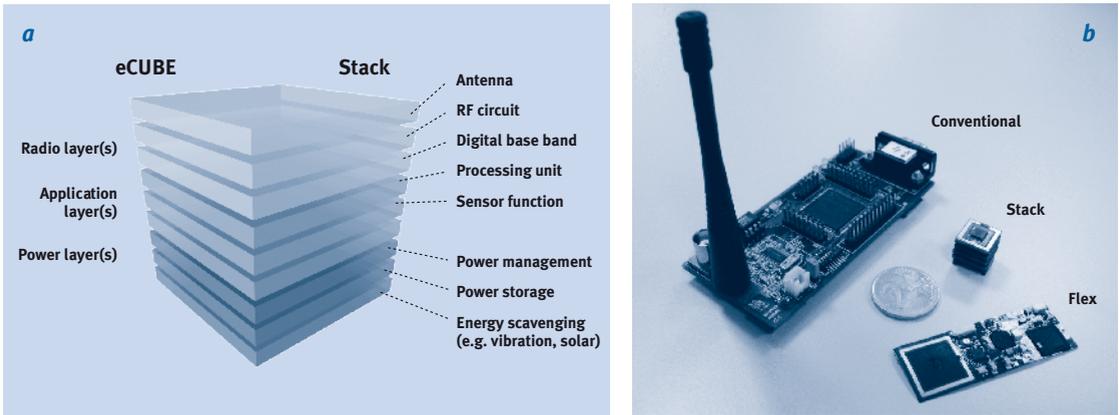


Figure 10

Example of a 3D-SiP application: schematic e-cube (a) and subsequent embodiments (conventional large system and miniaturised 3D stack or 3D flex embodiments): from 30 cm³ to 1 cm³ (b).

The limitation of this 3D-SiP stacking technology is the minimal size to be obtained. As the package size is by default larger than the chip size, even smaller form factors will require different integration schemes (see further). At present, a rather practical limitation of 3D-SiP is the lack of standardisation of packages, which limits a straightforward modular integration of 3D-SiP packages.

3D-WLP

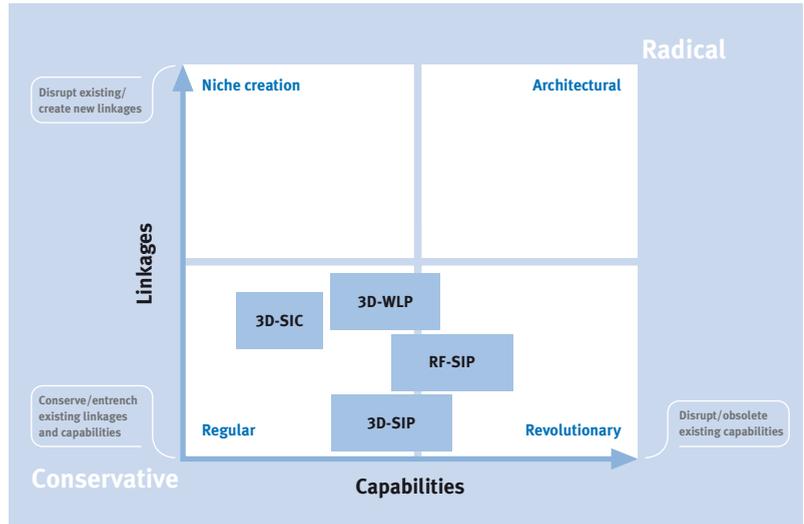
The 3D-WLP technology is based on wafer-level packaging infrastructure, as used for flip chip bumping and redistribution metallisations. Using additional technology elements developed for MEMS-technology, such as deep anisotropic Si-etching, 3D electrical connections can be realised at the wafer level.

This technology permits higher integration densities than 3D-SiP. Two different approaches are possible: die-to-die stacking and ultra thin chip embedding. In the first technology, a combination of wafer thinning, through-wafer interconnects (so-called ‘vias’) and micro-bump interconnects are used to realise stacked dies, in a wedding-cake style build-up. In ultra thin chip embedding, dies are thinned and embedded in dielectric layers, and thin-film technology (also called multi-chip-module technology) is used to reroute interconnects, at first laterally away from the die and then vertically through the dielectric layers to the next embedded die.

Applications of 3D-WLP technology include hybrid sensor (read-out systems, RF systems in 3D including RF-MEMS and antenna, and wearable microsystems using embedding in flexible substrates for, among others, on-the-body applications.

Figure 11

3D integration transience: 3D SIC as inside-IC regular innovation, and 3D-WLP, 3D-SiP (and its special case RF-SiP) as revolutionary innovations that are becoming established.



3D-SIC

The 3D-SIC approach uses the foundry platform technology to create ultra high density vertical interconnects. During the fabrication of the CMOS device, very narrow via holes (2-8 um diameter) are being etched into the silicon, filled with Cu (for electrical interconnection) and planarised. Then the standard CMOS back-end (i.e. a multilevel metal interconnect scheme) is processed. In order to interconnect different layers, the wafers are thinned to reach and expose the buried Cu vias. Their interconnections are realised by using Cu-Cu thermocompression or could involve very small solder bumps.

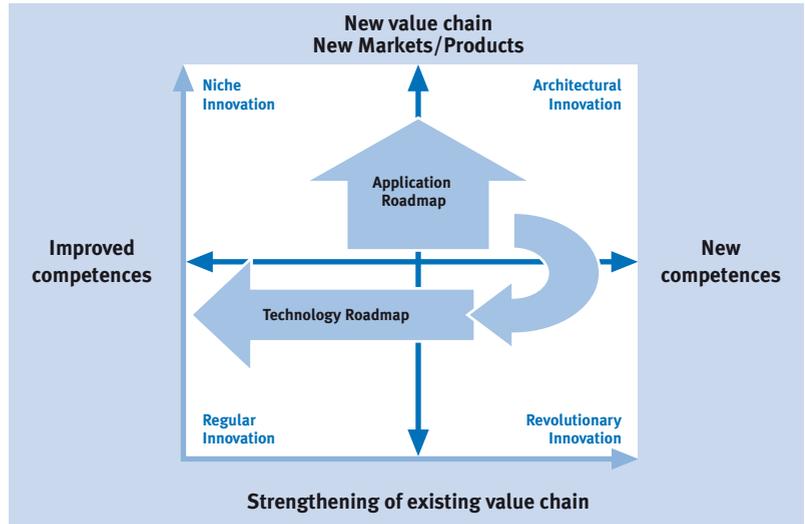
Applications of 3D-SIC integration are the hybrid integration of various types of memory on processor chips, 3D stacking of CMOS circuits and 3D stacking of memory banks.

TECHNOLOGY FORECASTING USING THE ABERNATHY AND CLARK PERSPECTIVE

The 3D systems presented are above all situated in the lower half of the Abernathy and Clark map, and in particular 3D-SIC can be mainly considered as an add-on to regular CMOS (Figure 11). This has facilitated and will facilitate their adoption. 3D-WLP and 3D-SiP are revolutionary technologies, but the technology disruption is limited. Particularly RF-SiP (including RF-MEMS) is clearly a revolutionary innovation.

The technological hurdles needing (cost-effective) solutions are extreme wafer thinning (10-20 um remaining thickness), high-aspect ratio (i.e. very vertical) narrow through-wafer vias, and their metallisation, microbumping, and temporary carrier bonding. Solutions for these hurdles will transfer these revolutionary innovations to regular technology.

Figure 12 (see next page)
Example trajectories of application roadmaps versus technology roadmaps.



MORE THAN MOORE ROADMAP DRIVERS

INTRODUCTION

In a rather fixed/existing value-chain, i.e. particularly for regular innovation, technology roadmapping is clearly desirable and highly beneficial. The ITRS roadmaps in the more Moore arena are sufficient proofs of this. More than Moore technologies emerging as a consequence of such regular innovation can in many cases be roadmapped, because the ‘underlying’ CMOS requires such evolutions (driven by power, performance, size).

Examples of ‘roadmappable’ More than Moore technologies of this kind are:

- New RF technologies (above-IC RF-System-on-chip and RF-System-in-Package using integrated passive devices).
- 3D-Stacked-IC (3D-SIC) technology.

Some More than Moore revolutionary innovations can be roadmappable as well. This may also depend on the amount of technology disruption. Selected examples are:

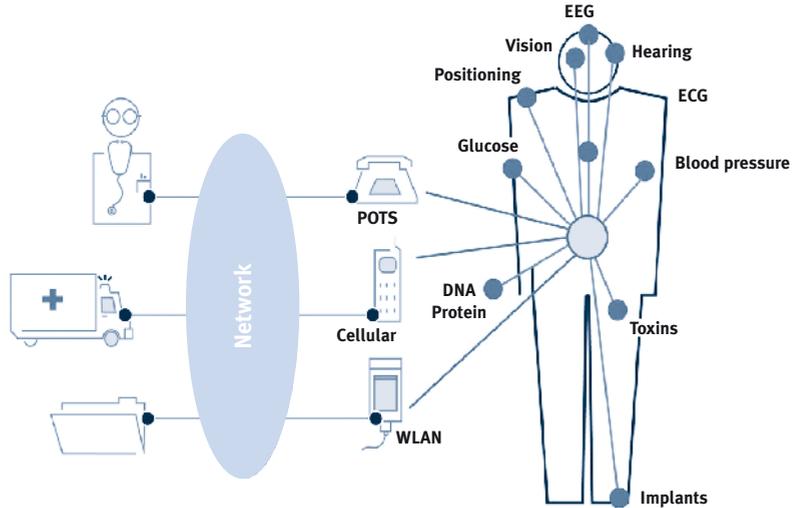
- 3D-Wafer-Level Packaging (3D-WLP).
- 3D-System-in-Package (3D-SiP).

Many More than Moore innovations cannot be roadmapped, as there is no clear (generic or specific) driver or set of drivers such as performance, power consumption or size, assuring the relevance of the products in the course of time, thus avoiding obsolescence. Examples are:

- Above-IC polySiGe MEMS.
- RF-MEMS/NEMS such as (switches, resonators, ...).

Figure 13

HUMAN++ visionary application programme: wireless autonomous diagnostic microsystems for health and comfort monitoring applications.



In particular for the latter emerging technologies and in general for most More than Moore technologies, visionary application drivers may provide guidance and may allow the extraction of technological needs as a function of time. These evolving needs may not be a logical evolutionary roadmap but a set of milestones needed at points in time. Furthermore, such application drivers may also point at a possible/desirable realignment of linkages. Whereas technology roadmaps are typically ‘horizontal’ trajectories, application roadmaps can be seen as vertical innovators (Figure 12).

The following section presents an example of a More than Moore application roadmap, and how it allows the creation of technology foresight. In addition, an example technology roadmap is discussed.

APPLICATION ROADMAP DRIVER FOR NICHE/ARCHITECTURAL INNOVATIONS: THE HUMAN++ CASE

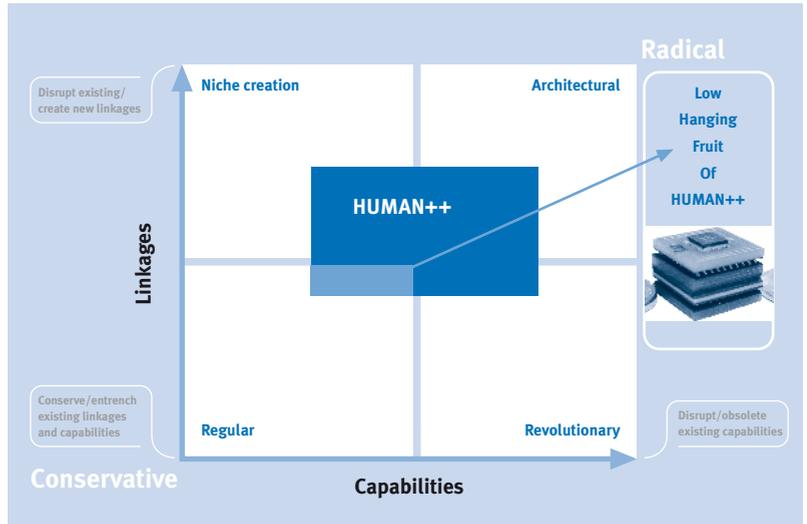
Introduction

As indicated above, visionary application drivers or scenarios may provide guidance. The Human++ programme from IMEC and HOLST is an example of such a visionary application programme.

Its vision is the following: in the future, a large number of state-of-the-art devices for medical, entertainment, comfort and sport applications will make use of sensors and actuator systems in and around the body. Device manufacturers are seeking opportunities to improve the functionality of devices for diagnostics and therapeutics, while at the same time keeping down the cost and improving user convenience (see Figure 13).

Figure 14

HUMAN++ positioning. Use of regular technology for improved solutions (or niche creation) is the so-called low-hanging fruit of the application programme (e.g. miniature wireless sensor nodes, as shown in the inset).



In a broader context, wireless autonomous transducers might find more widely spread use, not only in medicine/lifestyle, but also in process automation, agriculture, mobile gaming. The underlying hardware platforms are nevertheless very similar.

In order to make these applications reality, niche or architectural innovations will be needed. One exception is opportunistic low-hanging fruit such as miniature wireless sensor nodes. These innovations are examples of regular innovation or a marginally niche creation (Figure 14).

Figure 15

HUMAN++ R&D phases from hardware R&D to network R&D and application demonstration in selected application domains (medical, industrial, agriculture, gaming).

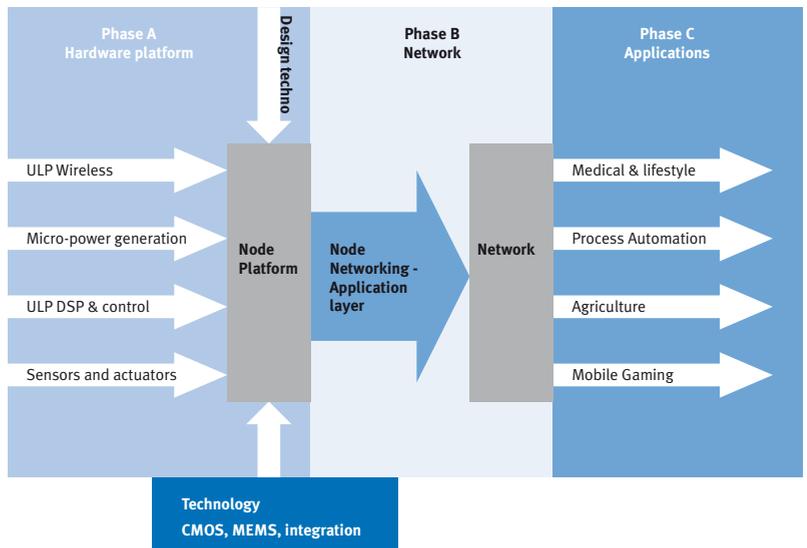


Figure 16

Subset of the HUMAN++/WATS technology roadmaps distilled from the application.

	2004	2005	2006	2007	2008
	ultra low power radio - IEEE 802.15.4A based				
				ULP radio optimized for biomedical	
			ULP ASIP for biometric DSP		
		Thermal micro-P generation			
	High-f mechanical micro-P generation				
		Low-f mechanical micro-P generation			
		Micro-needles for in vivo applications			
	3D PCB stacking				
			3D chip stacking		
	Flex polyimide				
		Biocompatible and stretchable substrates			
		Chip in a wire			

Guidance through application roadmapping

Although the applications may be visionary (not necessarily driven by customers), they allow the extraction of underlying technological requirements. To that end, the ingredients of the HUMAN++ hardware platform/system (sensors and actuators, power generation/storage, signal processing, wireless communication) (see Figure 16) are further broken down into mono-disciplinary component needs/requirements. For each component the availability of successive technology generations can be listed. This is particularly helpful as the technologies themselves are not clear at present (and their benefits are only just emerging).

As it can be inferred from Figure 16, the necessary roadmaps concern protocols, radios, digital signal processing, various methods of energy scavenging (thermal, vibrational, motion), probes, integration and packaging (3D stacking, flex, biocompatible packaging, chip embedding).

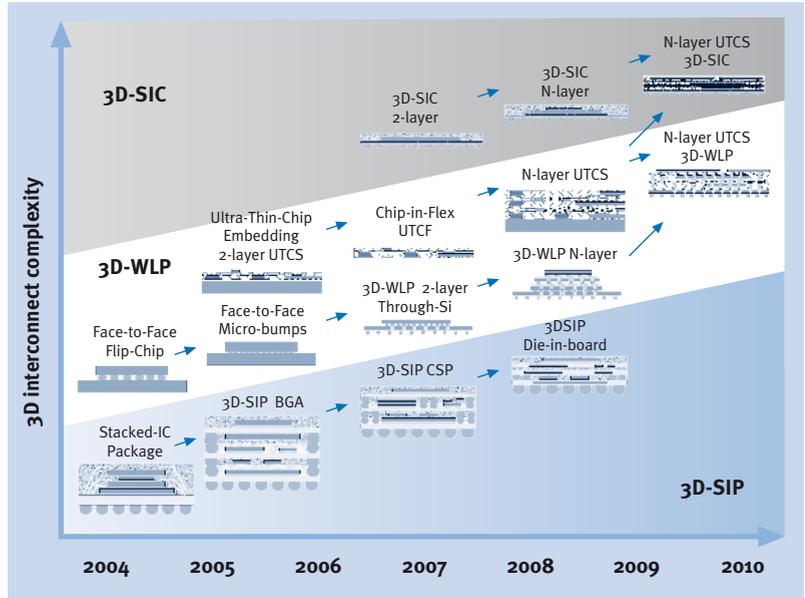
A more elaborate description of the necessary HUMAN++ technology programmes can be found in [Gyselinckx et al., 2005]. Apart from a careful alignment of necessary enabling technologies, such compound technology roadmaps also visualise the compound risk of the applications.

THE 3D TECHNOLOGY ROADMAP

Example of conservative or revolutionary innovation

In the paragraph ‘3D Integration’ three 3D integration technologies and their application ranges were introduced. Individual applications may require different flavours of an integration/packaging technology, and this would severely hamper technology roadmapping. The solution is the extraction of a common denominator technology that was found to be based on the combined needs

Figure 17
IMECs 3D technology roadmap.



of (in this case IMECs) industrial partners. Technology roadmaps have been drafted based in system needs as a function of time (see Figure 17).

The three roadmaps address the needs of different (sufficiently wide) application ranges.

System needs drive the 3D technology roadmap

The 3D-SIC roadmap (see Figure 17, top) particularly addresses the needs coming from memory and logic integration. It can therefore be based on these tools and materials available in advanced front-end and back-end CMOS. As an example, the through-wafer interconnect approach is based on Cu-damascene technology. Existing linkages with equipment manufacturers and material suppliers are strengthened in this innovative technology. It is driven by the need to interconnect ‘N’ (typically identical) memory layers to a logic block.

The 3D-WLP roadmap (see Figure 17, middle) shows a gradual evolution from regular flip-chip to face-to-face integration in at first two and ultimately ‘N’ layers. In order to avoid restrictions in the technologies and wiring of intermediate dies (leading to a wedding-cake style 3D integration), a more generic approach adopts ultra-thin chip embedding/stacking. As indicated in the paragraph on 3D Integration, 3D particularly addresses RF-integration and ambient intelligence applications, and is an essential More than Moore enabler. As it is strictly post-CMOS fabrication, it can be an add-on in most CMOS foundries and even more generalised in many silicon process facilities (e.g. MEMS

foundries). It increases the value of a CMOS die by adding functionalities (RF, MEMS, sensing, wireless, ...) in a much smaller footprint than when using hybrid or packaging technologies. It avoids the materials and temperature restrictions that above-IC MEMS faces, for example, and this is an asset.

Whereas 3D-WLP is very much 'IC-centric packaging', 3D-SiP is a packaging technology that is more related to packaging houses. It is a form of advanced packaging where certain innovative approaches (e.g. chip embedding) make a drastic miniaturisation and an increased value possible because of the creation of a system functionality (see Figure 17, bottom). In view of its technology, it can be considered an extension rather than a disruption of major packaging houses. It may require more advanced tools than currently present, for instance very precise die-thinning to much smaller dimensions than used in a normal packaging environment.

Particularly in 3D-SiC and 3D-WLP, the different generations on the roadmap also point out necessary technological innovations, such as new processes (coatings, carrier wafers, via filling), new materials (conductive polymers, silicone dielectrics/embedding materials, carbon nanotubes for interconnects). These innovations make this emerging revolutionary technology a regular innovation.

CONCLUSIONS

In the More than Moore domain, of which heterogeneous integration is a key part, innovations span the four quadrants of the Abernathy and Clark transilience map. The complications to be faced in case of increasing technological disruptions (top and bottom right quadrants) are listed, and examples are provided.

Apart from regular innovation, short excursions such as niche innovations or revolutionary innovations are attractive and provide the so-called low-hanging fruit in the More than Moore domain. The attraction of exploring the low-hanging fruit does not imply that only regular or incremental innovations will be successful.

Technological forecasting remains very complex. It becomes less daunting in those cases where there are clear drivers that can be translated into technological roadmaps. For those More than Moore cases where the drivers are not obvious, visionary application programmes with visionary (example) application scenarios may help to provide focus and therefore plan the technological

innovation needs. This leads to possible trajectories and increases the chances of success of such innovations.

REFERENCES

- Abernathy, W.J., K.B. Clark (1985). Innovation: Mapping the Winds of Creative Destruction. *Research Policy* 14, Nr 1. 3-22
- Beyne, E. (2004). *3D Interconnection and Packaging: Impending Reality or Still a Dream?* Proceedings of the IEEE International Solid-State Circuits Conference, ISSCC 2004, 15-19 February. San Francisco, CA, USA. 138-145
- Carchon, G., X. Sun, G. Posada Quijano, D. Linten, E. Beyne (2005). *Thin-Film as Enabling Passive Integration Technology for RF SoC and SiP*. IEEE International Solid-State Circuits Conference ISSCC 2005, 1, 6-10 February. San Francisco, CA, USA. Digest of Technical Papers, 398-399
- Franke, E., D. Bilic, D.T. Chang, P.T. Jones, T.-J. King, R.T. Howe, G.C. Johnson (1999). *Post-CMOS Integration of Germanium Microstructures*. 12th IEEE International Conference on Micro Electro Mechanical Systems (MEMS 99). Orlando, Florida, January 17-21. 630-637
- Franke, A.E., J.M. Heck, T.-J. King, R.T. Howe (2003). *Journal of Micro Electro Mechanical Systems* 12, 160
- Gad-el-Hak, M. (2001). *The MEMS Handbook*
- Garrou, Ph. (2005). *3D Integration: A Status Report*. Proceedings 3D Architectures for Semiconductor Integration and Packaging. RTI international. Burlingame, Tempe, Arizona, June 13-15
- Gyselinckx, B., C. van Hoof, J. Ryckaert, R.F. Yazicioglu, P. Fiorini, V. Leonov (2005). *Human++: Autonomous Wireless Sensors for Body Area Networks*. Proceedings of the IEEE CICC 2005. 13-19. See also http://www.imec.be/ovinter/static_research/human.shtml and <http://www.imec-nl.nl/getfile.php?id=61>
- ITRS (2005). *The International Technology Roadmap for Semiconductors: 2005*. Semiconductor Industry Association
- Karnezos, M. (2004). *3-D Packaging: Where All Technologies Come Together*. IEEE/SEMI 29th International Electronics Manufacturing Technology Symposium, July. 64-67
- Madou, M.J. (2002). *Fundamentals of Microfabrication: The Science of Miniaturisation*. CRC
- Petersen, K.E. (1982). *Silicon as a Mechanical Material*. IEEE 70 (5). 420-457
- Sedky, S., P. Fiorini, M. Caymax, A. Verbist, C. Baert (1997). *Thermally Insulated Structures for IR Bolometers, Made of Polycrystalline Silicon Germanium Alloys*. Solid State Sensors and Actuators, IEEE. New York, 1525. 237-240

- Sedky, S. (2005). *Post-Processing Techniques for Integrated MEMS*. Artech House
- Tilmans, H.A.C., W. de Raedt, E. Beyne (2003). MEMS for Wireless Communications: from RF-MEMS Components to RF-MEMS-SiP. *Journal of Micromechanical Micro-Engineering* 13, 139-163, and references therein
- Ulrich, R., L. Schaper (2003). *Integrated Passive Component Technology*. IEEE Press. J. Wiley & Sons

Large-area Printable Electronics

Frank Simonis¹, Herman Schoo²

INTRODUCTION TO LARGE-AREA ELECTRONICS

When discussing the future of nanoelectronics it seems paradoxical to talk about large-area electronics. However, in a world that is more and more influenced by microelectronics, ICT and ambient intelligence, the demand for large-area electronics is rapidly growing. Touch screens, flat panel displays and electronic paper are typical examples of products based on large-area electronics. The introduction of ambient intelligence will not only lead to a larger demand of displays ('displays everywhere') but also of other kinds of surfaces that can interact with the environment and its users by sensing, signalling, illumination, actuation, memory, power or energy scavenging.

¹ TNO Future Technology Center, Eindhoven, the Netherlands.

² Holst Centre, Eindhoven, the Netherlands.

Whereas the semiconductor industry can be characterised by an ongoing extension of Moore's law toward smaller and smaller device dimensions, thus providing ever higher function density for the same costs, the display industry is driven by 'more area' in order to fulfil the demand for larger displays, with similar decreasing cost scenarios as for the semiconductor industry. More electronic area at lower costs is the main target. The flat panel displays can be regarded as the original drive behind large-area electronics. This development started with the TFT-LCD displays by using plasma CVD deposition of thin, transparent amorphous silicon on glass panels followed by lithographic patterning of transparent transistor matrices. This technology is almost mature and widely spread but needs large investments in the race to increase yield at increasing dimensions. Going from a 6th generation fab, running on 1.5 x 1.85 m substrates, to a state-of-the-art 7th generation fab on 1.9-2.2 m to the next coming 8th generation on 2.2 x 2.5 m substrates has driven the fab investments up from about 1 to over 6 billion dollars; big figures, even for a high-volume market. Technically speaking, the plasma CVD route makes it possible to deposit polycrystalline Si for high-speed circuitry, even on flexible polymer foils. However, these technologies have not been commercialised on a large scale as yet.

Apart from these large-area silicon developments, electronic polymers came into the arena, starting with OLED displays and later on with PLED technology featuring cheap printing technology instead of expensive lithographic techniques. The fab investments for printable polymer electronics are lower, typically in the range of several tens of millions of dollars, thus providing a lower cost alternative to the existing multi-billion dollar investments in fabs for TFT-LCD technology. Furthermore, printable polymer electronics also provide promising opportunities for the development of new electronic applications. Although silicon is far superior in some electronic properties, electronic polymers offer other unique features, such as the possibility to use flexible foils as a substrate, light-emission properties, sensing capabilities and ease of integration into products. Compared to large-area amorphous Si technology, technological progress in polymer electronics and particularly in printable electronics is more disruptive and underlies promises for many future innovations. This chapter will then further discuss the developments in this latter field.

POLYMER ELECTRONICS

The history of electronic polymers starts in 1977 with the discovery that the conductivity of trans-polyacetylene increases seven orders of magnitude upon doping with iodine. The Nobel Prize in Chemistry for 2000 was awarded

to the three scientists — Alan Heeger, Alan MacDiarmid, and Hideki Shirakawa — the co-discoverers of electrically conductive polymers. Their work provided the starting point for recent developments in polymer electronics technology.

Polymer electronics holds out the prospect of new products with reasonable times-to-market and a large revenue potential. One of the key advantages of polymer electronics lies in its ability to create products of a kind that actually never existed before, such as electronic paper, light-emitting foils, roll-up displays, photovoltaic cell or sensor-laden laminates or coatings, and low-cost optical interconnects. There is also a considerable industry push behind this technology. Several of the largest materials and electronics firms — Samsung, DuPont, Kodak, Philips, Siemens, Sony, Xerox and Agfa, for example — already sell or develop polymer electronics products. Also large chemical companies, such as Merck and Sumitomo are entering the field.

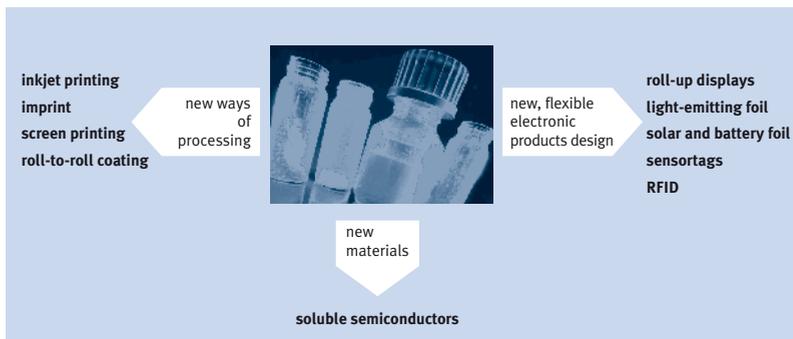
Organic (semi-)conducting materials used for polymer electronics can be either processed by vapour phase deposition (for small molecules) or by solution-based deposition (for small and large molecules), using techniques similar to those of inkjet printing or rubber stamping thus reducing the need to build giant fabs. For economic reasons, because of the combination of a high throughput and low equipment costs, solution-based processes such as inkjet printing provide the most promising process technology for large-area applications. Apart from the large-area applications, vacuum deposition of small molecules still offers clear advantages for smaller devices and for complex applications. It is therefore assumed that both technologies will continue to exist in the future.

Since the discovery in 1977, the number of patents filed in the field has considerably increased. Since 1996, related patent trends can be observed in inkjet printing and organic luminescence. The key factors behind this interest in polymer electronics are:

- use of relatively simple process technologies such as printing, roll-to-roll coating, etc.;
- large-area, low-weight, thin, flexible applications such as roll-up displays, light-emitting foil, solar and battery foil, sensor tags, RFID;
- integration of these devices on a variety of substrates such as plastics and plastic foils;
- relatively simple, intrinsically low-cost technology offering the opportunity to open up new markets for electronic products;
- relatively low entrance costs provide a low barrier to entry for small/medium-size companies.

Figure 1

Innovation aspects: printing electronic systems on large-area flexible foils.

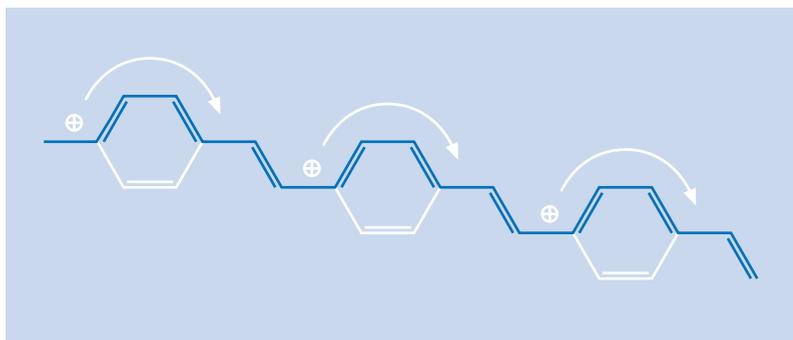


STATE OF THE ART

Electronic polymers are materials with metallic or semiconducting characteristics and with mechanical properties known from polymers, a combination not found in any other class of materials. In general, these materials have an extended conjugated p-electron system along their backbones, giving them the ability to transport positive and negative charge carriers with high mobilities along the chains. The doping of conjugated polymers, such as polyaniline, polypyrrole and polyethylenedioxythiophene (PEDT, PEDOT), leads to the presence of electronic states in the band gap (hopping states). At sufficient dopant concentrations, the band gap effectively disappears and the polymer acts as a metal with a high conductivity, hence the term ‘synthetic metal’ (see Figure 2).

Figure 2

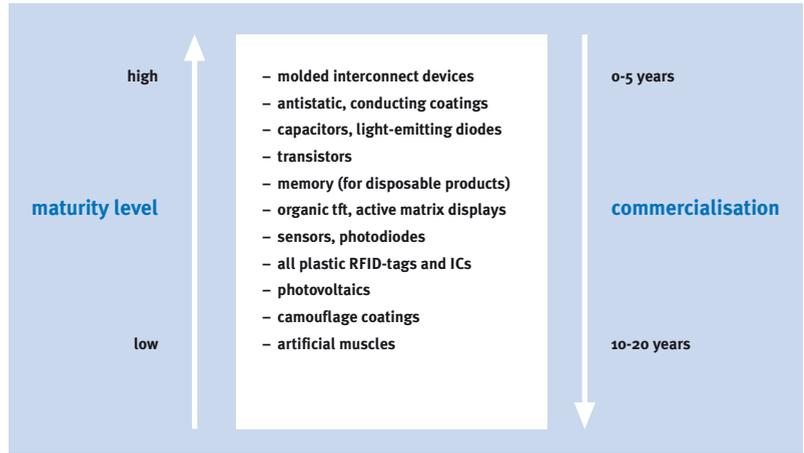
Electronic polymers like PPV are sometimes called ‘synthetic metals’ because doping of these conjugated polymers leads to the presence of electronic ‘hopping’ states in the band gap. This results in a metal- or semiconductor-like conductivity, depending on the doping level.



The exploration of conjugated polymers for semiconductor device applications such as photovoltaic cells, field-effect transistors, light-emitting diodes (LEDs) and diodes, has become a major focal point of interest. Some of the polymer electronics applications are already mature or close to maturity such as anti-static coatings and organic LEDs. Other applications are only at an early stage of development (photovoltaics, artificial muscles). An indicative ‘maturity’ list would give the following rankings (see Figure 3).

Figure 3

An indicative 'maturity' list of some of the polymer electronics applications.

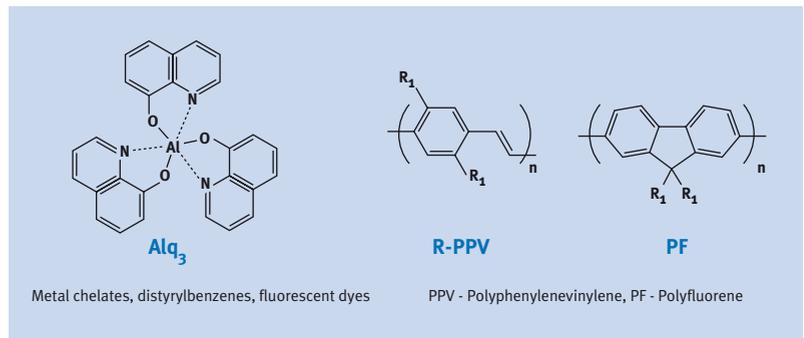


Light-emitting polymers

The development of light-emitting polymers was originally initiated for flat panel displays in order to come up with brighter and cheaper displays to replace LCD and plasma. It started with OLED systems using existing vacuum deposition technologies and subsequently vapour phase small-molecule electronic polymers. This has led to several commercial display products. The pressure on high-throughput production of large-area systems has moved the interest to printing with soluble polymers (PLED system). PPV (polyphenylenevinylene) has been one of the most studied series of these light-emitting polymers due to its excellent luminescent and mechanical properties. The PPV family of polymers serves as a prototypical conjugated polymer class both for application and for a fundamental understanding of the electronic processes in conjugated polymers. The goal is to modify the chemical structure of PPV to achieve an electroluminescence spanning the visible and near-infrared regions (see Figure 4).

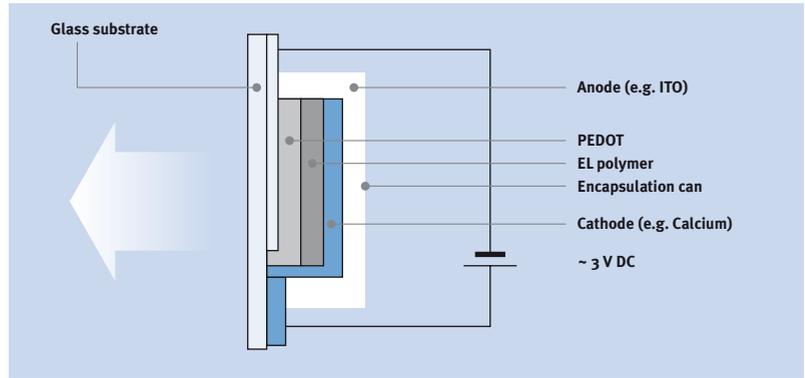
Figure 4

Left: Typical OLED materials, small-molecule, vacuum. Right: Typical PLED materials, solution-based.



At present, PLED systems are not only developed for displays. The prospects of PLED have also been recognised for applications in (large-area) lighting and signage devices.

Figure 5
Schematic setup of a polymer LED.



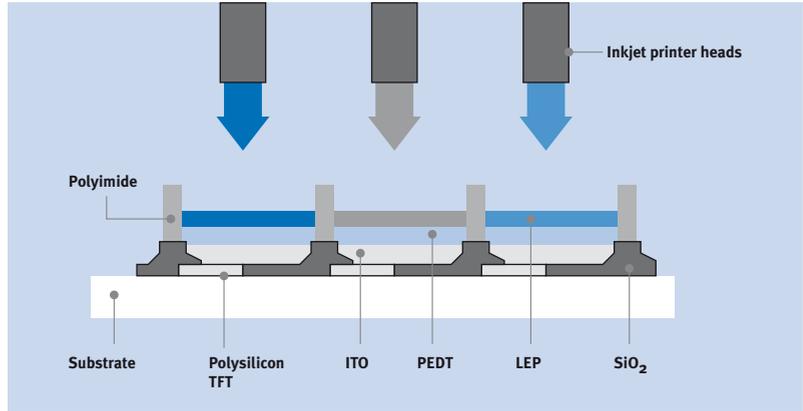
Polymer ICs

Polymer logic and integrated circuitry are possible with organic semiconductors, such as pentacene and polythiophene both in printed patterns or patterns made by lithography. The limiting factor in practical systems is the relatively poor charge mobility. Up to now, the best mobility in small-molecule (vacuum) organic FETs has been $10 \text{ cm}^2/\text{Vs}$ and in a polymer FET only $0.1 \text{ cm}^2/\text{Vs}$. This limits the operation window to low frequencies, up to the kHz range and with some examples up to the MHz range (polymer RFID tags at 13.54 MHz, PolyIC, Philips). Compared to CMOS technology, polymer ICs are currently low in performance and only suited for low-cost, large-area applications, such as low-end TFT-displays, electroactive displays, cheap memory functions and RFID-tags. In combination with the intrinsic flexibility of the devices, however, one of the killer applications of this technology may prove to be the one in rollable displays (Polymer Vision) (see Figure 6).

Figure 6
Rollable display concept from Polymer Vision. Source: Polymer Vision.



Figure 7
Inkjet printing PLED displays.



Patterning technologies

Processing technologies for polymer electronics are essentially an example of microtechnology. The patterning of polymer electronic devices requires micro-scale accuracy (typically 1-2 μm) instead of the nano-scale accuracy of modern CMOS processes. However, this micro-scale accuracy needs to be realised on a large area. Another technological challenge is set by the substrate, preferably a polymer foil, with an inherent poor dimensional stability. It puts high-end equipment makers to the test to keep the patterning in control under high-throughput and yield requirements (see the Figures 8 and 9).

A selection or combination can be made of the following patterning technologies, based on the feature sizes and accuracy required by the application.

- Optical: large-area litho, laser writing/curing/ablation.
- Printing: offset, screen printing, inkjet, embossing, imprint.
- Liquid coating: flow or spin coating, roll or web coating.

CHANGING THE VALUE CHAIN

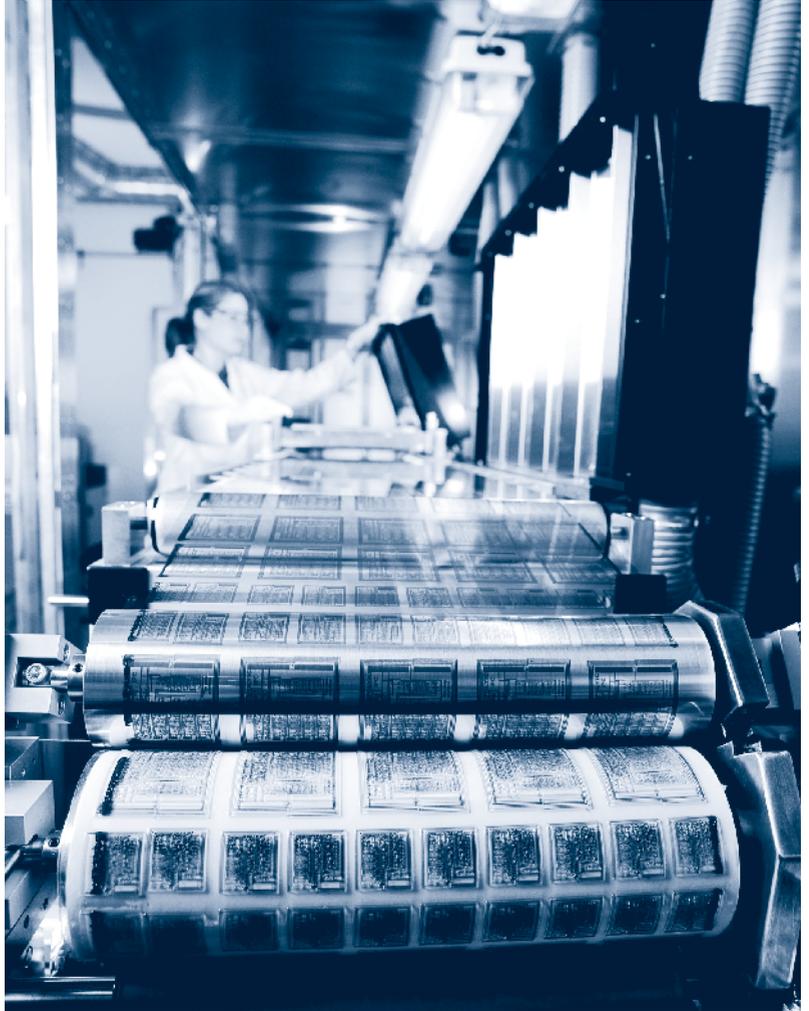
The upswing in polymer electronics seems to be boosted by two major, more or less independent technological developments: electroluminescent and semiconducting polymers (since 1990) and printing technologies (since 1993).

The development in inkjet printing technology started in the early 1990s, stimulated by the demand of home pc-consumers. The potential of this technology for the microstructuring of industrial products was recognised only later. The interest in luminescent and semiconducting polymers was boosted by the growing demand for flat panel displays.

It is assumed that polymer electronics offers some radically new directions for electronics, including the creation of a range of entirely new products

Figure 8

Roll-to-roll printing by PolyIC. ©
PolyIC GmbH&Co.KG, Fürth.



that could not be manufactured using conventional approaches, such as CMOS. There are five fundamental reasons why polymer electronics is special [Nanomarket, 2005]:

- novel material properties and product features;
- manufacturing economies;
- lower cost of entry;
- open and faster innovation;
- new industry boundaries.

Novel material properties and product features. The flexibility of thin films themselves suggests new product directions, including roll-up displays, conformal lighting, low-cost RFIDs, sensor arrays, and flexible photovoltaic. Polymer electronics also generates very little heat and uses small amounts of power, alleviating major problems associated with conventional electronics.

It is assumed that the approaches to polymer electronics with the greatest commercial prospects are the ones that emphasise these advantages to the fullest — that is, the ones offering the lowest manufacturing costs and using flexible substrates for the production of large-area devices: the domain of large-area electronics.

Manufacturing economies. The manufacturing processes that will ultimately be adopted for building polymer electronic products remain in a state of flux. However, it is clear that the economic side of polymer electronics will be much more attractive than state-of-the-art CMOS manufacturing. It is not necessary to build fabs costing billions of dollars. Instead, a new paradigm is created in which electronic circuits are printed using inkjet technologies, stamping or some other similar process. This means that polymer electronics products can be economically produced in relatively short runs and can be customised to meet the needs of low-volume customers.

Table 1
Manufacturing economies, now and in the future.

	CMOS electronics	Polymer electronics
Materials, products	hard, inorganics, metals	soft, polymer, organic
Structuring	lithography, vacuum deposition	printing, self assembling
Function integration	system integration in a package	all-in-one printing and laminating
Fabrication infrastructure	ultra clean-rooms	self-contained
Fabrication equipment	highly specialised, expensive	relatively simple, inexpensive
Manufacturing economics	high volume, standardisation	low and high volume, customised
Innovation cycle	high threshold, closed group	low threshold, open innovation
Players in value chain	small group of multi-nationals	many big and small newcomers

One consequence of these dramatic differences between conventional and polymer electronics is that the introduction of polymer electronics and the related emergence of a new value chain could considerably change the structure of the electronics sector.

Lower cost of entry. The new production methods decrease the cost of entry into the electronics business. If electronic circuitry can be created with something akin to an inkjet printer, semiconductor firms can start producing their own circuitry at relatively low capital costs. This reverses the trend toward

Figure 9

Printing line for PLED displays,
Orgatronics/OTB. Source:
Orgatronics B.V.



fab-less firms, which simply cannot afford to get into the manufacturing of silicon chips.

Open and faster innovation. The lower entry costs plus the attractive manufacturing economics for the customisation to low-volume needs will boost the innovation process, since these factors will decrease the threshold for testing new product concepts in the market and enable a fast adaptation to changing consumer needs. The innovation cycle will become shorter and the cost of innovation will decrease. This will also have a beneficial effect on the number of players that will be able to enter the polymer technology arena, integrating polymer electronic components in their products.

New industry boundaries. As polymer electronics is all about printing with organic inks on flexible substrates, it offers opportunities for firms in inkjet printing technology (such as HP, Xsaar, Seiko Epson and Canon) but also for companies with a history in screen or offset printing (e.g. Kurz with Siemens in PolyIC). Even more important, materials firms, such as Sumitomo, Bayer, Merck and AGFA, are likely to see polymer electronics as an emerging opportunity.

While all this may suggest that we are on the verge of a revolution in the electronics sector, it is worth noting that there are still some significant issues and uncertainties that have to be dealt with in order to develop the polymer electronics field into a viable and competitive part of the electronics sector. These include the following:

- materials and production uncertainties;
- market uncertainties;
- the limits of polymer electronics.

Materials and production uncertainties. Conductive polymers and flexible substrates that are capable of supporting polymer electronics are commercially available. But the amount of research in this field increases and no-one knows as yet what will be the standard materials platforms for polymer electronics in the future. Long-term stability of such materials, protection against moisture and oxygen with barrier coatings and smart interconnecting laminates are currently topics of a particular interest in research (e.g. Holst centre). The same can be said of production technologies — everyone knows that ‘polymer electronics’ will be ‘printable electronics,’ but no-one is quite sure what standard forms of printing will exactly consist of.

Market uncertainties. Whether there is a real market for polymer electronics-based products remains to be seen. It seems obvious that a large roll-up display that can help turn a cell phone into a computer would ultimately provide a significant demand, but this cannot be stated with total certainty. The same applies to flexible and conformable lighting. The appealing product concepts enabled by polymer electronics are genuine novelties — but so are their markets.

The limits of polymer electronics. The current generation of polymer electronics-based products such as displays, lighting and signage, addresses markets in which there will be no direct competition with CMOS. However, no-one really knows how and where the two materials/technology platforms will ultimately compete. Polymer electronics still seems to be far removed from providing an alternative to CMOS-based processing and logic. Still, some of the theoretical work that has been done suggests that organic material may be used to create processors up to 1 THz — if only the right material could be found.

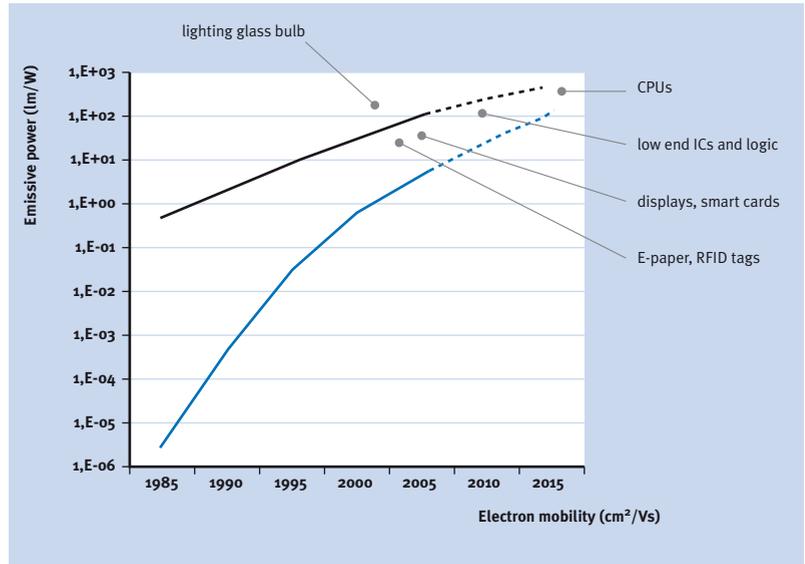
FUTURE OUTLOOK

The future of polymer electronics will be determined by products that best exploit the disruptive aspects of polymer electronics. These aspects are:

- the printing technology:
 - production of electronics on large areas and on flexible foils;
 - low entry and running costs (roll-to-roll printing fabs);
 - all-in-one processing and function integration (smart lamination).
- the specific functionalities of electronic polymers:
 - a variety in functionalities: conductivity, logic/memory, light emission, sensing, power generation, and all this in specific combinations if needed for integrated devices.

Figure 10

Rate of improvement in electron mobility and light-emissive power of electronic polymer materials.



In comparison to the existing display, lighting and semiconductor technologies, polymer electronics technology is relatively young. In only 15 years, considerable progress has been made in the improvement of polymer properties, not only in electron mobility, but also in light-emissive power. Figure 10 indicates the rate of improvement. The power efficiency of polymer LEDs has already surpassed the level of that of the light bulb. The development efforts are now focused on achieving a similar efficiency and lifetime as those of the fluorescent tube. These achievements now push polymer electronics toward existing markets for displays, lighting, ID-tags and smart cards. In these markets, polymer electronics becomes more and more competitive in terms of performance (instead of cost) as it brings added value through weight reduction, flexibility, low power consumption and a short product development cycle in the future.

NO MORE MOORE SCENARIO

Despite its progress in performance over the past years, it is unrealistic to assume that the performance of polymer electronics can or will be further developed in a Moore's law scenario. Not only the material itself is a limiting factor (for example, the theoretical limit for P/OLED is 200-500 lm/W), but also the back-lag in performance compared to silicon technology makes it unrealistic to think that polymer electronics will become a serious competitor in existing semiconductor applications. The future playing field for polymer electronics will be in those areas where it can outperform other technologies based on its specific strengths. The top ranking list in future market volumes (expectations up to US 50 billion dollars in 2015) is assumed to be:

- displays;
- lighting;
- memory, RFID, integrated devices (smart cards);
- solar, thin film batteries;
- sensors.

SCENARIO BASED ON LARGE-AREA AND FLEXIBILITY: DISPLAY AND LIGHTING MARKETS IN THE LEAD

The recent history of the technological and market successes of the flat panel displays shows that existing markets (i.e. the CRT tube) can be successfully conquered, provided that consumers are offered added value in terms of quality, performance, price, dimensions or other sorts of advantages. There are two major existing markets that are attractive for polymer electronics:

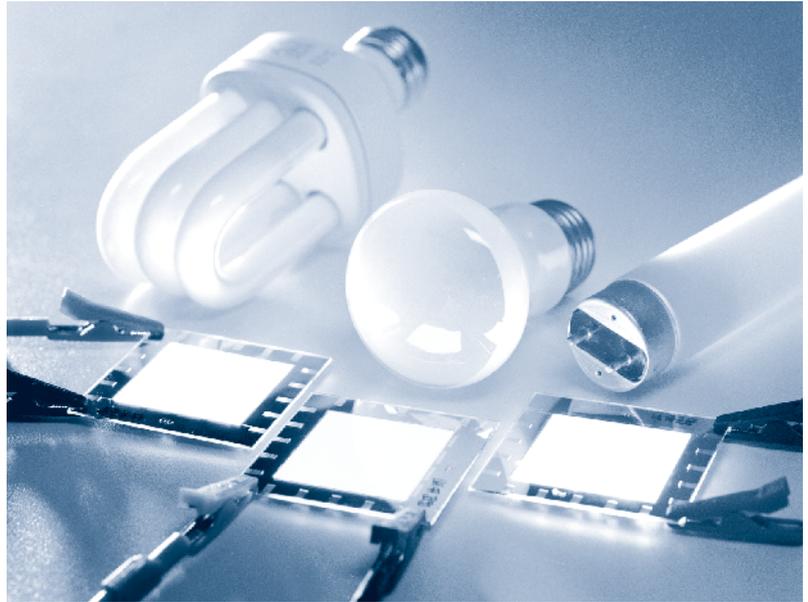
- the display market where polymer electronics can offer jumbo-sized displays and/or flexibility and roll-up displays (outperforming LCD and plasma);
- the lighting market where polymer electronics can offer conformal, large-area, lightweight and low-power lighting (outperforming light bulbs and fluorescent tubes).

Non-flexible polymer LED displays were introduced in niche markets already some years ago, but were not able to successfully compete with standard LCD displays to a significant extent. The future of polymer LED therefore seems to lie in products that offer a radically different value proposition, such as products using flexible foils as a substrate. Another major breakthrough is expected to be in large-area lighting applications employing organic LEDs that will most probably appear first in flat non-flexible forms (e.g. backlights, LCD displays, signage), to be followed by large-area lighting in flexible foils. Both markets are attractive as to volume, and it is not surprising that large multinationals (electronics, lighting and chemicals) started to direct their attention to the opportunities emerging in these market sectors. More recently, large multinationals often leave product development and market introduction of such products to start-up and spin-out companies, such as CDT, PolyIC, Polymer Vision, LiquaVista.

These large market perspectives are important, because they will stimulate the necessary technological developments that are still needed, especially with respect to electrical performance, durability and life span. In the slipstream of the progress gained there, other applications can be more easily achieved and developed. Based on the market pull, it is expected that the following areas will be developed for polymer electronics in order of time.

Figure 12

Organic LED light sources have the potential to replace today's conventional light sources. Source: © Philips.



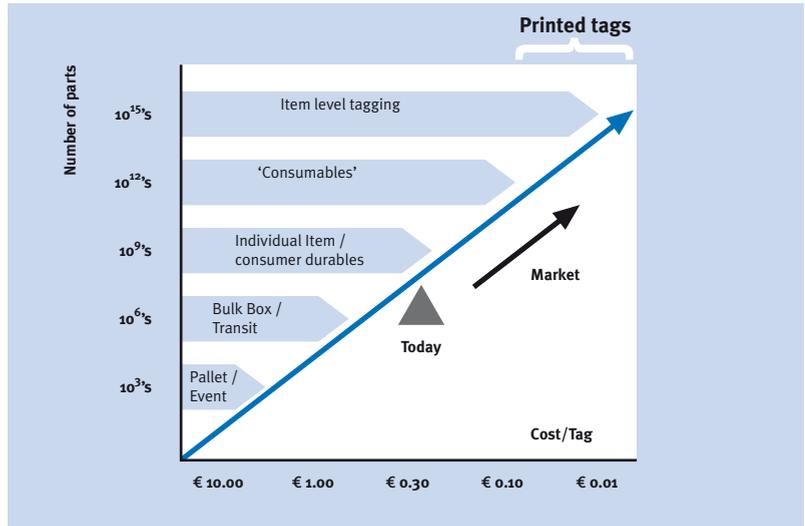
The final point is probably the most important: The comparatively low-investment level in printing technology will lower the barrier to entry for new entrants in the lighting market (see figure 11).

Tags, sensors and logic

In particular the labelling and packaging industries are looking for sensing capabilities (see figure 14) in order to signal the condition and safety of packed goods. Many sensing capabilities of electronic polymers have already been proven (optical, chemical, rf). Such applications are expected to first enter the market as niche products. In the same field, tracking and tracing of goods with RFID-tags is a very hot topic. The market for this technology is expected to grow much more rapidly than the market for sensing tags thanks to the anticipated costs savings in logistics. For tracking and tracing, polymer electronics has to compete with Si-RFID technology. For Si-RFID, the production of an integrated device with cheap but very tiny silicon chips is becoming a major cost factor. This is where polymer electronics can offer an alternative as it provides excellent integration capabilities due to its printing technology: Both the RFID chip and the antenna can be printed and integrated in a foil or label during a roll-to-roll printing process. Up to now, the limiting factor in polymer electronics-based RFID devices has been the electronic speed. At present, the state-of-the-art polymer RFID technology is capable of producing 13.54 MHz chips at the most. PolyIC has announced to introduce their printed polymer 13.54 Mhz RFID tag 'polyID' in the course of 2007.

Figure 13

Dropping prices for RFID tags in different markets. Source: AUTO-ID Center.



Because of the excellent integration capabilities, expansion of the RFID functionality with sensing and memory capabilities are most likely to be future features for polymeric tags. It will open up markets for RFIDs (identification, tracking and tracing) with sensing capabilities to monitor products during their lifetime (temperature history, moisture, bacteria content etc.).

Thin-film power

An advantage of polymer electronics is that the powering can also be produced by polymer electronic solutions, such as thin-film polymer batteries and/or thin film polymer solar cells (see figure 14). These solutions can be integrated into polymer electronic devices in a relatively simple way due to the similar production technology involved. At the moment, both the thin-film

Figure 14

Capabilities and linkages in the Abernathy and Clark diagram for tags, sensors, logic and thin-film power.

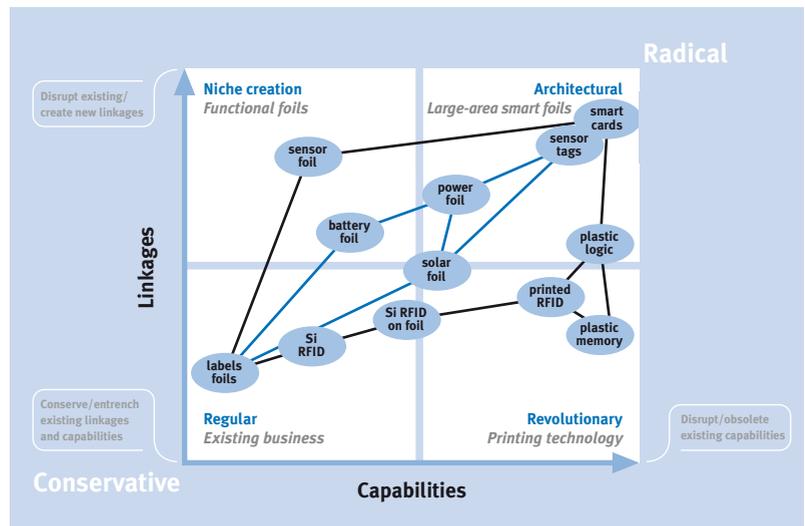


Figure 15
Powerpaper.
Source: Power Paper Ltd.



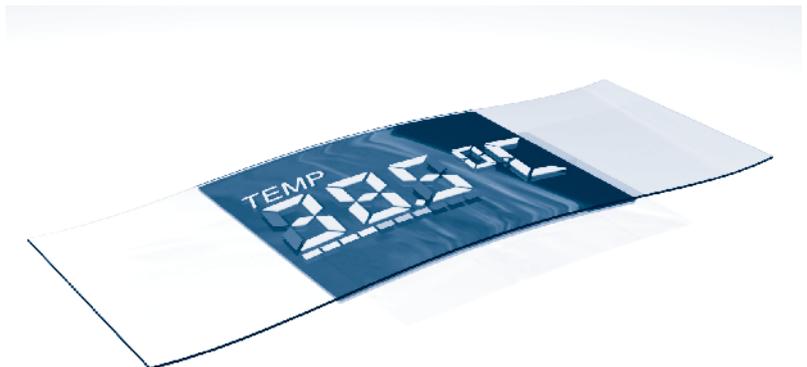
flexible batteries and the polymer solar cells are considered as niche products, but their impact will grow when the need for technology integration increases, e.g. in thin-film polymer devices that require an on-board power source.

Integrated devices

It is expected that the future success of large-area electronics will very much depend on its capabilities to integrate more than one function in a foil at an acceptable cost level. Examples are found in the field of self-signalling sensor tags (sensing + logic + signage + power) and devices, such as smart cards (logic + memory + display + power). Like More than Moore, function integration will be the key for large-area electronics. It will require further technology development in the fields of high-speed/large-area patterning, smart lamination, interconnects and encapsulation/barrier films in polymer electronic foil systems.

As printing technology minimizes the need for intermediate bonding and handling steps, polymer electronics offers excellent integration capabilities.

Figure 16
A clinical thermometer in plaster
form (concept Holst Centre). Source:
Holst Centre.



Potentially, all electronic functionalities, such as logic, display, sensing, power and memory, can be printed on a foil. Integration in one production system, however, seems only feasible for very high-volume consumer applications. And it still requires a great deal of material development in terms of barrier coatings, encapsulation, smart lamination, interconnecting foils and stability aspects.

Some examples of concept studies in this field are:

- a clinical thermometer in plaster form with display and power supply based on polymer electronics (concept Holst Centre, see Figure 16);
- a smart card with display function (concept (Avesodisplay)).

Depending on the complexity of data handling and the processing power needed, combinations with silicon chips are also a possibility, leading to hybrid organic-silicon devices.

CONCLUSIONS

For ambient intelligence properly adapted input and output devices will be needed. Because displays are the main way to present information-rich content to the user, displays are needed that are flexible, not only physically (being bendable, rollable), but also as to production (customisable or small-volume production by printing processes) and use (for multiple applications). An example might be a rollable display with a wireless interconnection for a new type of content, such as e-newspaper displays.

Novel manufacturing techniques such as printing will enable very low-cost displays that may even be used for packaging goods. Foils can contain integrated systems with embedded electronics, sensors, powerpacks and signal/display functionalities to meet the consumers' needs. This may also enable 'living' packages with small video sequences or packages with sensor tags that can autonomously signal condition, history and identification.

The specific product and technology developments will follow different routes, as is indicated in the Abernathy and Clarke diagrams in the Figures 11 and 14:

- Anticipated opportunities in high-volume markets accelerate the development of electronic printing technology. Printing technology, developed for large-area flexible displays, can be used to produce flexible signage and lighting applications at a later stage. Furthermore, printing technology is considered to be a promising option for the manufacturing of low-cost RFID tags.

- Niche markets emerge for newly created functionalities:
 - labelling industries looking for added value products are expected to be interested in sensor foils;
 - the increasing demand for lightweight, thin-film power for portable systems is expected to stimulate demand of battery and solar power foils.

With low-cost printing technology, a high level of customisation can be obtained; the possibilities for applications are almost endless. The best way to exploit this technology is therefore in an open innovation setting where end-users, distributors, OEM-ers, material suppliers, equipment makers together with researchers contribute their joined creativity and technological skills.

The future success of polymer electronics will depend on the ability to integrate functions in one autonomous system, similar to the situation for 3D microelectronics (see chapter Van Hoof ‘More than Moore and Heterogeneous Integration’). The future of polymer electronics will most likely lie in a ‘system in a foil’, instead of in a ‘system in a package’ (SiP).

REFERENCES

- Nanomarkets (2005). *Emerging Nanoelectronics Markets*. Report. www.nanomarkets.net
- Photonics (2006). *Towards a Bright Future for Europe*. Strategic Research Agenda, April

WEBSITES

- www.holstcentre.com
- www.oe-a.org
- www.orgatronics.com
- www.otbdisplay.com
- www.philips.com
- www.photonics21.org
- www.polyic.com
- www.polymers.nl
- www.polymervision.com
- www.powerpaper.com
- www.tno.nl

Architectural Innovations in Perspective

Kees Eijkel¹, Erik Knol², Steven T. Walsh³

INTRODUCTION

Departing from the discussion in earlier chapters of innovation from within the existing value chain of the semiconductor industry (see chapter Raaijmakers ‘Innovation within the Nanoelectronics Value Chain’) this chapter discusses examples of innovations in nanoelectronics that initially do not link-up with an existing value chain. All the examples discussed in this chapter combine the introduction of technological novelty with the creation of new networks of linkages. On the one hand novel technologies are introduced that radically depart from existing technological capability and skill sets. On the other hand, the formation of a new network of linkages is needed to create a new value chain providing market access. As such, the examples provide insight into the dynamics of architectural innovation, an innovative setting that corresponds to the upper right quadrant of the Abernathy and Clark framework [Abernathy and Clark, 1985].

¹ University of Twente, Mesa +, Enschede, the Netherlands.

² Qeam, Leiden, the Netherlands.

³ The University of New Mexico, Albuquerque, USA.

One goal of this chapter is to create a greater awareness of the relevance of innovation in this context, despite the high level of uncertainty associated with such ventures. In the examples discussed, there are no clearly defined technological capabilities and no established rules for the competitive game like those in the existing microelectronics value chain. Therefore, specific strategies for product development, manufacturing and commercialisation have to be developed and have to be continuously redefined to adapt to changing circumstances. As a result, there is a large variety of innovation pathways shaped by the actors involved and by the specific characteristics of the selection environment — in particular the linkages that can be built with business partners and customers in due course. Although the unpredictability of innovation in this context implies a high level of risk and volatility, the promise of future returns justifies the necessary investments and motivates entrepreneurs to take up the associated challenges.

As this study underscores, the dynamics of technological convergence, but also technological branching, is a source of new technological options opening up opportunities for revolutionary and radical innovation. In this chapter, MST (Micro Systems Technology) was selected as an exemplary technology with relevance in the nanoelectronics field to illustrate this dynamics of technological change and innovation associated with convergence and branching. The focus on MST makes it possible to illustrate the wide variety in value creation activities, innovation pathways and emerging value chain structures that emerge as a reflection of the introduction of a limited but shared set of technological capabilities. The five examples that constitute the core of this chapter take the perspective of entrepreneurial firms developing novel MST technologies for applications outside the existing value chain through a combination of technological capabilities inside and outside of semiconductor and MST manufacturing. Despite the differences between the examples, a discussion of the examples allows for the identification of some factors that are essential to successfully innovate in an architectural setting. These factors are then used to formulate recommendations for business and policy actors interested in architectural innovation in nanoelectronics.

MST: A FACTOR IN THE ELECTRONIC DEVICES INDUSTRY

Manufacturers of MST based devices employ semiconductor microfabrication technologies to take advantage of the mechanical properties of silicon rather than (or in addition to) its electrical properties. Examples of MEMS based devices are for instance DNA-chips (e.g. Affymetrix), electrostatic sensors (e.g. Analog Devices), inkjet heads (e.g. HP and Canon), hard disk heads (e.g.

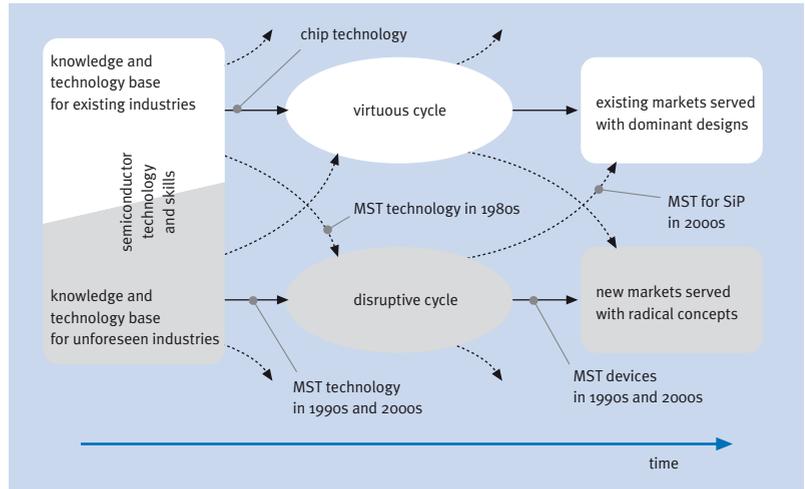
Seagate) and microsieve-based inhalers (e.g. Medspray). Since MST devices were first introduced in the 1980s, the field has basically evolved disjunctive from the semiconductor sector, and MST were not considered a key element for the semiconductor industry. Nevertheless, there was a mutual influence and value exchange, for example through equipment manufacturers such as STS or ASMI that were active in both fields.

Since its conception, companies operating in the microsystems field have faced the challenge how to expand and speed-up business development in a very fragmented industry and without a significant level of product standardisation (through, for instance, a dominant design or unit cell). The current dynamics in the MST field can be characterised by the following statement: Every product requires its own unique technology platform, package technique and testing procedure [Eijkel et al., 2005]. Although some application-specific dominant technology-product paradigms have become established, there is no industry-wide standard for packaging designs as yet, as opposed to, for instance, the situation in CMOS electronics. This has to do with the fact that the functionality of a MST device is generally based on specific hardware settings (e.g. constructions and materials) and a specific interaction with its environment, whereas functionalities in digital integrated circuits are basically ‘software-programmable’, either through circuit design or through today’s programmable device concepts, and connected with its environment through standard interfaces. This specific character of the MST field provides an extra barrier to standardisation, large-scale infrastructure development and cross-industry learning.

New developments, as presented in previous chapters, show that lately attempts are made to integrate MST devices with electronic device technologies in one single package, using a System-in-Package (SiP) approach. After a decade of separate evolution, MST technologies are now recombined with other semiconductor technologies and thus become part of the nanoelectronic palette. One example is the HUMAN++ concept described in Van Hoof’s contribution ‘More than Moore and Heterogeneous Integration’. Figure 1 schematically depicts branching and convergence in the development of semiconductor-related technological capabilities and skills: on the one hand toward incremental innovation in the electronic devices industry that manufactures integrated circuits and on the other hand branching off toward the MST sector that emerged in the 1980s. Since a couple of years, developments in MST have started to interact with developments in CMOS IC technology through for instance the introduction of System-in-Package product designs. (The concepts of a virtuous cycle and a disruptive cycle presented in Figure 1 are further worked out in the paragraph ‘Architectural innovations and actors in the disruptive cycle’ of this chapter.)

Figure 1

Semiconductor and MST technology and skills creating and serving different branches.



EXAMPLES OF ARCHITECTURAL INNOVATION

TEXAS INSTRUMENTS — DIGITAL LIGHT PROCESSING

Texas Instruments is a high-tech, multinational firm active in a multitude of markets with its solutions based on digital signal processing and analogue (semiconductor) technologies. Texas Instruments is an example of an industry leading firm studying new technology and applying it, not only to improve existing product-market combinations but also in order to ‘parachute’ the technology into new markets.

The Digital Light Processing (DLP) division, initially called the Digital Micromirror Device Project Division, was set up by Dr Hornbeck, now a vice president of Texas Instruments. Within Texas Instruments, the Digital Micromirror Device project occurred as a result of investigating the convergence of MST and semiconductor microfabrication technology. The resulting DLP technology uses an all-digital chip to project and display images (e.g. [Hornbeck, 1996; Texas Instrument, 2006]). This chip consists of a CMOS logical device on top of which a rectangular array of up to a million hinged, microscopic mirrors is mounted. In a DLP projection system, red, green and blue light is alternately projected onto the mirror array, with individual mirrors switching on and off in response to a video signal fed into the chip. The mirrors can switch at a rate of up to 5,000 times per second. The light they reflect is directed through a lens onto the screen creating an image.

Today, DLP technology is considered to be the single largest success story in the MST field as it was first introduced in a large range of media projection applications and more recently in display applications. These include business

projectors, home cinema applications, professional video walls (for example, command and control centres used by telecommunications and utility companies), commercial entertainment applications (for instance, concerts, award ceremonies and casinos) and applications that require the ability to quickly, easily and accurately modulate light.

Despite this successful outcome, the DLP division was nearly eliminated a number of times since its inception. Just like many other product offerings based on newly introduced technology, the initial product that was developed did not provide the value that had become expected by Texas Instruments. However, the second and third product generation based on this technology have fared far better, although the innovation journey for these products also knew some bumps.

This technology was a novelty, not only for Texas Instruments but also for the existing projection and display businesses. As the DLP system substitutes traditional display and projection technologies, Texas Instruments had to compete directly with firms in this sector. For them the DLP system formed a radical departure from their traditional product concepts. In addition, the technological capabilities required to produce a DLP system bear no resemblance to those required for the manufacturing of traditional projection or display systems. The radically novel character of the new product concept was a source of problems but it also gave Texas Instruments the time it needed to probe the market and learn about customer needs, while their competitors were stuck in the 'old' technology-product paradigm. While Texas Instruments focussed on the development of their DLP system, their competitors' response was to accelerate the learning in their traditional technology lifecycles. But as Texas Instruments found out, a product driven by a radical technology may not enjoy instant commercial success, even if it performs much better, is more reliable and is much cheaper than existing products. The company faced problems when trying to engage designers of projection and display systems in design activities. Further, Texas Instruments had to overcome production problems resulting in considerable cost overruns (some say billions of dollars) that were needed to overcome manufacturing problems. But through perseverance the DLP division developed into a more than \$ 1 billion business.

The DLP device can be seen as an architectural innovation [Abernathy and Clark, 1985]: A combination of new and existing knowledge of display systems, MST and semiconductor technologies enabled the development of a complete new device that allowed Texas Instruments to enter a completely new market. To be successful, existing value chain structures had to be severely challenged. Traditionally, the cinema (projector) business has been based on analogue content and equipment. In this fragmented business, the introduction of

digital content and digital equipment was extremely important for the success of DLP systems. Further, the continued financial and strategic backing that Texas Instruments has provided at the highest level to the DLP initiative has been essential for the fledgling division to learn and to cross the chasm (see the paragraph ‘Architectural innovations and actors in the disruptive cycle’). Mr Hornbeck’s vision and drive to overcome internal barriers within Texas Instruments has allowed those resources to continue. It is exceptional that a large firm like Texas Instruments initiates large scale investments for architectural innovation developments. But the initiative has survived the disruptive cycle (see the paragraph ‘Architectural innovations and actors in the disruptive cycle’) and DLP systems became firmly established in its markets and can now be considered a mature technology. The entrepreneurial activities in new technology and market areas and the perseverance on a multitude of aspects have resulted in a successful DLP division.

I-STAT — MICROFABRICATED BIOSENSOR CHIPS

The company i-STAT Corporation — founded in the early 1980s — develops biosensor chip technologies in order to create point-of-care-diagnostics systems. These biosensors are used in light-weight, handheld bedside readers and a variety of single-use, disposable cartridges. With the micromachined sensors these systems can measure the level of care-critical blood parameters (e.g. sodium, potassium, chloride ions, glucose) in very small (60 µl) blood samples and produce results in about two minutes (instead of a day or more when samples are sent to a laboratory). The concept revolutionises the value chain of health care diagnostics and treatment. A variety of cartridges is available for the measurement of dozens of blood parameters. i-STAT, the first company to make biosensors using semiconductor wafer technology, now annually produces and ships tens of millions of these biosensor devices.

i-STAT entered into a strategic alliance with Abbott Laboratories for point-of-care testing in 1998. The agreement included marketing and distribution agreements and a stock purchase agreement, along with research and development and license agreements for certain new diagnostic products. Abbott Laboratories is a more than a century old pharmaceutical, nutraceutical and diagnostics company with worldwide sales of more than \$ 22 billion and earnings of \$ 3.4 billion in 2005. Abbott Laboratories’ acquisition-based growth made it today’s leader in point-of-care diagnostics with an outstanding market channel in the medical field. Through this deal i-STAT got the market access to expand its business at a low risk. But in 2002, the company announced its intention to end its deal with Abbott Laboratories. I-STAT was to pay tens of millions of dollars as a termination fee and return payment. The initial investments of Abbott Laboratories in i-STAT did not continue.

Then, in 2003, Abbott Laboratories [Abbott Laboratories, 2003] agreed to acquire the shares of i-STAT it did not already own for a net transaction value of approximately \$ 392 million. Yet — as shown above — just a little while earlier Abbott Laboratories disinvested in i-STAT. Abbott Laboratories, which had had internal discussions regarding the utility of point-of-use care, now stated that i-STAT “.. provides an excellent fit with our long-term strategy of expanding our capabilities in diagnostics while targeting medical needs at the point of patient care.” Contrary to its earlier intention, the chairman of the Board of i-STAT said: “Abbott is the ideal fit for i-STAT. Our leading technology complements Abbott’s broad capabilities in the worldwide diagnostics market.”

For a firm like Abbott — strongly linked to the virtuous cycle (see paragraph ‘Architectural innovations and actors in the disruptive cycle’) — it is hard to fully oversee the potentials, implications and cannibalising effects of acquiring innovative small firms that offer architectural innovations and therefore operate in a disruptive innovation cycle. Whether to invest or disinvest in such firms is a question that has to be continuously re-evaluated by the incumbent. In the end, Abbott Laboratories strategically decided to let the i-STAT concept, together with other (to be) acquired concepts, be part of Abbott’s expanding product and services portfolio. In terms of the framework of Abernathy and Clark [Abernathy and Clark, 1985], i-STAT created an architectural innovation that in due time evolved into a niche innovation and even a next generation regular innovation as its biosensor-based point-of-care-diagnostics systems were successfully adopted in the market. The implications of its system for health care diagnostics have been fundamental.

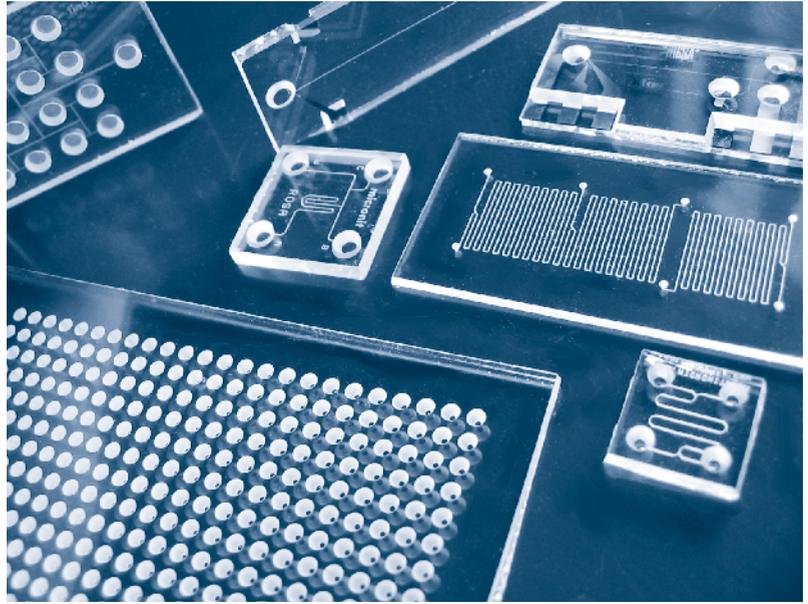
The case further shows that partnering offers good possibilities for a small company to move through the above-mentioned innovation path from architectural to niche to regular innovation. Such a partner can provide the capital necessary for investment in research and development, marketing support and, above all, a distribution channel. Nevertheless, investing partners such as Abbott Laboratories also continuously evaluate their strategic agendas. Innovative concepts such as the i-STAT system make them aware they need to balance interests over the years: to monitor and support high-tech entrepreneurial companies that develop interesting architectural innovations or to expand their existing products and service portfolio via the acquisition of those companies with the risk of losing entrepreneurial mindsets in these organisations.

MICRONIT MICROFLUIDICS – GLASS CHIP TECHNOLOGY

The Dutch technology platform company Micronit Microfluidics designs, simulates, prototypes, develops and manufactures custom-made glass and silicon

Figure 2

*Overview of glass chip devices
[MicroNews, 2004]. Source: Micronit
Microfluidics.*



microfluidic chips for detection purposes (contact-based, contact-less conductivity, amperometric detection) and laboratory purposes (mixing, reaction, heating or electrophoresis analysis) [MicroNews, 2004], Figure 2). Applications for its chips and microfluidics systems include capillary electrophoresis, blood analysis, DNA analysis, micropipettes for clamping DNA molecules and micro-needles for painless blood collection and drug delivery [Micronit Microfluidics, 2006; MicroNews, 2004]. Microfluidics is a multidisciplinary science and technology domain that studies and applies the behaviour of fluids at microscale and mesoscale, combining physics, chemistry, engineering and biotechnology. The results of Microfluidics are used in the development of a broad variety of devices and systems, such as DNA microarray technology, lab-on-a-chip technologies, pneumatic microvalves, chemical microreactors, microdispensers, printheads and microthermal and micropropulsion concepts.

The privately held company was founded in 2001 by a team of young entrepreneurs. Today, it employs 20 persons in R&D, production and marketing & sales (April 1, 2006). The company's production capabilities were recently upscaled. Over the years, it has operated in close cooperation with the MESA+ research institute of the University of Twente (research on materials, micromachining, microelectronics, microsystems and nanosystems) and technology and business partners. This cooperation has a complementary character as to research, technology and business. Micronit Microfluidics utilises several micromachining-related technologies, such as micropowder blasting, metal sputtering, advanced etching techniques (hydrofluoric acid etching, heated potassium hydroxide etching and deep reactive ion etching), electrodes

integration and substrate bonding. Due to its being embedded in research and business networks, both locally and internationally, Micronit Microfluidics appears to be able to attract and develop relevant knowledge and competencies so as to upgrade its technology platform portfolio and to expand its business and revenue positions.

Knowledge and technologies, appropriate connections with partners and, above all, an entrepreneurial mindset of a small company have created abilities to revolutionise cost-effective and flexible detection and laboratory functionalities in life sciences, pharmaceutical and chemical industries. It might be interesting to see in what way Micronit Microfluidics will be able to expand strategic partnerships in order to stimulate its worldwide positions in existing and new value chains so as to create market access for its microfluidics and lab-on-a-chip functionalities.

Micronit Microfluidics combines semiconductor and micromachining technologies to manufacture customised glass microfluidic chips and lab-on-a-chip devices that are used in various non-electronic industries. At the moment, and in connection with the Abernathy and Clark framework [Abernathy and Clark, 1985], niche and architectural innovation movements can be observed: A combination of new and existing MST knowledge and technologies enables the development of technology-product platforms that address specific niche segments in fields that are not addressed by the electronic devices business. Similar innovation settings are applicable to the microarrays of Affymetrix based on semiconductor manufacturing techniques and glass chip technology, Medspray's aerosol technology for drug delivery based on microlithography processes and microsieve technology and Ford's micromachined silicon fuel injector nozzle with highly uniform and rectangular orifices. In the future, as microfluidics technologies addressing specific industry segments become more mature, the innovation dynamics can be expected to become of a more regular nature. Unless, of course, new (radical) technologies, competencies, actor linkages and entrepreneurial ambitions activate or reactivate niche and architectural innovation movements.

This example shows that technologies commonly used in or connected with the semiconductor industry make radical technology and innovation developments possible in other industries. Micronit Microfluidics operates in a very entrepreneurial way. It pushes its new technology to newly emerging market segments in a process of architectural innovation, at the same time attempting to make it part of a more regular innovation setting.

ZYVEX — FROM MICROASSEMBLY TECHNOLOGY TO MOLECULARLY PRE-CISE MANUFACTURING

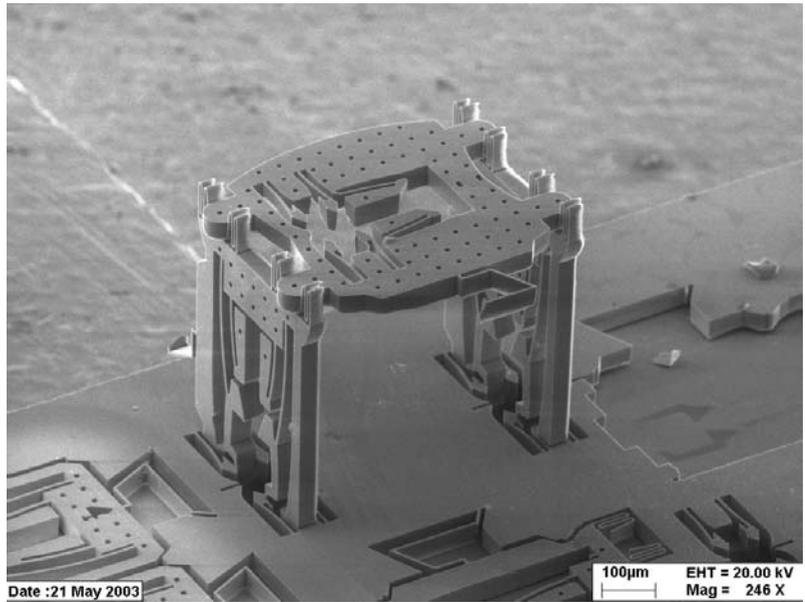
Zyvex Corporation is an ambitious high-tech small firm operating in the US. It was founded by Mr James Von Ehr II in 1997 and employs more than 60 persons (April 1, 2006). Its vision is to become the worldwide leading supplier of tools, products and services that make adaptable, affordable and molecularly precise manufacturing possible. Parallels can be seen with Ford Motor Company in its early days: Not being the inventor of technology but rather the innovator that has a vision of the future of an industry [Walsh, 2004a; Thukral et al., 2006]. This could be linked to an architectural innovation vision potentially becoming a regular innovation setting [Abernathy and Clark, 1985]. In connection with its vision, the high-tech company focuses on a rapid transformation of its scientific breakthroughs into commercial applications and licensing opportunities in the fields of materials, tools, and structures. It sees relevant markets in aerospace, defence, health care, medical applications, the semiconductor industry and in telecommunications. The company and its key employees are embedded in a variety of academic, business and governmental policy networks. Zyvex has utilised government research funding through US agencies, such as NIST-ATP (National Institute of Standards and Technology — Advanced Technology Program).

The stated ambition of Zyvex Corporation provides the organisation with a strong long-term orientation, reflected in a drive to build up a strategic portfolio of breakthrough competencies. In this approach, the company tries to profit from its developing competencies while concurrently focusing on its long-term objectives. The financing structure of the company makes this combination of short-term and long-term positioning possible: So-called ‘patient money’ is provided by individuals that are closely involved with the firm. This differs from a financing structure based on traditional venture capital, where strong revenue results are expected to be attainable by the rapid introduction of new product-market combinations.

Although the competencies required to support Zyvex’ ambition of molecularly precise manufacturing are still under development, concrete products were already commercially introduced. The company has developed products in the fields of microassembly (e.g. MEMS (micro-electro-mechanical systems) grippers, automated microassembly concepts), nanomanipulation (such as nanomanipulators for studying and testing nanostructured materials and probe advanced semiconductor chips) and nanomaterials (for instance, the functionalisation and processing of nanotubes). The company is able to build component-based three-dimensional structures and devices (Figure 3). By using proprietary MEMS and NEMS (nano-electro-mechanical systems)

Figure 3

Overview of microassembled structure. Source: Zyvex Corporation.



libraries of end-effectors, handles, connectors and sockets, Zyvex routinely achieves high positional accuracies for a large number of components in automated processes. The technology is suitable for applications such as high-precision alignment, high-precision automated mechanical assembly and other industrial applications, where high-precision assembly is desirable (see e.g. [Tsui et al., 2004; Sarkar, 2005]). One of the opportunities pursued by Zyvex is the development and commercialisation of tools specifically aimed at the bio-, medical and pharmaceutical industry.

Zyvex Corporation needs to continuously learn about the value of its competencies in order to be better able to position its technologies and solutions in the market. Therefore, the firm wants to provide solutions for actual customer needs from the beginning. The formation of partnerships is one way to build this understanding. Zyvex thoroughly reviews its partnership opportunities and rejects nearly 90% of these as not having a strategic alignment and corporate stretch [Walsh, 2004a]. The company differentiates potential partners in sectors, such as knowledge and technology intermediaries and suppliers like Johns Hopkins, equipment manufacturers such as Becton Dickinson, market channel giants, such as Johnson, and Johnson and others [Walsh, 2004a]. The company is also tentatively negotiating with large health care providers.

Zyvex Corporation is a long-term vision-driven innovator combining long-term platform and product development with short-term commercialisation aspirations. It is one of the very few true nanotechnology firms that are actually able to sell nanotechnology based products and to build strategic partnerships

with partners that move in tandem with their own strategic intent. Zyvex actually commercialises enabling technologies that have the potential to become disruptive.

The question is how Zyvex Corporation will be able to simultaneously invest in and focus on exploration — needed to build its long-term oriented portfolio of competencies — and exploitation — keeping track of short-term customer needs, to learn, to adapt and to generate cash flow. With respect to the framework of Abernathy and Clark [Abernathy and Clark, 1985], Zyvex intends to develop and introduce architectural innovations. On the other hand the company needs to build partnerships in order to create access to markets and in an attempt to shift existing customer needs, oriented at the products produced in a regular innovation context — toward the more radical innovations they intend to develop themselves. In this setting it is imaginable that an IPO (initial public offering) affects the short-term/long-term balancing activities of Zyvex Corporation.

The example of Zyvex illustrates that the ambitious focus on molecularly precise manufacturing gives Zyvex Corporation, as a high-tech small firm with appropriate financial and partnering positions, interesting possibilities to potentially revolutionise industries.

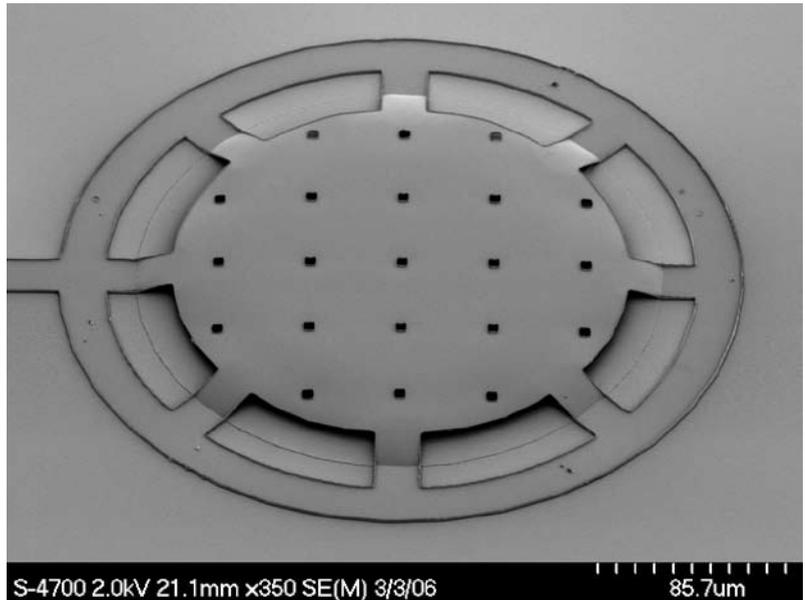
ELESCCI — EMBEDDED ELECTRON CHARGE TECHNOLOGY

The start-up Elecsi Corporation — founded in the US in 2004 — develops a platform technology of engineered electronic materials that ‘harnesses’ energy from the surrounding environment due to principles of embedded electron charges (EEC; trapped electronics) in materials [Elecsi Corporation, 2005]. EEC is a phenomenon where electrons become permanently trapped at the interface of certain layered insulator materials, resulting in a relatively permanent charge. Research performed at the Rochester Institute of Technology has provided the scientific and technological fundamentals for the start-up initiative. Its technology platform is based on standard CMOS manufacturing processes, which makes an integration of the material into silicon devices and low-cost, high-volume manufacturing possible. At the moment of writing, the Elecsi Corporation has an intellectual property portfolio of 9 issued patents and dozens of patent applications.

The company foresees devices in ‘design families’ related to stand-alone EEC applications, energy harvesters, sensors, actuators, RF MEMS and levitators (Figure 4). Its first applications will be energy harvesters and self-powered sensors for which there is a wealth of opportunities in multiple vertical markets, (for instance automotive, medical, consumer electronics and defence). Not only has this technology platform the opportunity to substitute technolo-

Figure 4

Micro-energy harvester device.
Source: Elecsi Corporation.



gies in existing products (such as accelerometers, microphones, bearings), but it can also be used in completely new applications, such as heel strike power generators or wall-hanging concepts based on electrostatic bonding. Apart from these innovative applications of EEC technology, the potential of Elecsi's technology is based on the compatibility with CMOS manufacturing.

Elecsi expects that through this combination the technology could ignite new markets and bring about revolutions in a variety of existing markets. The disruptive cycle (see the paragraph 'Architectural innovations and actors in the disruptive cycle') can be recognised here. But the new and ambitious company has to work on finding ways to create and penetrate these potential markets for their 'energy, sensor and bonding concepts'. The creation of business alliances with existing companies that are already active in the targeted markets may be a way to create customer awareness and to identify early adopters of the technology. With regard to the innovation framework of [Abernathy and Clark, 1985], it could be interesting to see how Elecsi Corporation is going to position itself in existing value chains and business networks in order to make the step toward a more regular innovation setting (for example in the market for self-powered tire-pressure sensors for the automotive industry or micro-pressure transducers for hearing aids). The start-up company with a radical technology portfolio that is now apparently focussed on innovation in a disruptive cycle could then become a platform provider that operates in the setting of a virtuous cycle. However, this orientation toward short-term revenue generation could then be used to further invest in product-market propositions with a more radical character (for instance man-powered energy

harvesters that can be integrated in shoes or bio-implantable energy harvesters for neural stimulators or cardiac pacemakers). Referring to the framework of Abernathy and Clark [Abernathy and Clark, 1985], this shows a tendency toward architectural innovation positions by serving or even co-building new value chains.

ARCHITECTURAL INNOVATIONS AND ACTORS IN THE DISRUPTIVE CYCLE

This paragraph will highlight architectural innovation activities seen from the perspective of the so-called disruptive cycle. Technology development follows an S-curve. Product adoption based on novel MST or semiconductor technology heavily relies on the ‘lead user’ [Von Hippel, 1986] and ‘crossing the chasm’ concepts [Moore, 1991]. In the initial phase of technology development, early adopters will utilise a nearly completed solution while a direct benefit offsets reliability issues and any difficulty of use. In the next phase the product will be developed in order to cross the chasm and meet the needs of early majority users. In this phase, it becomes clear whether or not the new technology-product paradigm has ‘traction’. When the technology is ultimately accepted by the late majority and sceptics, it has made existing technologies obsolete. It slowly proves its full potential and becomes the new sustaining technology. The struggle for architectural innovations in the electronic devices industry to become mainstream by ‘climbing’ the S-curve is related to the above-mentioned process. Companies developing new, enabling technologies — for example i-STAT or Elecsci Corporation — transform or embed their new technologies in existing and emerging value chains so as to make the transition to a regular innovation regime. Strategic collaboration with partners within this emerging value chain is essential.

As stated earlier, architectural innovations located in the upper right quadrant in the framework of [Abernathy and Clark, 1985] represent a double challenge: implementing radically new technologies and operating in environments where new linkages have to be set up. There is another useful model that can be used to conceptualise the differences in innovation setting of various enabling technologies. This model distinguishes between the so-called disruptive innovation cycle and the virtuous innovation cycle [Walsh and Kirchhoff, 2002; Walsh et al., 2004c], (see Figures 1 and 5). Architectural innovations can largely be related to the disruptive cycle.

Worldwide, thousands of high-tech small firms currently develop radical micro-technology and nanotechnology concepts with potential benefits directed at unmet customer needs. In this cycle, the key activities are creating and pick-

ing-up radical, enabling technologies, pushing them forward together with partners and through alliances, creating new cash flow, generating product-market combinations and stimulating their business positions. It appears that organisations with entrepreneurial drive and less organisational inertia are generally the most effective in crossing the chasm as they can operate in both newly created and existing value chains. See, for example, the cases of Zyvex and Micronit Microfluidics. This process is driven by high-tech entrepreneurship and intrapreneurship (e.g. [Kassicieh et al., 2002]). These forms of entrepreneurship are mostly related to small firms and start-ups, although the case of the DLP device shows that a vision-based entrepreneurial mindset can also be successful from within a multinational company, such as Texas Instruments. However, organisations that are already active in the virtuous cycle deal and work with sustaining technologies tend to focus on cost reduction through economies-of-scale and to listen to the needs of their existing customers. They therefore generally learn incrementally with regard to product design and manufacturing process design [Walsh and Kirchhoff, 2002; Walsh et al., 2004c] (see Figures 1 and 5). In the semiconductor sector, companies active in the virtuous cycle focus on the development of standard-based electronic devices, incorporating new — but not too radical — technologies that are suitable for high-volume production.

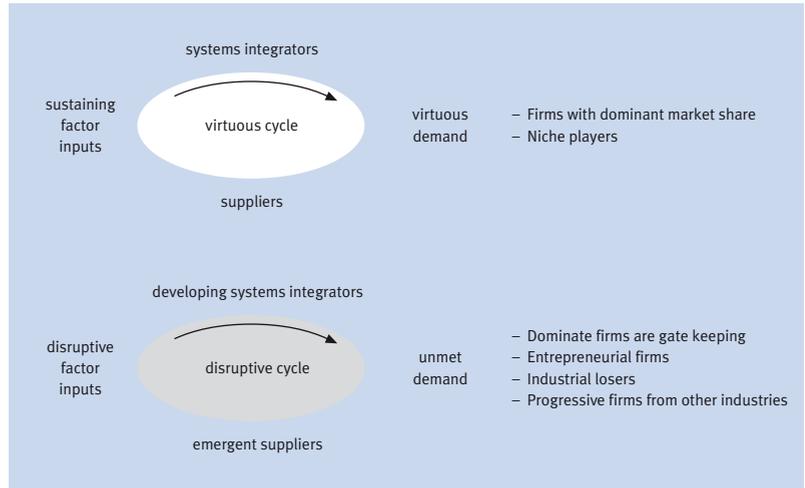
The process of pushing forward semiconductor or MST technologies with yet unknown business implications by actors typically linked to a disruptive cycle can be characterised as ‘playing soccer in the fog’ even without knowing whether there is a soccer goal. The challenge is to instantly pick up and interpret signals and operate entrepreneurially in order to understand and develop the shape and position of the innovation playing field (see also Linton and Walsh, 2004). Roadmaps and scenarios play a role in this process (e.g. [Walsh, 2004b; Knol, 2004]). Examples are NEXUS roadmaps and MANCEF roadmaps.

In such a disruptive cycle, actors can be identified with different roles and characteristics. The public knowledge institutes, such as universities, not only generate knowledge but also mediate between actors via transfer activities and commercialisation and spin-off programs. The cases Micronit Fluidics and Elecsci Corporation have shown how the involvement of academic research institutes can support technology and platform developments in small high-tech firms. Spin-offs operate as learning entities to generate added value with new knowledge and technologies. An ecosystem of companies and knowledge institutes can provide the entrepreneurial teams that lead spin-offs and start-ups with the proper interactions needed to co-develop and commercialise innovations.

The companies discussed in our case studies have different technology devel-

Figure 5

Aspects related to the virtuous cycle and to the disruptive cycle.



opment and innovation characteristics. In general, various types of companies can be distinguished. We will briefly summarise them. One type of company is the so-called innovator with platform and product development and commercialisation aspirations. Companies, such as C2V, Lionix and Zyvex are examples of this category. Another type of company is the product company aiming at a few specific product-market combinations; examples are Gemidis, Affymetrix, i-STAT, Medspray, Microflow, Nantero and SiTime. The technology platform company attempts to broaden its range of product-market combinations using the same technology base in an attempt to serve multiple market segments. Micronit Microfluidics and Elecsci Corporation are examples of this category. A type of company with a more service-oriented character is the foundry. It operates as a third party company to allow the development and production of specific (MST) devices, components or systems. Colibrys, Micralyne, HL Planar and HT Micro fit into this category. With regard to this typification, large firms such as Texas Instruments and Philips generally play multiple roles. Finally, a category for 'other types of companies' consists of facilitating companies, for example software specialists, business and technology consultants, IP and legal services, investment firms, etc. A disappearing type of company in the MST business is the engineering service provider focusing on concept developments for third parties. At the early stages of the MST industry, such service providers had some commercial success, but as the industry matured the added value of these companies evaporated because the by then established technology and product companies and foundries did not need this type of service anymore.

DISCUSSION AND FINAL REMARKS

This chapter discusses examples of MST based developments to illustrate the dynamics of technological convergence and architectural innovation in the More than Moore domain. The MST field was chosen because, years after branching off from mainstream electronics, developments in the MST field recently started to converge with other fields in the More than Moore domain. The chapter describes examples of specific innovations that are based on MST technologies and require both the development of new technological capabilities and the creation of a network of linkages to assure access to markets. In terms of the Abernathy & Clark framework, all these innovations started out in an architectural innovation setting. The examples thereby illustrate how promising innovation opportunities also exist outside existing value chains. For such innovative ideas to be successfully realised, an other mindset and environment are required than in an existing value chain. The next sections will discuss the lessons learned from these examples, in terms of the management of the innovating company, its ecosystem and the role of policy makers in shaping this ecosystem.

IMPLICATIONS FOR THE COMPANY'S MANAGEMENT

Architectural innovations on the move

Successful architectural innovations (upper right quadrant) will evolve toward regular innovation setting (lower left quadrant) over time in order to fully realise their promise of value creation and growth. Successful architectural innovations, often based on several complementary developments, then often 'creatively destroy' existing technologies, competencies and value chains (for example, Micronit Microfluidics and i-STAT's point-of-care-diagnostics). Alternatively, an architectural innovation could also be transformed and absorbed by existing value chains (for example, Elecsi Corporation's self-powered sensors for the automotive industry). Between these different evolution paths, the potential for value creation and growth of the architectural innovation will differ. The challenge for the entrepreneurial team is to find ways to 'cross the chasm' between early adopters and the early majority in a way that combines continuity (acquire capital, activate multiple-market strategies, serve launching customers, pick-up market feedback, generate early revenues) with a strong long-term vision of a clear radical value proposition in a nascent value chain. Long-term vision and perseverance are essential ingredients for such investments that require a combination of exploitative and explorative mindsets and activities [March, 1991] (for instance, the cases of Zyvex and Texas Instruments show an exceptional long-term vision and perseverance). Small, result-driven innovation steps in line with a long-term vision

are essential for the entrepreneurial team to successfully realise the potential of an innovation idea, meeting the needs of internal and external stakeholders (such as investors, partners, customers and governmental policy makers).

Strategies to exploit architectural innovations

Companies addressing architectural innovations can use several (complementary) strategies.

- First of all, the business case may need a relatively large space to evolve in order to adapt to changing circumstances and new findings. Especially for radical propositions, uncertainties are high and therefore the priority of various potential technology-product combinations may considerably shift throughout the process. A technology platform may be helpful to provide this flexibility: It enables the team to develop the technological skills needed, while keeping options open toward various applications promises (e.g. Elecsi Corporation).
- If the company already focuses on a specific combination of one technology and one application, another strategy is needed. Because resources and information are focused, the chance of success increases. However, for a proposition with a radical character, the many uncertainties related to building the value chain could result in challenges for the business case (for example, Texas Instruments' DLP initiative) and require an exceptionally strong long-term commitment of financiers, launching customers and other key partners.
- Thirdly, building on the above-mentioned technology platform strategy, temporarily a dual strategy can be appropriate, offering services based on the key expertise of the business to support cash-flow, in combination with a clear product paradigm. Apart from providing cash flow, this can provide the team with relevant networks and market information. If such a dual strategy is combined with a clear long-term product-market focus, it can result in a strong basis for further growth.
- A fourth strategy also leans toward services: offering customers innovation on the basis of microtechnology and nanotechnology, while developing suitable platforms into separate product business units or spin-outs (e.g. Zyvex Corporation).
- A fifth strategy revolves around finding core technological skills and offering them to a customer, such as a foundry that combines production with co-development (e.g. Micronit Microfluidics).

In order to succeed in value creation, a strong vision about the value proposition and the perseverance to pursue it are both critical for a firm to stay on track when pushing its architectural innovation idea toward a regular innovation setting. Further, adequate knowledge about markets, networks and

technologies is helpful in order to develop strategies to find a way across the chasm and move the business into new phases of innovation and business generation. International networks such as MANCEF and environments such as universities can support such information needs.

Entrepreneurial behaviour

Architectural innovations come with a low degree of structure and predictability. In such situations, the entrepreneurial quality of the team will be a determining factor in the success of the business initiative. In particular, the ability to accept risks and a flexible attitude are necessary. With regard to risk acceptance and flexibility, teams with young people are expected to perform better because they generally have a more open attitude toward the creation of new networks and the need to change established systems. Most probably, the inertia of vested interests and personal commitments is lower in a young team (e.g. Micronit Microfluidics). For large firms, focussing on radical innovation, the key challenges are the risks associated with the introduction of a radically new technology, the limited availability of design standards and the low production volumes and turnover in the early phases of development (e.g. DLP initiative of Texas Instruments). In contrast, small firms run the risk not to pay sufficient attention to opportunities on the business side, being tempted to focus on technology push strategies [Berry and Taggart, 1998; Oakey, 2003]. Bringing in experienced leadership is a way to strengthen the young team but should be balanced in order to retain ground-breaking potential, vision and entrepreneurial behaviour with regard to the original business initiative (such as the involvement of experienced founders in the Zyvex and Elecsi Corporation initiatives).

THE COMPANY'S ENVIRONMENT

The success of a business initiative depends not only on the entrepreneurial factor, but is also strongly related to environmental factors, such as the geographical location and collaborations. A technology-based architectural innovation is generally created and developed by collaborating organisations: small and large companies with or without their own research and development facilities, high-tech start-ups, universities, governmental-funded research organisations and customers (see, for example, the partner management approach of Zyvex). Companies pursuing architectural innovations often link up with (public) knowledge infrastructures. Here they find bright, young people with a low risk aversion, interesting innovative ideas, an infrastructure for research and development and independence of players with vested interests in established value chains who might strangle entrepreneurial initiatives (for example Elecsi Corporation's link with the Rochester Institute of Technology, and Micronit Microfluidics' interaction with the MESA+ Institute).

For actors in such an environment, growth management and capital require special attention, since these actors do not have the culture and lack the experience to deal with such factors.

In general, an open knowledge system and a collaborative culture can contribute to the nucleation and growth of complementary new business initiatives. Furthermore, the chance to network with players in existing and new value chains can be of great help to create access to markets (for instance, i-STAT partnering with Abbott Laboratories, and Texas Instruments' difficulties in involving actors in the projection business). Finally, for the firms collaborating in such networks, the building of a shared vision and perseverance are essential to successfully develop and commercialise new technologies in the long run.

IMPLICATIONS FOR KNOWLEDGE PRODUCTION AND POLICY

To a certain extent, governments operating at supranational, national and regional levels tend to focus on generic innovation-related policies, for example in the form of R&D programmes. However, generic policies are not fully adequate to support architectural innovation, as specific realignments of scientific and technological disciplines, changes in roles of actors and reconfigurations of networks are necessary to succeed in value creation. It is relevant that policy makers are aware of the potential economic implications of innovation in an architectural context. Policy-oriented actors should recognise the innovative output and its importance for a vital industry. Reconfigurations of existing networks can only be effectively made with shared long-term visions and objectives.

That is why policy makers have to work in concert with their academic and industrial counterparts to build such a vision and to develop specific policies to realise it. Such policies should be aimed at the creation of nurturing environments around specific public research organizations that motivate and enable organisations and entrepreneurial individuals to produce, develop and commercialise these so-called architectural innovations. So as to benefit from the opportunities of converging technologies, knowledge institutes have to actively create linkages between established scientific and technological disciplines, thereby promoting the necessary combination of various capabilities. Further, a vision-based policy should provide continuity in the development of research and development infrastructures so as to reduce risk for potential investors in the companies that make use of this infrastructure. Alternative financing models are needed that allow for an increase in the availability of capital. This requires a more market-driven approach, not only in the companies themselves, but also among the broader set of stakeholders. Finally,

governments can foster an entrepreneurial mindset through education programmes, the facilitation of cross-learning and the provision of facilities.

REFERENCES

- Abernathy, W.J., K.B. Clark (1985). Innovation: Mapping the Winds of Creative Destruction. *Research Policy* 14, 3-22
- Abbott Laboratories (2003). *Abbott Laboratories to Acquire i-STAT Corp.* Press Release of Abbott Laboratories, December 15
- Berry, M.M.J., J.H. Taggart (1998). Combining Technology and Corporate Strategy in Small High Tech Firms. *Research Policy* 26, 883-895
- Eijkel, K., J. Hruby, G. Kubiak, M. Scott, V. Saile, J. Brokaw, S. Walsh, C. White, D. Walsh (2005). The Strategic Importance of a Unit Cell, Nanolithographic Patenting Trends for Microsystems, Microfabrication and Nanotechnology. *Journal of Microlithography, Microfabrication, and Microsystems* (1), 11014
- Elecsi Corporation (2005). *Presentation for the Future Trends Forum 'Nanotechnology'*, Spain, November 30
- Hippel, E. von (1986). Lead Users a Source of Novel Product Concepts. In: Moore, W.L., M.L. Tushman (eds.). *Readings in the Management of Innovation*. Ballinger Publishing Company, Boston, MA, 352-366
- Hornbeck, L.J. (1996). *Digital Light Processing: a New MEMS-Based Display Technology*. Paper presented on the Technical Digest of the IEEJ 14th Sensor Symposium, Kawasaki, Japan, 297-304
- Kassicieh, S.K., B.A. Kirchoff, S.T. Walsh, P.J. McWhorter (2002). The Role of Small Firms in the Transfer of Disruptive Technologies. *Technovation* 22, 667-674
- Knol, W.H.C. (2004). *Nanotechnology and Business Opportunities: Scenarios as Awareness Instrument*. Proceedings of the 12th Annual International Conference High Technology Small Firms, Enschede, the Netherlands, 609-621
- Linton, J.D., S.T. Walsh (2004). Integrating Innovation and Learning Curve Theory: an Enabler for Moving Nanotechnologies and Other Emerging Process Technologies into Production. *R&D Management* 34 (5), 513-522
- March, J.G. (1991). Exploration and Exploitation in Organisational Learning. *Organisational Science* 2 (1), 71-87
- Micronews (2004). Micronit Microfluidics: Customised Chips from Prototype up to High Volumes. *Micronews Newsletter of Yolé Developments* 29, October
- Micronit Microfluidics (2006). *Information on the Corporate Website*. Website: <http://www.micronit.com>

- Moore, G.A. (1991). *Crossing the Chasm: Marketing and Selling High-Tech Products to Mainstream Customers*. Harper Business, New York
- Oakey, R.P. (2003). Technical Entrepreneurship in High Technology Small Firms: Some Observations on the Implications for Management. *Technovation* 23, 679-688
- Sarkar, N. (2005). *Applying Microassembly to Real-World Applications*. Zyvox Application Note 9712. <http://www.zyvex.com/Documents/9712.PDF>. Zyvox Company
- Texas Instruments (2006). *DLP Technology Information on the Website of the DLP Division of Texas Instruments*. Website: <http://dlp.com>
- Thukral, I., J. von Ehr, S.T. Walsh, A.J. Groen, P.C. van der Sijde (2006). Emerging Markets Emerging Technology: Commercialisation Pathways. Forthcoming in: *International Small Business Journal*
- Tsui, K., A.A. Geisberger, M. Ellis, J.D. Skidmore (2004). Micromachined End-Effector and Techniques for Directed MEMS Assembly. *Journal of Micro Mechanics and Microengineering* 14, 542-549
- Walsh, S.T., B. Kirchhoff (2002). Technology Transfer for Government Labs to Entrepreneurs. *Journal of Enterprise and Culture* 10 (2), 133-149
- Walsh, S.T. (2004a). *Entrepreneurial Firms Harnessing Nanotechnology: the Zyvox Case*
- Walsh, S.T. (2004b). Roadmapping a Disruptive Technology: a Case Study; the Emerging Microsystems and Top-Down Nanosystems Industry. *Technological Forecasting & Social Change* 71, 161-185
- Walsh, S.T, R. Giasolli, J. Elders (eds.) (2004c). *The Second Edition of the International Micro–Nano Roadmap*. MANCEF, Naples, Florida

Discussion and Recommendations

Fred van Roosmalen¹, Maurits Doorn²

THE CASE STUDY

Nanoelectronics is the all-pervasive hardware enabler for the physical layer of ambient intelligence. It underpins the worldwide semiconductor-based market in high-tech products and services, a steadily growing market that represents already more than 6 trillion euro today. Main objective of the case study is to provide insight into the dynamics of nanoelectronics innovation and industrialisation, and to show what paths can or must be followed today in anticipation of future requirements in this complex multi-disciplinary landscape of converging technologies.

1 Philips Semiconductors,
Eindhoven, the Netherlands.

2 STT, Den Haag, the Netherlands

Throughout the case study, it is demonstrated that nanoelectronics is more than 'just' the crossing of the 100-nm line of minimum dimension in the production of advanced high-density semiconductor digital logic and memory. In the paradigm of ambient intelligence, digital logic and memory are the 'brains' of electronic systems. But brains alone is not enough; a fully integrated solution also needs a 'body' to carry the brain and execute its instructions. A quickly expanding suit of disciplines is gathering under the nanoelectronics umbrella in order to bring life to this 'body'. Continuing in the 'body' metaphor, this combination of largely non-digital system functionalities can be labelled the 'arms, legs, ears, and eyes'.

Minimum pattern size and maximum silicon wafer size drive the digital-logic part of nanoelectronics. Innovation here is complicated and costly but relatively predictable because industry has agreed on a worldwide roadmap for implementing Moore's Law, the industry-wide economic theorem forecasting digital logic circuit complexity and cost-down to evolve exponentially at roughly the same rate.

For the non-digital-logic part of nanoelectronics, miniaturisation is governed by parameters other than minimum pattern size. More than Moore is the name given to the complex suit of technologies and functionalities addressing this challenge; SiP (System-in-Package) denotes the concept of combining these multiple functionalities in a single product outline, a concept requiring a challenging portfolio of dedicated technologies in itself.

MEMS is one example of the technologies and functionalities addressed by More than Moore, that is used extensively throughout this case study. MEMS (micro-electro-mechanical-switch) refers to a broad range of devices in More than Moore (and SiP) that provide mechanical functions next to electrical ones. Typical examples are pressure sensors, accelerometers, resonators, ink-jet printers, and micromirror projectors. MEMS has been recognised recently as a major enabler for integrated intelligent products in volume markets. (Of course there are other examples of More than Moore functionalities and technologies such as fluidics, optics or bio-electronics.) A still embryonic element of nanoelectronics is LAE (large-area electronics), providing SiP-like macro-integration through functional polymers. LAE makes it possible to literally provide the 'hands-on' system interface for human interaction.

INDUSTRY AND INNOVATION DYNAMICS

In the world of digital logic and memories that is governed by Moore's Law and advanced CMOS technology, major and continuous investments have to be made by all actors along the existing value chain to keep up with the pace of innovation. For each new technology generation, the expenses go up significantly, while the market growth decelerates steadily since the mid 1990s. The result of these conflicting trends is an ongoing process of segmentation and specialisation in the industry, with only few players remaining that can provide sufficient R&D mass.

Capital requirements in More than Moore and SiP tend to be low compared to the needs of advanced CMOS; in many cases process know-how and infrastructure can be used that is inherited from past generations of digital logic manufacturing. That More than Moore and SiP are still very disruptive stems from the breakthroughs they cause in the overall system architecture, not from the underlying processing. The moderate investment level together with the opportunity it gives to shift up the value chain to capture more value from the end system explains why semiconductor component manufacturers are becoming more and more interested in these technology families. On the other hand, the low capital requirements tend to discourage interest in the equipment suppliers in the current value chain.

MEMS devices are on the market already for many years, though mostly in niche markets. Penetration into volume applications came only after the moment that the required special processing — micromachining and deep-trench etching — became available through 'regular' semiconductor production. This breakthrough in MEMS manufacturing occurred relatively recently and is one of the main reasons why the MEMS segment today is growing faster than the semiconductors market as a whole. The number and diversity of options and actors in MEMS is still very large, making it difficult to decide what will be the winners. Value chain consolidation is expected once the main volume applications in this segment have stabilised.

Like MEMS, LAE is a new approach for building circuits and macrosystems that promises not to require large investments in manufacturing. But LAE is hampered by the fact that its basic steps — producing functional polymer structures through printing and reel-to-reel processing — are quite unlike current semiconductor practice, even though they are considered conventional in, for example the chemical industry. Next to the issue of lacking main industry acceptance, LAE is faced with uncertainties with respect to the functional limitations of polymer electronics materials.

What all above categories have in common is a growing proliferation of options and an exploding diversity of materials, making it difficult for all actors to realise sufficient critical mass, both in know-how and in business volume. This is a major challenge, especially for the industry that produces these highly specialised materials and builds the necessary production equipment.

MODEL ANALYSIS

The Abernathy and Clarke diagram has been used to map the various areas of interest in the nanoelectronics case study. While analyzing the technology dynamics in the various fields of work, the authors have added a new element to the original diagram; they have highlighted trajectories across the diagram demonstrating the evolution of individual products, technologies and innovations over time. In the resulting ‘transilience’ maps, it is shown that lines can be drawn to connect subsequent step-wise, incremental developments from the field of ‘regular’ innovation (bottom-left in the Abernathy and Clarke diagram) reaching to any of the other quadrants, including the field of ‘architectural’ innovation (top-right).

After a series of these step-wise innovations a new status quo can be reached. In the new status quo, the technology becomes established and will form the starting point for subsequent incremental innovation. In other words, it redefines the relative positioning of the bottom-left field in the Abernathy and Clarke diagram. Technology and application roadmaps can be used to connect future shifts of the point of reference in the diagram in horizontal and vertical direction, respectively.

Each and any of the steps, taken along a trajectory as described above, can be relatively conservative, while the overall end result can be completely disruptive. Looking back in history, the successful paths are clearly visible. En route, a judgment on where to go and what to do is far more difficult, as multiple paths toward the future will be possible. An attractive and workable approach to this dilemma is the assumption of an evolutionary, ‘Darwinistic’ model. In such a model, the best path will be selected ‘naturally’ provided that sufficient options for continuation are available at the same time and place in a competitive environment.

Looking at the result of the technology mapping, it becomes evident that the present case study covers all four fields in the Abernathy and Clarke diagram. Raaijmakers starts from the ‘regular’ innovation in the existing value chain (bottom-left). Van Hoof focuses on ‘niche creation’ innovation (top-left) pro-

viding a path toward new architectures through literally building on top of existing capabilities in the ‘above-IC’ and ‘3D-integration’ approaches. Simonis shows the implications of working through ‘revolutionary’ innovation (bottom-right) to create breakthroughs with functional polymers. Eijkel et al. describe the difficulties encountered by actors starting from ‘architectural’ innovation (top-right) that will have to reconstruct a connection down to ‘regular’ innovation and industry (down-left) in order to be able to enter into volume markets, either by building linkages with an existing value chain or by (partly) creating a new one. The particular challenge for the last category of innovators is to strike the precarious balance between, on the one hand, the formation of a protected space where they can focus on the realisation of their original innovation idea and, on the other hand, the adaptation to and integration in existing value chains and networks to gain timely access to markets for their short-term survival.

FUTURE PERSPECTIVE

A conclusion common to all areas in nanoelectronics is that proliferation of new functions and technology options will continue to be strongly driven by upstream extension throughout the semiconductor value chain, up to annexation of parts of the present realm of system integrators. By doing so, the leading semiconductor industrial actors are able to maintain growth in their overall value proposition, and compensate for the ongoing slowing down of the market for ‘traditional’ semiconductor products, such as digital logic and memories. This broadening of scope is already visible today through the more than proportional business growth in MEMS and SiP technologies.

What new products will emerge in volume from these emerging technologies is hard to predict. Ambient intelligence provides a guiding vision, but a detailed extrapolation from application roadmaps into tangible products is not straightforward and to an extent even not feasible, today. Consequently, industry is largely technology-driven, creating multiple opportunities in which the consumer eventually decides. Inevitable downside of this approach is that the relative R&D spending cannot stabilise — as would be needed in the present maturing market — but needs to go up.

The case study shows that the future evolution for the multitude of technologies emerging in the nanoelectronics playground can be judged by mapping them on the Abernathy and Clarke diagram, followed by application of an evolutionary model where the winning way forward is selected by its competitive environment. In this model, evolution is assessed through tracing possible

trajectories, both historically and anticipatory. Insight into such trajectories can help in determining what will be the consequences of planned next steps in the development of the technology but also in judging what changes are needed and feasible in the selection environment at this point and further down the road.

As technologies progress in the playing field that is represented by the Abernathy and Clarke diagram, the actors need to break existing linkages and new linkages must be created. Public action can significantly help in increasing the speed of building these new linkages in both technologies and markets. In terms of Abernathy and Clarke again, these directions in evolution represent the horizontal and vertical axes, respectively.

COOPERATING IN ECOSYSTEMS

The deceleration seen in ‘traditional’ semiconductor businesses will cause a decline in R&D spending by the industry involved, as they need to meet the requirements from their bankers. At the same time, it is clear that the semiconductor industry continuously needs to extend its technological capabilities in order to achieve the added functionality for upstream value chain expansion as described earlier in this chapter. The big risk for the whole sector is that the overall R&D spending may decline so fast that emerging and interesting new opportunities are not detected and matured in time. Such a scenario can apply to the bottom-right ‘revolutionary’ field in the Abernathy and Clarke diagram, where the cost of innovation will be high and difficult to predict, but also to the top-left ‘niche creation’ field, where investors and companies need to survive the inevitable delays until market acceptance in volume applications. In the case study, several authors highlight public support as the essential element to provide continuity in bridging these gaps.

Furthermore, many of the new technology options will be generated from start-ups and other innovative SMEs (small and medium enterprises) emerging from academic research. To bridge the inevitable gap between a good idea and true market success, such SMEs will on some point need to attach to large industry in order to get access to volume manufacturing as well as to become sufficiently visible for leading customers. One needs methods for creating this linkage that does preserve the innovative SME as a separate entity. This requires a different way of thinking about cooperation.

In order to sustain innovation at any substantial speed, cooperation across the entire value chain is essential, for small and large companies alike. Along the

way, this may lead to the emergence of new business models, including new management models for intellectual property rights (IPR) and structures for intensified cooperative research. Multiple players from industry and academia need to be brought in proximity to create the linkages that will stimulate development of new technology options. At the same time, this proximity of key actors will build the competitive environment needed to drive the competitive selection process that is the essential element in the Darwinistic innovation model. Moreover, the different financial characteristics in the More than Moore field, specifically the much lower capital intensity as compared to the More Moore field, will also lead to new business models being successful.

Realising that it is impossible to predict what products will be winners and when the associated volume markets will take off, well-organised R&D 'ecosystems' are needed that foster parallel emerging technology developments. Such ecosystems must enable cross-fertilisation in an open innovation atmosphere while protecting IPR of the actors involved. Internal as well as external communication is essential throughout the ecosystem to enable the actors to decide at the right time on the continuation of winner technologies and the discontinuation of less promising options. In the ideal ecosystem, very innovative R&D infrastructures are in close proximity with traditional production methodologies; this will stimulate convergence of know-how from all domains and reduce the inevitable struggle of innovative concepts to become accepted in volume applications.

Ideally, the R&D ecosystem for nanoelectronics will be a fusion of large and small industry, notably start-ups, together with universities and institutes. But also the public authorities must join as a full partner, and assist in creating linkages in market and technology, building and concentrating R&D ecosystems, and securing IP leadership by adapting legislation where needed. European IP leadership can, for example, be stimulated by making it easier and more cost-effective to obtain pan-European coverage for a patented invention. In addition, tax incentives may help to stimulate cross border licensing and use of IP.

Discussion and Conclusions

Maurits Doorn¹, Hans de Wit²

Now that we have become acquainted with the two cases in which the dynamics of converging technologies are set out, we can observe interesting similarities and differences, but also inquire into the conditions that allow converging technologies to productively develop and achieve their promises. This chapter presents such a comparison of the characteristic features and patterns identified in the two cases and provides clues as to what can be done to facilitate an innovative ecosystem in order to nurture the potential benefits of converging technologies to society.

¹ STT, Den Haag, the Netherlands.

² Technische Universiteit, Delft, the Netherlands.

Although the pattern of technological convergence is a prominent feature in both case studies, considerable differences are to be observed as well. In nanoelectronics, there is a combination of established trajectories and newly emerging fields, suddenly opening up a multitude of new possibilities for technological development. These possibilities are associated with a variety of completely novel value propositions. In contrast, in regenerative medicine there is one long-term objective: combining findings from different fields in the life sciences en medical research and translating these into clinical therapies for the regeneration of impaired tissue. There is an ongoing process of trial and error to fulfil this promise. Although many attempts cannot meet the sometimes over-extended expectations, from time to time something succeeds. Such successes combined with often serendipitous new scientific findings give rise to new hope, but there remains the risk of over-extended expectations, hype and eventually disappointment.

COMPARING THE CASE STUDIES

It is worthwhile to further explore the differences and similarities between the case studies.

SOURCES OF NOVELTY

The case studies illustrate that there is variety of ways of how novel technological options and innovations can be created through convergence. There is, of course, the general distinction in the chain link models (see Figure 1 ‘Chain link model of innovation’ in the chapter ‘Anticipating the Dynamics of Converging Technologies’) between research processes and innovation processes. Converging technologies appear at the research side as new technological options, created through combinations of knowledge from, for instance, different scientific disciplines and in innovation processes as new products and process technologies introduced into markets. Whereas the novelty in regenerative medicine mostly stems from new technological options created at the research side, in More than Moore the novelty is based on a mixture where ongoing innovation processes in established technological trajectories are combined, for instance through advanced device designs. Large-area electronics combines the two electronic polymers, a new technological option stemming from the research side, with complementary processing technologies derived from printed circuit boards manufacturing or office equipment (inkjet).

CONFIGURATIONS

Another difference arises from the characteristics of the broader technical configurations as part of which converging technologies have to work. Whereas

the devices discussed in nanoelectronics function as part of hierarchically organised, modular systems with well-defined interfaces, in the biological domain of regenerative medicine there is no such structure. Living systems, such as tissues and organs, are complex. The remarkable properties of living tissue are the result of the complex arrangement and interaction through feedback loops between different levels and subsystems of increasing complexity — biomolecular, cellular, tissue, organ, and organism.

The typical modular design of electronic systems, with well-defined interfaces for the components, permits the introduction of novelty at different levels in the hierarchy. Such a modularisation makes it possible to abstract from the complexity of underlying levels, an abstraction that is much more difficult, if not impossible in the biological domain. This abstraction allows the ‘black-box thinking’, the key enabler for the engineering efficiency required for today’s increasingly complex range of electronics products. Thus, in Moore’s law, convergence takes the form of a building block approach, where the integration of new and existing functionalities such as logic, memory, sensing, actuation, power, etc is made possible through novel chip design. Some of these functionalities are part of established trajectories in which they are implemented as separate components and devices and integrated on a printed circuit board (instead of integrated into one package). Other things, such as biosensors, are new technological options that are in a more exploratory phase of development.

VALUE CHAINS AND INDUSTRY STRUCTURE

Whereas in nanoelectronics value chains are extensively discussed so to understand the dynamics, a discussion of value chains is absent in the discussion about regenerative medicine. This difference can be explained in terms of the development phases of the respective technologies. The products and processes discussed in nanoelectronics are largely created in the context of innovation processes, and the discussion aims to anticipate the technical and commercial feasibility of various (combinations of) possible trajectories. By contrast, most novelties in regenerative medicine concern new options derived from research and small-scale attempts to apply them in medical practice. The large-scale technical and commercial feasibility of such options can be only tested at a later stage, after the agenda for the field has been better articulated. In regenerative medicine, the tissue-engineering paradigm promised to be the start of a new trajectory, as a next step in tissue replacement therapies, but failed to meet expectations. Now, the field is back in a phase of agenda setting and resource mobilisation. A greater variety of techniques (cellular, biomolecular, etc.) is currently investigated, and the focus on the in vitro trajectory of tissue engineering is complemented by a much broader search

incorporating new results from research in the life sciences (such as genomic, proteomics and stem cell research). But in response to the lessons learned from the tissue engineering, there is now also an increased interest to integrate other essential sources of knowledge, about clinical practice, markets, complementary innovations, regulation and ethical issues. The material integration of new functionalities into integrated electronic devices in the More than Moore domain is reflected in the dynamics of value chains. For instance, as integrated device manufacturers integrate new components into their electronic devices, they also capture the added value that was first created by firms manufacturing the separate components. Added value that was first positioned on the printed circuit board now ends up as a packaged electronic device. Thus, for System-in-Package (SiP) devices, the value added by back-end manufacturing becomes much more important. As a consequence, firms can then go out of business or at best become a supplier of the integrated device manufacturer instead of the electronic system integrator. By contrast, the modularity of the new devices of course offers opportunities for design houses to provide IDMs with improved or new subsystem designs. Innovations in the More than Moore regime are challenging for parts of the existing industrial value chain, but primarily innovations in More than Moore attempt to extend existing value chain structures. Printable large-area electronics represents a new value proposition that creates a new space for the application of integrated electronic devices. Not only may this technology offer an alternative for existing signage and lighting technology, it may also allow the integration of RFID in packaging materials, biosensing functionality in textiles or solar cells on construction materials. The cross-linking of technological paths and the related transgression of traditional borders between industrial sectors that is characteristic of converging technologies is clearly visible in this domain. Ultimately, it could be speculated that the trajectories in More than Moore and large-area electronics may converge at system level, as they are both necessary to make the promises of ambient intelligence possible.

For regenerative medicine, the aforementioned phases of agenda setting and resource mobilisation may eventually lead to a restructuring of the related industrial partners. However, this is not yet visible while the trajectories are not clear.

ROADMAPS

The difference in phases also explains the absence in regenerative medicine of the kind of roadmaps used in nanoelectronics. Roadmapping only makes sense as a vehicle for vertical and horizontal coordination in value chains that emerge once the first contours of a trajectory become visible. Knowledge about such a trajectory can then be used to define further action, not only with respect to technology development, but also as a guide for the actual

translation of these technologies into applications in clinical practice and toward the formation of the value chains needed for a successful commercial introduction.

LINKING OF DIFFERENT DOMAINS

A remarkable feature in both case studies is that converging technologies result in the creation of new links between previously separate domains. One example that currently receives much attention in discussions about converging technologies is the emergence of links between the domains of the biological and the synthetic. Examples discussed in this book are synthetic materials designed to trigger tissue responses, the integration of biosensors in electronic devices (bio-MEMS) or the idea to incorporate electronic components into the body. But there are other examples, such as the combination of analogue and digital components in one device. Such innovations are often regime-challenging as they transgress boundaries between disciplines, necessary to mount the needed expertise, or boundaries between sectors and value chains, as new networks of linkages have to be created for market access.

DYNAMICS OF PROMISES AND EXPECTATIONS

Finally, both case studies feature a dynamics of expectations and promises where the players attempt to anticipate future developments so as to position themselves with respect to potential technological paths.

HANDLING CONVERGENCE

Technological convergence implies by definition a venture into unexplored territory. Scientific research and technological change have their own dynamics, full of serendipity and surprises, and are mutually shaped by social and economic processes. Because the possibilities and promises of converging technologies transgress traditional boundaries, between disciplines, technological fields, product categories, economic sectors or markets, the embedding of converging technologies in society is characteristically accompanied by a period of turbulence and struggle, through which it is difficult to navigate. Despite the differences in both case studies, there is a comparable dynamics of expectation and promises, where the players try to position themselves with respect to possible future trajectories. The case studies illustrate how the players deal with such anticipation dilemmas and provide some clues as to how to deal with them.

In the early phase, before trajectories are visible as in regenerative medicine and also in large-area electronics, there is a need for well-planned broad, but

dedicated long-term research programmes. For later stages, when a trajectory takes off as in nanoelectronics, roadmapping becomes possible and an ecosystem promoting open innovation is necessary.

At the start of a trajectory, a value chain starts to emerge and roadmapping becomes possible. Roadmapping is a methodology aimed at the development of a shared vision of the future in order to timely address a problem or to fulfil a market need. A good roadmap emphasises the commitment of all stakeholders as made clear in the case study on nanoelectronics. The coherence between the various levels of abstraction, such as technology, product and marketing planning, are made explicit in the roadmapping process in order to steer the planning and decision-making. Aspects of scenario planning are taken up in this process, so that relevant issues and developments can be placed on a time scale and clearly specified future milestones can be defined, typically 5, 10 or sometimes 20 years from the start of the process. Then, backcasting to the present, the steps that need to be taken to achieve the stated objective can be defined and placed on a time scale, thus making good planning possible. The steps include technology development, R&D projects and organisational issues. It is important to understand that roadmapping also remains a dynamic process in an activated system with many cross-over points, where creative decisions have to be taken all the time. Moreover, a road map should not be considered a static plan: It should be regularly revisited so as to adapt it to lessons learned and changing circumstances and to make the planning more realistic. This immediately shows why no roadmap was available in the case study on regenerative medicine: A well-articulated value chain was not available as yet. That is why the stakeholders were not listed or committed.

Through roadmapping we can arrive at dedicated research projects directly aimed at the objectives of the roadmap and new R&D strategies, which can nowadays only thrive in an open innovation approach, where converging technologies are naturally embedded, because of their inherent need for cross-fertilisation in an open communicative system. Converging technologies reach out to creatively solve complicated issues and provide options for completely new products.

Based on the developments observed in the case studies, we stipulate that, despite the fact that predictions on the outcome of innovation processes are hardly possible, a facilitation of the right R&D and societal ambience, in short the right 'ecosystem', will create solutions to complicated problems in product development and societal issues.

In fact, we have seen that in the right ‘ecosystem’ both technological and organisational patterns can evolve, steered by various players at short term, whereas long-term outcomes are uncertain. Nevertheless, understanding the dynamics of the ‘steered’ evolution of these patterns or trajectories, by looking at the examples in hindsight, provides possibilities to further develop technological options and new value propositions.

In the case study about regenerative medicine the need for broad, multidimensional and dedicated research programmes with strong cohesion was emphasised. Such a programme should be based on a long-term vision that creates a creative tension between a realistic assessment of what is possible and a desirable future. Such programmes should not only pay attention to science and technology, but also take into account contextual social and economical issues including regulations, ethics and reactions in society. A way forward can only be found if the non-technological issues are addressed simultaneously with research and technological development in a step-by-step process, including well-balanced information and education schemes about potential health care solutions. In short, a value chain may then emerge, which will enable better planning through roadmapping as described above and market introduction of the new technologies. Apart from these dedicated research programmes, open technology projects are needed to stimulate a new creativity for a future knowledge-based industry.

In the case study on nanoelectronics, emphasis is placed on the need for an open value chain approach. Cooperation across the entire value chain is essential, for small and large companies alike. Realising that it is impossible to predict which products will be winners and when the associated volume markets will take off, well-organised R&D ecosystems are necessary that foster parallel emerging technology developments. Such ecosystems should enable cross-fertilisation in an open innovation atmosphere while protecting the IPR of the players involved in a responsible manner. ‘Responsible partnering’ is an essential success factor in open innovation. Both internal and external communications are essential throughout the ecosystem to enable the players to decide at the right time on the continuation of winner technologies and the discontinuation of less promising options. In the ideal ecosystem, very innovative R&D infrastructures are in close proximity to traditional production methodologies; this will stimulate the convergence of know-how from all domains and reduce the inevitable struggle of innovative concepts to become accepted in volume applications. Ideally, the R&D ecosystem for nanoelectronics will be a fusion of large and small industry, notably start-ups, together with universities and institutes. It requires a different way of thinking about cooperation also between SMEs and bigger companies.

The proper ecosystem to enable converging technologies to play their optimal problem-solving roles as part of the open innovation paradigm is a combination of the ecosystems as described in these two case studies. Different aspects of the ecosystem play a role in the different development phases of the innovation process. It is clear that this ecosystem cannot be simply created through direct action by only one or two of the vast number of players in the field. All of these are involved but often not aware of their roles in the system.

The ecosystem, however, can be facilitated by public authorities and policy makers.

RECOMMENDATIONS

The overall message is that society can only profit from converging technologies in an open, innovative system if long-term commitment by the players is guaranteed. In a knowledge-based society the ‘ecosystem’ as described in this book should reflect a sustainable long-term vision supported by public authorities, scientists, technology developers and industry alike, backed up by consistent behaviour and actions over a period of no less than 10 years.

- Broad and dedicated long-term research programmes are needed, but we should not abolish open technology projects that are driven by creative curiosity.
- Public support is an essential element in providing continuity in R&D spending in those cases where short-sighted short-term financial issues risk an overall decline in R&D spending in an industrial sector. This is true for revolutionary innovations, where the costs of innovation are high and difficult to predict, but also for ‘niche-creation’ fields until volume applications have penetrated the market.
- Public authorities should not make choices in the market place but facilitate linkages and cross-fertilisation between various players in an innovative society.
- Public authorities can contribute to the wanted ecosystem by commissioning for innovative solutions of the great societal problems to public private consortia.

Index

Symbols	3D Integration	200, 203, 212, 214, 218, 219, 270, 282
	3D sculpting	173, 174
A	Abernathy and Clark	25, 30, 37-41 , 42, 187, 190, 193, 197, 201-203, 210, 214, 220, 237, 239, 241, 244, 248, 250, 252, 253, 255, 256, 257, 260, 269-271
	Agenda setting	16, 32, 35-37 , 135, 157, 276, 277
	Age of Reconstruction	74, 86, 158, 282
	Age of Resection	74, 282
	Ambient Intelligence	21-22, 24, 25, 170, 175, 178-179 , 190, 212, 219, 224, 241, 266, 267, 270, 277
	Anticipation	20, 22, 24, 266, 278
	Architectural	38-41 , 187, 188, 190, 193, 195, 196, 197, 201, 204, 216 , 217, 244-263, 269, 270
	Autogenous	62, 76, 77, 78, 79, 84, 85, 88, 89, 137, 282
	Autologous	78, 82, 89, 96, 114, 115, 116, 117, 120, 137, 138
	Autonomous choice	139, 140
B	Back-end	168, 202, 206-214, 219, 277
	Bell curve	191, 192, 193
	Bio-electronics	267

	Biomaterial	53, 78, 80, 95
	Bioreactor	119, 120, 126, 128, 129
	Biosensor	249, 250
	BMP	<i>SEE BONE MORPHOGENETIC PROTEINS</i>
	Bone Graft	71, 76, 77, 79, 82, 84, 85, 86, 88, 89, 90
	Bone Morphogenetic Proteins	77, 78, 80-84 , 89, 90
	Business models	188, 272
C	Capabilities	12, 19, 30, 32, 37-40 , 41, 42, 47, 101, 158, 184, 192, 196, 225, 238, 239, 240, 245, 246, 248, 250, 251, 260, 263, 270, 271
	Cell therapy	7, 24, 92, 94-99 , 101, 102, 103, 104, 105, 112, 113, 114, 115, 116, 134, 135, 137, 141, 144, 146, 147, 148, 158, 161
	Clinical study	81, 83
	Clinical Trial	98, 102, 117
	CMOS	35, 36, 173-174 , 201-202, 204, 205, 206, 207, 209, 210, 211, 212, 214, 215, 219, 220, 221, 229, 230, 231, 232, 234, 246, 247, 255, 256, 268
	Co-evolution	23, 41
	Conservative	37, 114, 201, 202, 204, 211, 218, 269
	Converging Technologies	11, 12, 14-15, 18-22 , 28, 29, 32, 35, 41-42, 78-79, 263, 266, 274-281
	Creativity	242, 280
D	Display	204, 225, 228, 229, 234, 235, 236, 237, 240, 241, 247, 248
	Disruptive	12, 25, 29, 37-39 , 172, 187, 191, 195, 203, 225, 234, 237, 246-259, 268, 269
	Disruptive cycle	246, 249, 250, 256, 257-259
	Dominant design	30 , 33, 246
E	Ecosystem	17, 171, 195-196, 197, 258, 260, 271-272 , 274, 279-281
	Efficacy	52, 82, 83, 88, 98, 101, 102, 110, 116, 125, 126, 144, 145, 146, 157, 162
	Electronic polymers	225, 223828, 234, 238, 275
	ENIAC	170, 176, 179, 185, 198
	Entrepreneurship	196, 198, 258, 265
	Ethical	11, 16, 24, 47, 52, 84, 96, 98, 104, 106, 105, 108, 109, 110, 115, 116, 119, 121, 134,

		135, 136, 138, 139, 140, 141, 142, 143, 147, 148, 149, 152, 153, 155, 159, 160, 162, 163, 277
	Ethics	106, 108, 135, 141, 142, 143, 149, 152, 153, 154, 155, 280
	Evolution(ary)	12, 19, 23, 33, 34-35 , 41, 42, 269-271, 280
	Exit strategy	64, 143, 150, 151, 152, 154
	Expectation	15, 35-37 , 40, 49, 50, 63, 84, 94, 278
F	Fluidics	169, 173, 258, 267
	Forecasting	35, 44, 55, 154, 171, 210, 214, 220, 265, 267
	Front-end	168 , 202, 206, 207, 208, 212, 219
G	Genomics	24, 52, 102, 148, 371, 158
	Government	2, 11, 52, 152, 182, 195, 204, 253, 265
	Growth factors	24, 53-54 , 62, 63, 67, 68, 76, 77, 78, 86, 87, 128, 130, 137, 158, 161
H	Heart Failure	24, 92, 93-94 , 98, 102, 114, 116, 159
	Heterogeneous Integration	7, 25, 174, 175, 200, 203, 211-214 , 220, 242, 246
	Holst Centre	196, 224, 234, 240, 241
	HUMAN++	216, 217, 218, 246
	Hype	15, 16, 19, 20, 23, 24, 35-37 , 43, 49, 70, 113, 158, 159, 163, 190, 275
I	IC	<i>SEE INTEGRATED CIRCUIT</i>
	Implant	68, 70, 120, 130, 157
	Implantation	53, 55, 62, 63, 116, 118, 120, 123, 129, 137, 156
	Informed Consent	139, 142, 153
	Inkjet	174, 201, 204, 226, 230, 232, 233, 245, 275
	Innovation	10-12, 25, 26, 29-41 , 46, 135-136, 149-153, 169-171, 179, 186-197, 257-259, 260-264, 266-271, 272-281
	Insurance	50, 136, 144, 145-147 , 159, 161
	Integrated Circuit (IC)	36, 167-168 , 171-175, 181, 190, 200, 201, 202, 203, 205, 206, 207, 208, 209, 210, 211, 212, 214, 215, 220, 246, 270

	Intellectual Property Rights (IPR)	17, 272, 280
	IPR	<i>SEE INTELLECTUAL PROPERTY RIGHTS</i>
	ITRS	36, 44, 168, 174, 176, 201, 215, 221
K	Knowledge infrastructure	163
L	LAE	<i>SEE LARGE-AREA ELECTRONICS</i>
	Large-Area Electronics	11, 25, 175, 224, 275
	LED	<i>SEE LIGHT EMITTING DIODES</i>
	Liberal	137, 139, 149
	Light Emitting Diodes	65, 79, 110, 170, 182, 227-239
	Linkage	32, 37-41 , 187-188, 191-193, 197, 219, 244, 245, 270-272, 278, 281
	Logic	24-25, 169, 172-174 , 189, 219, 229, 234, 238, 239, 240, 241, 267, 268, 270, 276
M	MEDEA+	171
	Medical devices	51, 52, 64, 121, 125
	Memory	25, 167, 173, 214, 219, 224, 229, 234, 236, 239, 240, 241, 267, 276
	MEMS	<i>SEE MICRO-ELECTRO-MECHANICAL-SWITCH</i>
	MESA+	251, 262
	Micro-Electro-Mechanical-Switch	25, 172-175 , 181-183, 200-208, 210-215, 219-222, 245, 253, 255, 264, 265, 267, 268, 270, 278
	Micro Systems Technology	245-248 , 252, 257-260
	Miniaturisation	166-174 , 181-183, 190, 202, 204, 211, 220, 221, 267
	Minimally invasive surgery	55, 85, 129
	Moore's Law	25, 33, 35, 36, 167, 168, 172-174 , 188-190, 225, 235, 267, 268
	More than Moore	172-175, 185, 194, 197, 200-205, 211, 212, 215, 216, 219, 220, 240, 242, 246, 260, 267, 268, 272, 275, 276, 277
	MST	<i>SEE MICRO SYSTEMS TECHNOLOGY</i>
N	Nanoelectronics	24-25, 40, 166-175, 178-184, 267-272, 277-280
	Niche	30, 38, 150, 159, 174, 195, 197, 201, 216, 217, 220, 236, 238, 240, 242, 250, 252, 268, 269, 271, 281
	Norms	140, 141, 144, 145

O	Open innovation	11, 12, 17, 32, 39-40 , 43, 196, 242, 272, 279, 280, 281
	Optics	69, 267
	Organ transplantation	47, 48, 139, 156
P	Paradigm	11, 40, 42, 56, 58, 60, 61, 65, 71, 119, 120, 127, 141, 142, 143, 157, 158, 196, 232, 248, 257, 261, 267, 276, 281
	Participation paradigm	142-143
	Path dependency	16, 35, 37
	PCB	<i>SEE PRINTED CIRCUIT BOARD</i>
	Pelvis	76, 78, 85
	Political-normative	146
	Polymer electronics	175, 225-242 , 268
	Power	169-173, 182, 184, 191, 202, 208-218, 224, 231, 234, 235, 236, 237, 239, 240, 241, 242, 256, 276
	Preventive medicine	129, 147, 148, 160, 162
	Printed Circuit Board (PCB)	171, 174, 175, 190, 218, 276, 277
	Promise	16, 20, 22, 23, 25, 34-36 , 40, 42, 49, 53, 112, 120, 130, 136, 148, 157, 160, 245, 260, 275
	Prospective	36, 40, 89, 103, 115, 116
	Protection paradigm	142-143
	Proteomics	24, 158, 277
	Public ethical	139, 149
Punctuated equilibrium	35	
R	Radio Frequency (RF)	181, 183, 200, 202, 203, 206, 208, 209, 210, 211, 212, 213, 214, 215, 219, 220, 221, 222, 238, 255
	Rationalistic	145, 146
	Regenerative Medicine	23, 32, 46-55, 58-70 , 74, 84, 86, 92, 95, 98, 118, 119, 121, 122, 127, 129, 130, 134-153, 156-164, 275-280
	Regulation	24, 41, 47, 51, 52, 105, 115, 150, 153, 159, 212, 277
	Replacement	23, 36, 38, 46, 48, 49, 53, 59, 60, 65, 75, 78, 82, 83, 86, 93, 95, 120, 121, 131, 132, 276
	Research Programme	134, 163

	Responsibility	137, 143, 149, 154
	Responsible	11, 17, 79, 80, 81, 147, 150, 280
	RF	<i>SEE RADIO FREQUENCY</i>
	Roadmap	17, 36, 168, 173, 174, 176, 190, 200, 201, 215, 216, 218, 219, 220, 221, 265, 267, 279
S	Safety	41, 52, 83, 88, 90, 101, 103, 105, 110, 114, 125, 127, 142, 144, 145, 181, 182, 238
	Scaffold	52, 54, 62, 63, 76, 77, 119, 125, 127, 129, 158, 161
	Scenario	17, 189, 190, 193, 196, 197, 235, 236, 271, 279
	Semiconductor	32, 42, 167-169, 172-174, 182, 190, 191, 195, 197, 198, 210, 221, 225, 227, 232, 235, 244-249, 252, 253, 257, 258, 266-268, 270, 271
	Sensor	181, 213, 217, 226, 231, 237, 240, 241, 242, 256, 264
	SiP	<i>SEE SYSTEM-IN-PACKAGE</i>
	SoC	<i>SEE SYSTEM-ON-CHIP</i>
	Spinal Fusion	7, 24, 36, 54, 74-88, 137, 141, 144, 146, 148, 158
	Spine	24, 76, 77, 79, 84, 85, 86, 87, 88, 89, 90
	Stem Cells	52, 62, 63, 71, 82, 83, 87, 96, 97, 98, 103, 104, 105, 106, 108, 109, 110, 113, 114, 115, 117, 119, 121, 130, 137, 138, 154, 155, 159, 161
	System-in-Package (SiP)	25, 173, 174, 181, 190, 203, 208, 209, 212, 213, 214, 215, 220, 221, 222, 242, 246, 267, 268, 270, 277
	System-on-Chip (SoC)	25, 173, 174, 208, 221
T	Technological branching	24, 245-246, 260
	Technological change	29, 34
	Technological convergence	245, 260, 275, 278
	Technological regime	29, 30, 36
	Technological trajectory	12, 16, 17, 19, 20, 21, 24, 25, 29, 30 , 34, 35-37
	Technology	32-33
	Tissue Engineering	23-24, 36, 47, 49-52, 54, 55, 56, 58, 62, 63, 64, 70, 71, 72, 114, 115, 118, 119, 120,

		121, 127, 129, 131, 132, 135, 137, 141, 153, 154, 158, 159, 163, 276, 277
	Tissue model	119, 120
	Transistor	167, 225
	Transplantation	47, 48, 58, 61, 71, 72, 78, 93, 94, 95, 96, 98, 99, 101, 103, 114, 115, 116, 117, 132, 139, 156
V	Value chain	7, 10, 11, 12, 17, 25, 39, 171, 175, 186-197 , 198, 200, 201, 204, 206, 207, 208, 211, 230, 232, 237, 244, 245, 248, 249, 257, 260, 261, 268-272, 277, 279, 280
	Value creation	28, 169, 193, 245, 260, 261, 263
	Virtuous cycle	246, 250, 256, 258, 259
	Voice	143, 144, 150, 151, 153, 154, 182, 183
W	Wafer	168, 173, 174, 175, 194, 202, 204, 207, 208, 210, 212, 213, 214, 215, 219, 249, 267

Survey Organization

ACKNOWLEDGEMENTS

This publication is the result of the STT foresight project about converging technologies and reflects the cooperation of a multidisciplinary group of experts from academia, research institutes and industry who took part in this project. STT owes many thanks to all those who have unselfishly put much time, enthusiasm and energy into this project.

STEERING COMMITTEE

Prof Dr Ir A.C. Brombacher	Technische Universiteit Eindhoven, Eindhoven
Prof Dr J.A. Jansen	Radboud Universiteit Nijmegen, Nijmegen
Drs N.P.J. Kuin	Océ-Technologies, Venlo
Prof Dr A. Rip	Universiteit Twente, Enschede
Dr Ir A.J. van Roosmalen	Philips Semiconductors, Eindhoven
Ir J.H. van der Veen	STT, Den Haag
Dr G.F.A. van de Walle	Philips Research, Eindhoven
Prof Dr J.H.W. de Wit (chairman)	Technische Universiteit Delft.

FOCUS GROUP REGENERATIVE MEDICINE

Prof Dr C.A. van Blitterswijk	Universiteit Twente, Enschede
Dr C.V.C. Bouten	Technische Universiteit Eindhoven, Eindhoven
Drs D. Delawi	Universitair Medisch Centrum Utrecht, Utrecht
Dr W.J.A. Dhert	Universitair Medisch Centrum Utrecht, Utrecht
B. Fernandes	Medtronic Bakken Research Center, Maastricht
M. Hendriks	DSM Research, Geleen
Prof Dr K. Horstman	Universiteit Maastricht, Maastricht
Prof Dr J.A. Jansen (chairman)	Radboud Universiteit Nijmegen, Nijmegen
Dr D.R.G.J. Meijer	Universitair Medisch Centrum Utrecht, Utrecht.

FOCUS GROUP NANOELECTRONICS

Prof Dr Ir A.C. Brombacher	Technische Universiteit Eindhoven, Eindhoven
Dr C.J.M. Eijkel	Universiteit Twente, Enschede
Dr Ch. van Hoof	IMEC vzw, Leuven, Belgium
E. Knol	Qeam, Leiden
I. Raaijmakers	ASMI, Bilthoven
Prof Dr A. Rip	Universiteit Twente, Enschede
Dr Ir A.J. van Roosmalen (chairman)	Philips Semiconductors, Eindhoven
Ir F. Simonis	TNO Industrie en Techniek, Eindhoven
Dr G.F.A. van de Walle	Philips Research, Eindhoven.

PROJECT MANAGEMENT

This study was organised by Maurits Doorn (project manager) and Rosemarijke Otten (project secretary).

Project Cooperation

The Dutch Advisory Council on Health Research (Raad voor Gezondheids-
onderzoek, RGO) has cooperated with this project. This cooperation has been
formalised in the context of the Dutch Consultative Committee of Sector
Councils for research and development (Commissie van Overleg Sectorraden
COS), of which both RGO and STT are members.



RGO

The Dutch Advisory Council on Health Research (Raad voor Gezondheidsonderzoek, RGO), established in 1987, advises the government, especially the ministry of Health, the ministry of Education and Science, and the ministry of Economic Affairs, on matters relating to health research, health services research and the infrastructure of such research.

Health research is defined as research on epidemiologic and etiologic aspects of disease, diagnosis, prevention, cure and care, and the development of relevant technology. Health services research concerns aspects of health services such as structure and organisation, its function, and the demand for health services. The RGO's main task is to set priorities for research aimed at the solution of problems in health and health services and to give recommendations on financial and infrastructural matters.

The RGO is one of four Sector Councils working together in a platform (COS). Their task is to gear scientific research to social needs by means of a close interaction between government, scientific investigators, and end-users of the results of research.

The following sectors are covered by the Sector Councils and the COS member STT: Health (RGO), Environmental issues, spatial planning (RMNO), Research for Development (RAWOO), Agricultural Research (Innovatienetwerk) and Technology (STT).

The recommendations by the RGO are given after a comprehensive investigation of the field of interest. Each report is based on a careful balance of the scientific requirements and the social needs for health (care) research.

For more information on the RGO please visit: www.rgo.nl



COS

The Consultative Committee of Sector Councils for research and development (COS) in the Netherlands is the collaborative platform for sector councils and other members specialised in foresight studies. Legal basis is the Sector Councils Framework Act on research and development (1989, as amended in 1997):

A sector council is a foresight body, comprising representatives from the scientific community, civil society (including trade and industry) and the

government (as an advisory member). They present an independent view of societal demands for knowledge and the consequent priorities for strategic research in their respective sectors. Their views are based on thorough studies, such as foresight activities, necessary to obtain a long-term perspective on societal and scientific trends. In order to acquire mass for a necessary comprehensive approach sector councils collaborate as to consider one domain in coherence with another. Sector councils also map developments in science and technology and interpret the implications for society.

The domain of the sector councils involves: Spatial Planning; Nature and Environment; Rural Areas and Agriculture; Health; Technology; Development Cooperation.

The possibility of a sector council or a sector council-style approach for Education; Public Administration, Justice and Security; Traffic, Transport and Infrastructure and for labour is presently investigated.

Functions of the COS as a collaborative platform are e.g. promoting a joint approach in foresight- and programming studies as well as studies on the development of methodology, funded by the COS Coordination Fund. Furthermore the COS sees to joint input in administrative consultations with ministries and other organisations. The COS is a member of the European Research Area (ERA) Network For Society in which 15 EU member states are working together on joint foresight activities en benchmarking.

For more information please visit: www.minocw.nl/cos

STT Publications

All publications with an ISBN number can be ordered from STT or from the bookshop.

The remaining publications are only available from:

STT

P.O. Box 30424

2500 GK The Hague

The Netherlands

Telephone +31 70 302 98 30

Fax +31 70 361 61 85

E-mail info@stt.nl

Website www.stt.nl

- 71 Converging Technologies: Innovation Patterns and Impacts on Society
 Edited by: Maurits Doorn, 2006 (ISBN-10: 90 809613 3 7 /
 ISBN-13: 978-90-809613 3 3)
- 70 Genomics 2030: Part of Everyday Life
 Edited by Mark de Graef, 2005 (ISBN-10: 90 809613 2 9 /
 ISBN-13: 978 90 809613 2 6)
- 69* Techniek als menselijk ontwerp; nieuwe opleidings- en loopbaanroutes
 voor jongeren
 Redactie: dr.ir. Remke M. Bras-Klapwijk, 2005 (ISBN 90 809613 1 0)
- 68* Beter bouwen en bewonen. Een praktijkgerichte toekomstverkenning
 Redactie: drs. Michiel D.J. van Well, 2004 (ISBN 90 804496 9 5)
- 67 Zee in zicht, zilte waarden duurzaam benut
 Redactie: dr. Esther Luiten, 2004 (ISBN 90 804496 8 7)
- 66 Zorgtechnologie, kansen voor innovatie en gebruik
 Redactie: dr.ir. Jessika van Kammen, 2002 (ISBN 90 804496 7 9)
- 65 Dealing with the data flood, mining data, text and multimedia
 Edited by Jeroen Meij, 2002 (ISBN 90 804496 6 0)
- 64 Betrouwbaarheid van technische systemen, anticiperen op trends
 Redactie: dr. M.R. de Graef, 2001 (ISBN 9084496 5 2)
- 63 Toekomst@werk.nl, reflecties op economie, technologie en arbeid
 Redactie: drs. Rifka M. Weehuizen, 2000 (ISBN 9084496 4 4)
- 62 Vernieuwing in productontwikkeling, strategie voor de toekomst
 Redactie: ir. Arie Korbijn, 1999
- 61* Stroomversnelling, de volgende elektrische innovatiegolf
 Redactie: ir. J.M. Meij, 1999 (ISBN 90 804496 2 8)
- 60 Nanotechnology, towards a molecular construction kit
 Edited by Arthur ten Wolde, 1998
- 59* Bouwwijs, materialen en methoden voor toekomstige gebouwen
 Redactie: ir. Annemieke Venemans, 1997 (ISBN 90 6155 816 6)
- 58* Gezonde productiviteit, innoveren voor betere arbeidsomstandigheden
 Redactie: ir. Arie Korbijn, 1996 (ISBN 90 6155 744 5)
- 57* Digitale leermiddelen in beroepsopleidingen (incl. cd-i en samenvatting)
 Redactie: dr. A. ten Wolde, 1996
- 56 Microsystem technology: exploring opportunities
 Edited by Gerben Klein Lebbink, 1994 (ISBN 90 14 05088 7)
- 55* Schone kansen, denkbeelden over ondernemerschap en milieumanage-
 ment
 Redactie: ir. E.W.L. van Engelen, J. van Goor, 1994 (ISBN 90 14 04929 3)
- 54* Goederenvervoer over korte afstand
 Redactie: ir. M.J. Venemans, 1994 (ISBN 90 14 04928 5)
- 53* Elektriciteit in perspectief, 'energie en milieu'
 Redactie: ir. E.W.L. van Engelen, 1992

* English summary available.

- 52* Inspelen op complexiteit
Redactie: drs. M.J.A. Alkemade, 1992 (ISBN 90 14 03883 6)
- 51* Plantaardige grondstoffen voor de industrie
Redactie: drs. W.G.J. Brouwer, 1991 (ISBN 9014 03882 8)
- 50 Opleiden voor de toekomst: onderdeel van bedrijfsbeleid
ir. H.B. van Terwisga en drs. E. van Sluijs, 1990
- 49 Grenzen aan techniek
Redactie: ir. A.J. van Griethuysen, 1989 (ISBN 90 14 03880 1)
- 48 Kennissystemen in de industrie
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1988
- 47 Kennissystemen in de dienstensector
Redactie: drs. A.Y.L. Kwee en ir. J.J.S.C. de Witte, 1987
- 46 Kennissystemen en medische besluitvorming
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1987
- 45 Kennissystemen in het onderwijs
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1987
- 44 Onderhoudsbewust ontwerpen nu en in de toekomst
Redactie: ir. G. Laurentius, 1987
- 43 Nieuwe toepassingen van materialen
Redactie: ir. A.J. van Griethuysen, 1986
- 42 Techniek voor ouderen
Redactie: ir. M.H. Blom Fuhri Snethlage, 1986 (ISBN 90 14 03822 4)
- 41 De toekomst van onze voedingsmiddelenindustrie
Redactie: drs. J.C.M. Schogt en prof.dr.ir. W.J. Beek, 1985
- 40 Bedrijf, kennis en innovatie
Redactie: ir. H. Timmerman, 1985
- 39 De kwetsbaarheid van de stad; verstoringen in water, gas, elektriciteit en telefonie
Samensteller: ir. G. Laurentius, 1984
- 38 Man and information technology: towards friendlier systems
Edited by J.H.F. van Apeldoorn, 1983
- 37 Nederland en de rijkdommen van de zee: industrieel perspectief en het nieuwe zeerecht
Redactie: ir. J.F.P. Schönfeld en mr.drs. Ph.J. de Koning Gans, 1983
- 36 Informatietechniek in het kantoor; ervaringen in zeven organisaties
Samensteller: drs. F.J.G. Fransen, 1983
- 35 Automatisering in de fabriek; vertrekpunten voor beleid
Redactie: ir. H. Timmerman, 1983
- 34 Flexibele automatisering in Nederland; ervaringen en opinies
Redactie: ir. G. Laurentius, ir. H. Timmerman en ir. A.A.M. Vermeulen, 1982

* English summary available.

- 33 Toekomstige verwarming van woningen en gebouwen
Eindredactie: ir. A.C. Sjoerdsma, 1982
- 32 Micro-elektronica voor onze toekomst; een kritische beschouwing
Samenstellers: burggraaf E. Davignon e.a., 1982
- 31-9 Micro-elektronica: de belastingdienst
Samensteller: ir. H.K. Boswijk, 1981
- 31-8 Micro-elektronica: het reiswezen
Samensteller: ir. H.K. Boswijk, 1981
- 31-7 Micro-elektronica: het kantoor
Samensteller: ir. H.K. Boswijk, 1981
- 31-6 Micro-elektronica: het bankwezen
Samensteller: ir. H.K. Boswijk, 1981
- 31-5 Micro-elektronica: het ontwerpproces
Samensteller: ir. H.K. Boswijk, 1981
- 31-4 Micro-elektronica: productinnovatie van consumentenprodukten en
diensten voor gebruik in huis
Samensteller: ir. H.K. Boswijk, 1981
- 31-3 Micro-elektronica: procesinnovatie in de sector elektrometaal
Samensteller: ir. H.K. Boswijk, 1981
- 31-2 Micro-elektronica: de grafische industrie en uitgeverijen
Samensteller: ir. H.K. Boswijk, 1981
- 31-1 Micro-elektronica: de rundveehouderij
Samensteller: ir. H.K. Boswijk, 1981
- 31 Micro-elektronica in beroep en bedrijf; balans en verwachting
Samensteller: ir. H.K. Boswijk, 1981
- 30 Biotechnology; a Dutch perspective
Edited by J.H.F. van Apeldoorn, 1981
- 29 Wonen en techniek; ervaringen van gisteren, ideeën voor morgen
Redactie: ir. J. Overeem en dr. G.H. Jansen, 1981
- 28 Distributie van consumentengoederen; informatie en communicatie in
perspectief
Redactie: ir. R.G.F. de Groot, 1980
- 27 Steenkool voor onze toekomst
Eindredactie: ir. A.C. Sjoerdsma, 1980
- 26 Bos en hout voor onze toekomst
Redactie: ir. T.K. de Haas, ir. J.H.F. van Apeldoorn, ir. A.C. Sjoerdsma,
1979
- 25 Arts en gegevensverwerking
Redactie: ir. R.G.F. de Groot, 1979
- 24 Toekomstbeeld der industrie
prof.dr. P. de Wolff e.a., 1978

- 23 De industrie in Nederland: verkenning van knelpunten en mogelijkheden
Redactie: ir. H.K. Boswijk en ir. R.G.F. de Groot, 1978
- 22 Materialen voor onze samenleving
Redactie: ir. J.A. Over, 1976
- 21 Stedelijk verkeer en vervoer langs nieuwe banen?
Redactie: ir. J. Overeem, 1976
- 20 Voedsel voor allen, plaats en rol van de EEG
prof.dr. J. Tinbergen e.a., 1976
- 19 Energy conservation: ways and means
edited by J.A. Over and A.C. Sjoerdsma, 1974
- 18 Mens en milieu: kringlopen van materie
Stuurgroep en Werkgroepen voor Milieuzorg, 1973
- 17 Mens en milieu: zorg voor zuivere lucht
Stuurgroep en Werkgroepen voor Milieuzorg, 1973
- 16 Mens en milieu: beheerste groei
Stuurgroep en Werkgroepen voor Milieuzorg, 1973
- 15 Technologisch verkennen: methoden en mogelijkheden
ir. A. van der Lee e.a., 1973
- 14 Techniek en preventief gezondheidsonderzoek
dr. M.J. Hartgerink e.a., 1973
- 13 Communicatiestad 1985: elektronische communicatie met huis en
bedrijf
prof.dr.ir. J.L. Bordewijk e.a., 1973
- 12 Elektriciteit in onze toekomstige energievoorziening: mogelijkheden en
consequenties
dr.ir. H. Hoog e.a., 1972
- 11 Transmissiesystemen voor elektrische energie in Nederland
prof.dr. J.J. Went e.a., 1972
- 10 Barge carriers: some technical, economic and legal aspects
drs. W. Cordia e.a., 1972
- 9 Het voeden van Nederland nu en in de toekomst
prof.dr.ir. M.J.L. Dols e.a., 1971
- 8 Mens en milieu: prioriteiten en keuze
ir. L. Schepers e.a., 1971
- 7 Electrical energy needs and environmental problems, now and in the
future
ir. J.H. Bakker e.a., 1971
- 6 De invloed van goedkope elektrische energie op de technische ontwik-
keling in Nederland
dr. P.J. van Duin, 1971
- 5 De overgangsprocedures in het verkeer
prof.ir. J.L.A. Cuperus e.a., 1969

- 4 Hoe komt een beleidsvisie tot stand?
Ir. P.H. Bosboom, 1969
- 3 Verkeersmiddelen
prof.ir. J.L.A. Cuperus e.a., 1968
- 2 Techniek en toekomstbeeld; telecommunicatie in telescopisch beeld
prof.dr.ir. R.M.M. Oberman, 1968
- 1 Toekomstbeeld der techniek
ir. J. Smit, 1968

Other publications

- New applications of materials;
edited by A.J. van Griethuysen, 1988 (ISBN 0 95 13623 0 5)
- Mariene ontwikkelingen in de Verenigde Staten, Japan, Frankrijk,
West-Duitsland, het Verenigd Koninkrijk en Nederland: organisatie,
aandachtsgebieden en budgets
Redactie: ir. J.F.P. Schönfeld en mr.drs. Ph.J. de Koning Gans, 1984
- Het belang van STT (toespraak bij het 15-jarig bestaan van STT)
door prof.ir. Th. Quené, 1983
- De innovatienota; een aanvulling;
H.K. Boswijk, J.G. Wissema, en W.C.L. Zegveld, 1980

Financial support STT

This study came about thanks to the financial support from companies, government and the Royal Institution of Engineers (KIVI NIRIA).

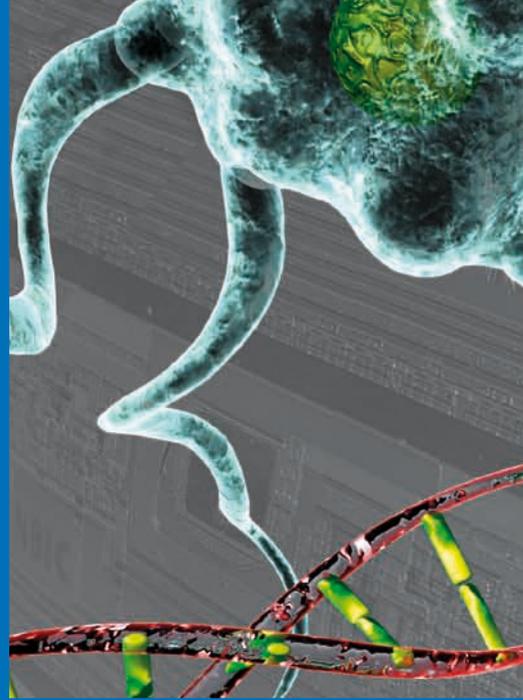
Aalberts Industries
Akzo Nobel
Arcadis
Atos Origin Nederland
Commissie van Overleg Sectorraden
Corus Group
DAF Trucks
DSM
Eldim
Fugro
Getronics PinkRocade
ING Bank
KEMA
KIVI NIRIA
Koninklijke BAM Groep
McKinsey&Company
Ministerie van Economische Zaken
Ministerie van Landbouw, Natuur en Voedselkwaliteit
Ministerie van Onderwijs, Cultuur en Wetenschap
Nederlandse Gasunie
Nederlandse Unilever Bedrijven
Océ-Technologies
Philips Electronics
Rabobank Nederland
Sdu
Shell Nederland
Siemens Nederland
Sogeti Nederland
Solvay Nederland
TNO
Vopak Oil Logistics Europe & Middle East



Currently, new interactions between previously separate fields of research result in qualitatively new technological possibilities and, perhaps, revolutionary impacts. Nanotechnology plays an important role as an enabling technology that, in combination with information technology, biotechnology and cognitive and neuroscience, can create major changes, for example in chips technology, drug delivery or implants. This shift is one example of recurring shifts of boundaries between technological fields, and associated changes in innovation patterns and broader changes in society that are often referred to with the label 'converging technologies'.

Converging technologies present a twofold challenge. First, to understand the complex dynamics of development of converging technologies in specific domains. Second, how to use insight into the dynamics to find a way forward and, where possible, to actively shape the developments. This challenge is addressed in this book, the result of a study about converging technologies carried out by practitioners from academia, public research institutes and industrial companies. Case studies about two specific domains, nanoelectronics and regenerative medicine, constitute the core of the book.

The publication is intended for everyone with an interest in the newly emerging technological possibilities at the crossroads of nanotechnology, life sciences and ICT and their possible impacts. It addresses the dilemmas of policy makers and managers in industry, government and research institutions who try to find a way forward through these complex developments.



ISBN 90-809613-3-7



Laser Proof

9 789080 961333 >