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SWEDISH POSSIBILITIES WITHIN TISSUE ENGINEERING AND REGENERATIVE MEDICINE

ANNIKA RICKNE - LUND UNIVERSITY & THE DAHMÉN INSTITUTE
ANNA SANDSTRÖM - VINNOVA

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Author: Annika Rickne - Lund University and the Dahmén Institute & Anna Sandström - VINNOVA
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Research and Innovation for Sustainable Growth.

Swedish possibilities within Tissue Engineering and Regenerative Medicine

by

Annika Rickne
Lund University & the Dahmén Institute

Anna Sandström
VINNOVA

Preface and acknowledgements

In December 2006, VINNOVA was assigned by the Swedish government to conduct an international benchmarking of the Swedish sectorial innovation systems in pharmaceuticals, biotechnology and medical technology. Case studies and international comparisons of different key technology areas are important in assessing and understanding the Swedish conditions for life science research and innovation. The area of tissue engineering and regenerative medicine (or TERM) was chosen as an interesting key technology area due to the perceived potential of and Swedish position in, the field.

The aim of this VINNOVA report is to identify, describe and analyse global players, trends and positions in TERM. The goal is to provide VINNOVA with a platform for making decisions on whether and how to support the emergence and growth of the field in Sweden. The study was conducted by Annika Rickne, Associate Professor at Lund University and Research Director at the Dahmén Institute and Anna Sandström, Analyst at VINNOVA . The section on Japan is to a large extent based on an ITPS report by Henrik Fridén, except for section 5.3.4, which has been written by Lennart Stenberg, both at VINNOVA. Astrid Szogs (Lund University) has contributed to the sections on German research initiatives and the EU regulation and Stian Nygaard (Lund University) to the chapter on research initiatives in the UK, the US and Japan.

In this report, the field of TERM is defined as the technologies and products that aim to synthetically or biologically substitute, restore, maintain or improve human body functions. It is a globally fast -emerging field that promises much in terms of curing or relieving diseases and impairments as well as economic growth. The report addresses the global development in terms of science, technology and product development, but also players and their locations as well the specifics of regions and countries. The end goal is to understand and highlight Sweden’s position and possibilities in this field. We would like to express our sincerest gratitude to the individuals and organisations that have freely shared their time, experience and views with us. Some of the material on Japan was collected and analysed as part of an ITPS project. In addition, crucial comments from a number of professors and experts were of significant value to the report.

VINNOVA in February 2009

Göran Marklund,
Director and Head, Strategy Development Division

Content

Executive summary

Summary of empirical results

This report discusses the current state and activities of an emerging and fast-moving knowledge field: that of tissue engineering and regenerative medicine, or TERM for short. In the present study, TERM is defined as medical treatments, be they biological or synthetic, which enhance, repair or replace cells, tissues and organs using bioengineered materials, cellular technologies as well as some forms of implants.

There are indications that Sweden and Swedish players can take an active role in contributing to the field as well as reaping its returns. Exactly how the field and its associated industries will evolve is highly uncertain and this goes for the timeframe of clinical applications as well as viable business models.

The aim of this study is to understand the Swedish position in an international comparison with that of some of the leading nations globally: two European countries, Germany and the UK; one Asian player, Japan; and the US (where interviews were focused in one state, California). The countries in focus have despite their difference in size, been chosen since they stand for a major part of the scientific and industrial development of the field. Players in these countries to a large extent form the TERM development and it is also with individual players in these countries Swedish research environments and companies are likely to compete and collaborate. Another aim is to identify what initiatives could stimulate knowledge creation and innovation processes leading to new therapies and products beneficial to patients and which might also ultimately contribute to economic growth in Sweden. The analysis in the report is based on a number of complementary sources including literature studies, interviews, mapping of academic and industrial players, bibliometric data as well as a mapping of public initiatives.

The scientific knowledge base for tissue engineering and regenerative medicine applications can be described as a multidisciplinary combination of materials science, fundamental biological sciences and pre-clinical and clinical medicine. Tissue engineering includes the development of therapeutic solutions based on a combination of a) scaffolds based on biomaterials, b) cells and tissue and c) biomolecules. It still very much remains to be seen how the industry developing tissue engineered products and services will mature but the field will affect for instance the pharmaceutical, orthopaedic and dental industries. In the five countries

selected for an in-depth analysis, 303 companies were identified, of which 73 firms are developing organ-specific, tissue-engineered products. The bulk of the companies (230 firms) are found in for instance the pharmaceutical industry focusing on drug discovery and development by using stem cells or are firms that develop drugs to be used in regenerative medicine (e.g. growth factors). A number of companies are developing tools for use specifically in TERM applications (e.g. for handling of stem cells) and there are biomaterial companies focusing on TERM applications.

USA has the most companies in all categories of organ-specific, tissue-engineered products in the international comparison of the five focus countries. The relative strength is especially pronounced in neurological and pancreas, kidney and liver applications. Germany has a strong position in skin, cartilage, bone and urological applications. Concerning cardiovascular applications only the USA and Germany have firms with products in clinical trials. The Japanese firm population is primarily found in fields like skin, cartilage, bone and urological applications and cardiovascular applications and UK firms in skin, cartilage, bone and urological applications. It is possible that our method for firm identification has underestimated the UK firm population leading to few firms developing organ specific tissue-engineered products being identified. The mapping has been most rigorously performed for Germany, Japan, California (US) and Sweden.

Companies in the area of biocompatible materials may in the future find that TERM products and services will compete with their established products and they may also enter the TERM field themselves. Few examples of mature biocompatible material implant companies moving in this direction have however been identified in the present analysis. While such products are not included in the definition of TERM, there has been a mapping of the relevant Swedish firms (but not in other countries), in order to relate the current Swedish strengths in this field to the potentials of TERM. The Swedish mapping thus also includes biomaterial firms not involved in TERM R&D. Almost 15 companies are developing stable biomaterial products, SMEs as well as large firms. There are also about five established firms and two recent start-up companies developing biodegradable biomaterials. As regards tools for cell handling there are three Swedish firms, two of which originate from the in vitro fertilisation field. Concerning pharmaceutical applications related to TERM, there are three small start-up companies and some of them show promising development, although no commercial success yet. Two small start-up companies are developing tissue-engineered products. Thus, to sum up the characteristics of the Swedish firm population, apart from the commercial strength in biomaterials there are eight companies in total and these are generally small, often academic spin-offs, and have a variety of TERM-related applications.

While the overall market for future TERM products is judged by most analysts to be large, for many companies this is still more vision than reality. In addition to being an emerging field, subject to market and technological risks, the specific challenges for TERM firms to reach the market include public and political acceptance, selection of type of cell source, types of business model and reaping the benefits or handling the drawbacks of a firm's specific location.

Europe has long lacked a synchronised agenda regulating market approval of tissue-engineered products but today a common regulation has been shaped aimed at advanced-therapy medicinal products. It includes products based on genes, cells and tissues and a centralised marketing authorisation procedure giving successful applicants direct access to the entire European market. Accordingly, Europe likely faces a much improved regulatory situation as compared to the previous one, where various countries had developed their own approaches concerning regulation, possibly leading to excessive costs for companies adapting their applications to different markets with dissimilar requirements.

For the TERM area to mature, it is important to have strong regional or national research and innovation environments and for those to be connected to international counterparts. Whilst it was clear that TERM is a prioritised area in the focus countries, they differ in the volume and profile of such investments. There are also variations as to policies and investments in regard to the relative focus on basic versus applied research, attention to inter-disciplinarity and translational research, profile areas, players involved in strategy formulation and implementation and absolute volume of investments.

In contrast to several other countries, even though TERM projects and centres are financed by both public and private organisations through the research and innovation funding system of Sweden, Swedish governmental agencies have not formulated overall strategies and programmes for the TERM area. In the recent research and innovation bill, a total SEK 65 million new investment in stem cell and regenerative medicine research and innovation during 2010-2012 was proposed. This funding will be distributed to universities after a call for proposal and evaluation procedure in 2009.

In order to understand the development of the scientific fields involved and identify important players and their interaction, scientific output in three areas were measured: a) stem cells, b) biomaterials and c) tissue engineering and regenerative medicine. In absolute terms, the US has the top scientific output in terms of publication volume in all studied scientific fields, the second country often being Japan, Germany or the United Kingdom. However, this is not true in relative terms, in other words the publication

volume in relation to population or GDP. Using those measures, the smaller countries like Sweden, Switzerland or the Netherlands often top the ranking depending on the scientific field.

A number of Asian countries such as China, South Korea, Japan and Taiwan show an impressive scientific development. This is the case even though some of them do not have a long history of excellent research in the scientific fields of this study.

Concerning the performance of individual research organisations, it is clear that Harvard University is outstanding in the field of stem cell research. Apart from US organisations, the top universities in stem cell research are located in countries like Japan, Sweden, England, Switzerland, Germany, Singapore, Italy and Canada. In stem cell research relating to neuroscience, the top non-US organisation is the Japanese Kyoto University in third position and the Swedish Karolinska Institutet is the top European organisation. Other prominent Swedish research organisations in stem cell research are Lund University and Gothenburg University. Thus, Sweden has world-class research environments in stem cell research with significant critical mass, as measured by publication volume as well as scientific excellence.

In biomaterials research fields, the US, Japanese, German and Singaporean research environments hold the most prominent positions. The Universities of Toronto, Kyoto, Singapore, Bern, Seoul, Michigan, Bologna and Texas appear in top positions in the statistics depending on biomaterial field. In the narrow field of osseointegration, known to be an area of Swedish strength, Gothenburg University outperforms most other organisations.

There may be top researchers in smaller groups in Sweden in other biomaterial fields. However, no research environment has been identified in any organisation with a sufficiently large critical mass to compete on publication volume with other top organisations.

The analysis indicates that researchers from smaller countries are more prone to international collaboration, especially if compared to researchers from the US. International collaboration is also more common when studying top-ranking journals than in analyses of all SCI-covered journals.

Thus, bibliometric studies indicate some definite Swedish R&D strengths in fields relevant to TERM. Many of the key competence areas involved are– present, at least in part and according to bibliometric data, Sweden has scientific excellence in some of these fields; specifically stem cells and osseointegration. In the stem cell field the top Swedish organisations are Karolinska Institutet, Lund University and Gothenburg University. In the field of Osseointegration, Gothenburg University takes top position in the

world among research organisations. This is measured by publication volume in top life science, medical or material science journals or Science or Nature. The study indicates a relative weakness in other biomaterial fields.

Discussion and suggestions for policymakers

Sweden has a distinctive position and definite strengths in the international development of the field. The present analysis shows strengths in regard to scientific profile and achievements, regulatory stance, and a firm population with some promising activities.

Some countries make impressive investments and achieves striking results in terms of scientific output but also in terms of (the early phases of) product development. In fact, it is clear from the overview of national initiatives that there are a number of countries which consider TERM highly prioritised. The US makes by far the largest investments as regards *input* in TERM-related R&D, which is to be expected considering it is the country with the largest public R&D budget. While other countries may have difficulty matching the US figures in absolute terms, significant and increasing investments are being made. As a consequence of the focus countries being much larger than Sweden they also contribute much larger investments in TERM R&D and have a larger TERM industry. A small country like Sweden is not likely to become a research or industrial leader in the overall area of TERM, but individual players or groups of players can still be leaders in a few subfields. These areas may be those where Sweden already has a strong position and where a critical mass of both research and industrial activities can be gained: According to the bibliometric data, Sweden has scientific excellence in stem cells, especially in the neurological field. In regard to biomaterials, the strengths relate primarily to osseointegration, a much narrower field than that of stem cells. Stem cell research is a growing and prioritised research field globally and the fact that Sweden has some strength in the field is a good foundation for future knowledge creation. Osseointegration is also a growing field according to the analysis but the patterns differ between countries, with some of the top countries having a steep increase and others showing a moderate one.

Research into new materials, bioresorbable materials, soft-tissue responses, biomimetics and scaffolds are areas of importance to the development of TERM. The trend is an increase in scientific output in these fields, especially in some Asian countries. Initiatives for the development of TERM in focus countries include such R&D efforts. However, according to the present bibliometric analysis, Swedish players show a weak performance in fields like matrices and scaffolds, ceramics and biomimetics. This may be due to lack of critical mass for such research environments

meaning that they are not detected in the analyses. Whilst individual eminent professors and groups do constitute important exceptions, research into new materials, bioresorbable materials, soft-tissue responses, biomimetics or scaffolds is generally not internationally leading. The Swedish focus may thus also include strategic areas deemed important for the future development of TERM where Swedish research is not currently as prominent. An additional way to strengthen scientific areas is for researchers to link to international nodes of scientific excellence. The environment however needs to be viewed as an attractive partner in order to accomplish this. By combining scientific world-class excellence in some subareas, with a more 'basic' level of national scientific competence in others, it is possible that Sweden can ground its position within TERM.

So far, Sweden has had no explicit or coherent policy agenda for the TERM area, and no national consensus around specific initiatives. An argument in this report is that a coordinated and strategic effort would likely complement the present funding of projects, centres and cluster development the field is receiving through the Swedish R&D funding system and lead to a more pronounced effect on research and innovation in this field. Coordination between governmental agencies on research and innovation investments and the formation of a working group with a variety of relevant players to formulate and follow up a strategy for this field are processes in other countries from which Swedish policymakers might learn.

The present study highlights the need to move in a more inter-disciplinary direction. This implies that not only is there an issue of handling multiple disciplines (multidisciplinarity), but also the interaction and potential integration between them (inter-disciplinarity). Also, in order for products to be developed, there must be a bridge between the biology and engineering of TERM and the medical aspects of the field. Likewise, there must be a bridge between research and the practical issues clinical practitioners and firms face when developing therapies, products and services in regenerative medicine. Thus, there is a need for a flow and exchange of knowledge between pre-clinical and clinical scientists on the one hand, and between academic scientists and companies on the other. This is also highly prioritised in policy measures initiated in other countries.

The life science industry is often argued to benefit from clustering of activities within a geographical area, such as the agglomeration of research, clinical practice, firms and venture capital firms in for instance California, Massachusetts and Copenhagen/Skåne (Medicon Valley). TERM is commercially still an area in early phase of development and the firm population in Sweden as in other countries, thus constitutes a relatively small part of the life science industry and the firm activities are primarily dispersed in prominent life science regions. On the research side, Swedish

policymakers have taken some steps towards creating critical mass through the establishment of centres of excellence in fields related to TERM. The firm population developing tissue-engineered products or in the TERM-related fields analysed in the present report indicates that Sweden has a versatile and somewhat fragmented pool of commercial competence which bears on TERM development. These firms are primarily found in the three major city regions. The area with a definite commercial strength at present is biomaterial products, not explicitly included within the TERM area but highly related. There is also an 'embryo' of a company population within TERM, with eight companies throughout Sweden. In order to spur the development, Swedish players need to provide good conditions for the existing companies to grow and for the establishment of new ones, and make sure that it is attractive for foreign firms to locate in the country. The question remains as to whether the companies cross-fertilise. The firms have a diversity of applications; many are very small start-up companies focusing on developing their first products/services and are geographically dispersed.

The introduction of therapeutic technologies and treatment based on regenerative medicine has so far been slow in most countries. One challenge is that of regulatory hurdles, another is reimbursement.

If policymakers wish to prioritise TERM and make a focused effort to stimulate a positive development of the field the analysis in this report leads to the following suggestions:

1 Multiplayer strategy development

In a number of countries, TERM strategies have been developed by multiplayer working groups which in some cases have also been involved in monitoring implementation of the strategy. It is likely that such a strategy development process would complement the present funding of projects, centres and cluster development and be beneficial for the development of TERM knowledge and innovations in Sweden. Such a working group could include government agencies, as well as relevant organisations in the R&D financing system, academia and industry.

Importantly, such broad engagement of players is also a way to remove uncertainty and create stability in the field. Interviews indicate that clarity and predictability concerning, for example, regulation and reimbursement issues are crucial to research and innovation processes in firms and academia. Regulation is mainly decided on the European level and it is important that the national strategy includes a thorough agenda based on Swedish players' viewpoints and a strong Swedish engagement.

2 Emphasis on the multidisciplinary and translational challenge

Seamless interaction between scientific disciplines, between science and clinical practice and between academia, the healthcare system and industry has been a problem in most countries engaging in the field. In other countries, one way of handling some of these concerns has been the initiation of centres to stimulate multidisciplinary TERM research, and connect pre-clinical and clinical efforts. Such aspects should be included in the proposed strategy development process and Swedish policymakers may thus learn from experiences in other countries. Issues such as an internationally competitive scale of R&D funding of specific initiatives and the balance between continuity and flexibility in funding for such ventures in a field in early phase of development, also need to be addressed in the strategy development process,.

3 Industry involvement and stimulation of innovation

While much research is performed by academic organisations and clinical practitioners, companies also perform both basic and applied research and take a dominant role in advancing research results into innovations. Their knowledge and experience should thus be involved in the strategy development process. They might also have an operational presence in the centre projects, facilitating commercialisation and promoting mutual learning between academy and industry. When building a successful research and innovation environment, it is also important to consider other issues concerning safeguarding IPR, thoughts on business models, reimbursement issues etc.

4 National networks of research and innovation environments

As part of an attraction and retention policy for the field, building strong research and innovation environments for attraction of investments, human capital, etc. should be included. This may spur growth of established ventures and stimulate indigenous innovations. Thus, public policy must ensure long-term stability of such environments and networks at the same time as a field in early phase of development needs a certain degree of flexibility. Such centres should have a balance between basic and applied research, between disciplinary and multidisciplinary research efforts as well as between pre-clinical and clinical projects. Commercialisation aspects, the involvement of industry and industrial needs should also be components in these centres of excellence; in some cases, perhaps emphasised in the longer-term perspective.

The strategy should formulate ways to build critical mass of activities at a selected number of geographical locations within Sweden functioning as nodes in a national network. There are interesting examples in other

countries, such as Japan and Canada, of how such national networks are promoted. Ways to handle initiatives in a cross national region such as Medicon Valley must also be taken into consideration.

A number of different sources and initiatives may thus come together to support such efforts, including peer reviews based individual research grants, centres-of-excellence and network funding, initiatives for cluster development, promotion of international collaboration and public private partnerships, and initiatives to stimulate commercialisation.

5 Strengthening international links and knowledge flows

A small country like Sweden needs international collaboration in order to link into and gain access to the most recent knowledge developments. The national TERM strategy should address such internationalisation, and consideration should be given to the issue of how to provide a basis (such as updated international mapping and benchmarking) for individual strategy implementation of various environments. The industrial and academic leadership (in, say, each field or region) may build such strategies on current collaborations and networks, new needs emerging, and an understanding of the relevant international nodes.

The present analysis indicates that Swedish players show a relatively weak performance in some field relevant to TERM. The Swedish focus may include such strategic areas deemed important for the future development of TERM. An additional way to strengthen scientific areas is for researchers to link to international nodes of scientific excellence. The environment however needs to be viewed as an attractive partner in order to accomplish this.

1 Background: The promises and challenges of TERM

1.1 The promises of TERM

This report discusses the current state and activities of an emerging and fast moving knowledge field: that of tissue engineering and regenerative medicine, or TERM for short. The concept contains two words: tissue engineering versus regenerative medicine. *Regenerative medicine* deals with the restoration of functions in the human body.[1] Often, it is said that the main aim of this field is to develop biological substitutes that can improve, refurbish or preserve the functioning of tissue. In fact, regenerative medicine aims not only to create tissue but to build entire organs. Importantly, this report includes not only biologically-derived products but also synthetic products which aim to repair or enhance body functions when combined with cellular technologies. Thus, in the report, regenerative medicine is defined as medical treatments - be they biological or synthetic - to enhance, repair or replace cells, tissues and organs using bioengineered materials, cellular technologies and some forms of implants.

Within TERM, the overarching competence field is that of tissue science and engineering – or *tissue engineering* for short (hence TE). This is an "emerging interdisciplinary area comprising different specialties such as medicine, material science, cell biology, genomics and chemical engineering" and applies principles of biology as well as engineering.[2] It represents "a radical new approach to the repair and replacement of damaged or diseased body tissues".[3] Other related competence fields used for regenerative medicine are biomaterials, stem cells, etc.

Many observers have proposed that the potential outcome from the competence fields of TERM for medical uses are vast and include generally improved quality of life, treatments of previously untreatable conditions such as severe burns, reduced cost of treatment for such things as diabetes, heart and liver failure, etc. TERM may also offer possibilities for areas other than the medical ones including detecting chemical or biological threats. Such development of sensors using tissue engineering principles is for example done at the Naval Research Laboratory in the USA, as supported by DARPA (The Defense Advanced Research Projects Agency). As a result, many countries and policy players have seen the possibilities. For example, within EU this field is seen as "an innovative and fast-moving biotechnology sector, which promises to offer a variety of new treatments opportunities".[4]

However, at this stage, such prognoses of the impact are to some extent only speculation and hopes. It is difficult to know what far-reaching results the competence fields will achieve and there are no specifics as to industrial segments. Far from all the currently operating companies have products on the market and many are still small. So far, the products within TERM on the market are mainly tissue products such as skin, cartilage and bone often in combination with biodegradable biomaterials. There are also specialised cells for things like toxicology tests or metabolic analyses within the pharmaceutical industry on the market, plus many other cell biology and biomaterial research tools. A few more complex structured tissues are nearing the market and some are already in clinical practice with permission for clinical trials. Some proponents anticipate that in the very long term perspective, TERM may eventually lead to the *in vitro* construction of human organs.

Clearly, TERM has emerged globally as an area increasingly competing for the overall biotech resources in terms of research funding as well as financial support for commercial purposes. Many nations are focusing on TERM research and it seems most countries with biotech-related research also have some activities within the field. While most industrialised countries seem to have a focused effort in the biotechnological area, some have also explicitly pointed out TERM as a main field of both research and commercialisation. Major players on the international arena include the US, Canada, Germany, the UK, France, Switzerland, Sweden, China, Japan, South Korea, India and Singapore. There are also a number of supporting organisations – such as the Tissue Engineering and Regenerative Medicine International Society (TERMIS) and others – promoting the field in important ways. The significant number of countries investing in the field and the mounting number of research groups and firms involved indicate a strong belief in major potential for the sector and that important outcomes in terms of both products and services and economic impact are likely. The question is, which countries that will take part in reaping the returns from these promises?

1.2 The challenges for an emerging industry

In terms of clinical use and industrial development, TERM is still at a very early stage. As an emerging field, it is subject to all the general uncertainties of evolving competence areas and industries. The assumption in this report is that industrial development is evolutionary in character and characterised by major uncertainty regarding science, technologies, applications, markets and competition.[5] Clearly, there are numerous alternative developments for each player – and for the knowledge field or industry as a whole. It is an experimental and evolutionary process, on the global and national level as

well as on the regional one. This means there is no way to predict which path will be selected. Instead, the path is partly dependent on each actor's competencies and history and thus dependent on the collected competencies and history of the players involved. In addition, the networks – those within a region or nation as well as those extending beyond it - entail spill-over and feedback loops between these players. At the same time, the paths are affected by the specific set of institutions in place; the laws, regulations and practices directing the players.

The uncertainties include both scientific and technological issues. In fact, in many ways TERM is an area where science is under constant development and there are debates about which scientific approaches will be viable. This could be illustrated by the discourse on the inherent potential of the various types of stem cells, where, for example, adult versus embryonic stem cells have their respective proponents. Such debates are ongoing for many other subareas as well and the scientific choices are many. Accordingly, the expected results of such scientific quests are far from certain.

Likewise, in terms of product development there are many technological pathways. As there are few companies that have tried the various alternatives, the examples that can serve as role models are limited. An example is the problem of how to design the scaled-up production process for cell-based products. This sometimes requires large volumes of cells and firms must choose between labour-intensive shift work, robotised production techniques, or other innovative options.

The uncertainties of an emerging field also largely relate to the market. In the case of TERM, this relates to a plethora of aspects such as who is the customer in terms of age, country, types of deceases, etc., as well as in terms of the purchasing process which differs greatly between countries. Importantly, there are distinct variations between societies regarding opinions on how various diseases and conditions ought to be prioritised, or what should be paid for by the state or the reimbursement system versus what should be handled privately. Examples of this include the extent to which cosmetic applications should be included in the reimbursement system, or opting to put resources into very severe illnesses which only affect a small part of the population or what are arguably 'lifestyle infirmities' such as type II diabetes. Making a market analysis is thus a daunting task for any analyst or firm and companies' choices of first application and market approach may be little more than informed (but nonetheless uncertain) guesswork.

As science and technology stabilises, some product design solutions often gain ground whilst others prove less successful. For some type of industries – especially where the products are assembled from a number of

components – specific 'dominant product designs' emerge over time and get a foothold on the market.[6] It is not a matter of course that such dominant designs will occur on these markets for regenerative medicine. Rather, various niche markets may be expected to coexist for customer groups or different geographical markets and with quite different design solutions. Nevertheless, the lack of specialisation currently forcing firms to develop everything from cultural media to production processes and hampering market growth will most likely be succeeded by more specialised suppliers.

1.3 Swedish possibilities

As described, the field of TERM has the potential to generate new possible treatments for diseases that are currently difficult or impossible to cure. Scientific and technological advances in TERM can lead to market improvements in medical treatments, "either by providing better outcomes than can be achieved with currently available techniques or by making available treatments for diseases or conditions for which there are no current alternatives".[7] TERM-related products and services may offer new therapies and increased quality of life for an ageing population. However, how the field and its associated industries will evolve is highly uncertain in regard to both timeframe of clinical applications and viable business models.

In the Swedish case, there are indications that the country and its various players can take an active role in forming the field, as well as in reaping the returns from it. Concerning research, there is a track record of successful Swedish players in both public research organisations and companies. For instance, within the stem cell field university groups at Karolinska Institutet in Stockholm, the Sahlgrenska Academy in Gothenburg and Lund Stem Cell Center are at the forefront. Historically, there is also a very strong research as well as industrial base within the adjoining field of biomaterials. Swedish research is outstanding in the field of osseointegration pioneered by Professor Brånemark. Through the mobility of people from this prominent research environment, the biomaterials field - more broadly defined than merely osseointegration and titanium - has developed in other parts of Sweden. Sweden has also been successful on the industrial scene and companies like Nobel Biocare have a significant market share in dental implants as based on osseointegration technology. Many other industrial applications have spun off from the biomaterials competence, including bone-anchored hearing aids developed by Entific Medical Systems (now part of Australian Cochlear Inc.) and orthopaedic devices. Concerning biodegradable implants there is also Artimplant AB, which offers products using a synthetic biomaterial for the treatment of osteoarthritis in hands and feet, shoulder and other soft tissue injuries as well as dental applications. This stronghold of biomaterials is intimately connected with the evolving

TERM area both in terms of knowledge intersection, similar or related applications and overlap in terms of research groups and companies moving between the fields. Moreover, TERM represents both an area of competition and a potential venue for diversification of these research groups, firms and industries. Thus, companies currently only involved in biomaterials applications can chose to see the TERM field as a competitive threat, or move into the area by such means as combining their products with stem cells and/or growth factors. The research and industrial stronghold in osseointegration and to some extent biomaterials in general is one of the foundations of Swedish possibilities within TERM.

Firms started with a competence in stem cells in Sweden include Cellartis and NeuroNova. Cellartis develops stem cell technologies and is focused on human embryonic stem (hES) cells for drug discovery, toxicity testing and regenerative medicine with a main objective of developing hepatocytes and cardiomyocytes from these cells. As another example, NeuroNova is a biopharmaceutical company developing therapeutic neurogenesis for the treatment of currently incurable neurodegenerative diseases.

There are thus activities on the industrial side in both newer firms and established ones. Thus, in this uncertain market phase, firms are already being set up or redeployed for commercial development of the some of the knowledge, intellectual property and know-how created within Sweden.

These research and industrial achievements may pave the way for future success. There are also examples of knowledge areas and intellectual property developed in Sweden but commercialised elsewhere. While global knowledge flows are both good and unavoidable, policymakers have to consider how to increase the likelihood that returns will also be reaped in Sweden. In a knowledge-based economy, it is therefore crucial to identify sectors in which a sustainable national competence base and industry of economic importance can be built. The TERM area may have some elements of such a national specialisation as there are already a number of strengths in the Swedish innovation system, as highlighted in this report. There are a number of challenges at hand, if Sweden is to draw on international advances within TERM and provide its citizens with the best health services possible. One challenge is how the Swedish government and other players can ensure its citizens access to the innovative treatments TERM may offer. Another question is how a small country like Sweden can take part in and contribute to the international scientific development in this interdisciplinary field, and how Sweden, with its rather limited firm population, may become an important player on the international arena of developing, producing and diffusing TERM-based products and services.

1.4 Aim and content of the report

This report aims to assess the position and opportunities for Sweden within the field of TERM. Swedish competences and resources as well as the global picture have been analysed. This report assumes that any analysis of potential strategic technology areas needs to start from an international assessment of the development potential and the various potential paths of the field and its related industries and relate such evolution to the specific national innovation systems in place. This is of course accented in a field such as TERM where long-term science-based processes dominate and regulatory decisions create inertia as well as country-specific opportunities, whilst customer demands and rapid changes are taking place in healthcare products and practices. The promise of this field has also led to a number of policy initiatives to stimulate knowledge creation and innovation processes in different countries. Information on initiatives being launched in other countries indicates the expectations that are put on this field and also what measures have been deemed relevant to support a positive development.

Thus, this study aims to understand the Swedish position in an international comparison and identify what initiatives could stimulate knowledge creation and innovation processes. These should lead to new therapies and products that benefit patients and ultimately contribute to economic growth in Sweden. To analyse this, the study was focused on some of the leading nations globally: two European countries, Germany and the UK; one Asian player, Japan; and the US (with interviews performed in California. Without diminishing the efforts made in other countries, these countries and regions were chosen as a focus for the analysis as previous reports have shown that important activity is taking place in these locations.

The analysis in the report is based on a number of complementary sources. Firstly, to form a general definition and understanding of the dynamics at hand, the analysis is built on the knowledge of the authors and interviewed experts in the scientific and industrial field.[8] Secondly, a large number of books, reports, articles and journal papers have been scrutinised, some of which have been specially noted in the list of references. Thirdly, in a case-study approach, detailed interviews with various types of players have been conducted – research, technology transfer offices, small firms, large companies, venture capital companies, policymakers, experts - in the five focus countries. A total of 58 interviews were conducted. Fourthly, a new and unique database of firms has been developed, including all companies identified globally, but paying special attention to get full coverage in the five focus countries. These firms are classified according to, say, type of cells used, type of application and phase of development. Fifthly, a catalogue of national initiatives, scientific environments and individual researchers working in the TERM area has been developed. This directory

does not aim to give full coverage to the whole dynamic area, but merely to illustrate the volume of investments and activities. Finally, through a bibliometric analysis, the report gives an estimate of the scientific output from such research environments.

The report is structured as follows: Section 2 presents and specifies the knowledge areas and applications. Based on this, an overview of the set of firms identified in the five focus countries – Germany, the UK, Japan, the US and Sweden – is laid out. Section 3 highlights the issues involved in moving the innovative technologies into products for a market. After this, the regulatory issues and solutions in the same countries/regions will be discussed (section 4). Section 5 introduces policy initiatives in Germany, the UK, Japan, US and Sweden, as well as the overall volume and situation of academic and institutional research in four of the five countries. For the US no such detailed analysis is presented, but instead the specific situation for stem cell research in California is highlighted. Thereafter the scientific output from the major research environments is analysed (Section 6). Finally, the main findings are summarised and recommendations are given for the Swedish context.[9]

2 Knowledge areas, applications and firms

The knowledge area of TERM and the products and services it may result in will most probably play a decisive role in a range of industries – pharmaceutical, orthopaedic, dental industry etc. The knowledge area may also give rise to new industries, which do not easily fit current industry definitions. TERM-related products may also be influential in various parts of the value chain - e.g. through development of materials, therapeutics, diagnostics, tools, or specialised services.

This chapter, gives the reader an overview of the population of firms active in the TERM field, with a particular emphasis on firms in the selected focus countries, the US, the UK, Germany, Japan and Sweden. Moreover, the knowledge areas are presented, as well as the applications and the active firms within each sub-area.

As often is the case, especially with emerging scientific areas and technologies, there are no clear boundaries to the field known here as TERM, or between this field and other connected areas. Rather, TERM can be seen as including a number of knowledge areas. The scientific knowledge base for tissue engineering and regenerative medicine applications can be described as a multidisciplinary combination of materials science, fundamental biological sciences and developmental biology as well as pre-clinical and clinical medicine. While these scientific knowledge areas are broad and include much more than TERM-related knowledge, the interest here is in the intersection and combination of these fields.

Firstly, the knowledge field of tissue engineering, including a) scaffolds based on various biomaterials, b) cells and tissue and c) biomolecules will be described. Various groups of applications such as artificial skin or other organ specific applications currently under development are then described and an overview is presented of the number of firms working on the various types of tissue-engineered products.

Secondly, a group of applications related to drug discovery and development will be discussed. These include the use of growth factors to stimulate regeneration, new stem cell-based platforms for drug discovery and drug delivery with the aid of biomaterials.

Thirdly, the various types of development tools required for TERM will be highlighted: complementary products, measurement and monitoring tools

and indicators, clinical testing as well as novel production technologies, manufacturing techniques and equipment.

Finally, biocompatible materials is an important field in and of itself as a constituent of such things as orthopaedic or dental implants. In the light of the Swedish stronghold within biomaterials, the way this field may evolve over time is discussed.

2.1 The firm population

Even though TERM is a young and emerging field, much industrial activity has already been undertaken, with product launches and firm growth in its wake. The prime movers were mainly North American firms chiefly located on the East coast (Massachusetts) or in California. Even though the US has a lead, there is currently also a lot of industrial activity in Europe and Asia. According to other studies, globally, 73 tissue engineering firms (as defined more narrowly) were identified in 2001 and 89 in 2002.[10] In Europe, the firm activity has rapidly expanded and while there were only 15 European companies in 2001, this figure had increased to 113 in 2003. In 2003, Germany and the UK were the leading European countries with 39 and 18 firms respectively, followed by France and Sweden, which each had 10.[11] In Europe, SMEs clearly dominated the sector: 91 companies out of all the TERM companies were SMEs. Concerning the industrial sectors, one study showed that 71% of all companies were biotech, 21% medical device and 8% belonged to the pharmaceutical sector.[12] A similar same systematic mapping of commercialisation in Asian countries has not been identified, but it is known that from a situation where TERM was a rather limited area, significant growth is now underway in the sector, mainly in terms of research but also as regards commercialisation. In fact, a study of Japan conducted in 2004 identified only seven active firms,[13] while the mapping reveals at least 33 firms in Japan in 2007 engaging in the TERM area. All in all, a noteworthy global augmentation of firm activity is presently taking place.

To substantiate this, the mapping as presented in this report shows there are currently at least 500 firms globally operating within the field of TERM. As full coverage was not intended, it is important to note that the global population may actually be larger. From this global overview, five specific focus countries were chosen for an in depth analysis – the US, the UK, Germany, Japan and Sweden. The coverage in these countries is more complete even though the dynamics of the industries and diversification of established life science companies into this field render a total population count most challenging. Of the 500 firms identified globally, 303 are located in the five focus countries.[14] [15]

The bulk of the companies (230 firms) are found in incumbent industries that are now becoming intimately connected to regenerative medicine. Importantly, any specific company may be found in more than one category but the general patterns are as follows: Firstly, within the pharmaceutical industry there are firms focusing on drug discovery and development by using stem cells (27 firms). There are also those firms that develop drugs (e.g. growth factors) to be used in regenerative medicine (27 firms). Secondly, a number of companies are developing tools for use specifically in TERM applications (94 firms). Thirdly, there are biomaterials companies focusing on TERM applications. The database has 148 such firms, including those with proven activities within TERM. There are also a few Swedish firms with the potential to play an important role on the Swedish arena, but which have not yet diversified into the TERM field. The coverage of this latter group of biomaterials companies is thus neither complete, nor are all the firms to be definitely included within the TERM definition.

Table 2.1 Number of companies identified in Sweden, Japan, the United Kingdom, Germany and the US as examples in fields related to TERM [a b]

Drug discovery and development using stem cells	27
Drug discovery and development for TERM purposes (e.g. growth factors)	27
Tools companies (products specific to TERM applications)	94
Biomaterials for TERM	148

Source: Database of TERM-related firms in five focus countries

[a] *The number of companies is approximate since some companies, as subsidiaries of a group, are not counted if they are involved in the same category of activity as the parent company.*
[b] *The listing is unlikely to be complete as this group of companies was not the primary target of the study.*

There are also companies developing organ-specific, tissue-engineered products combining stem cells with biomaterials. These may be seen as the primary target for the mapping exercise in this report.[16] Thus, 73 firms developing organ-specific tissue-engineered products have been identified (see Table 2.2) and as of 2007 are likely to be fairly well covered in the five countries for this application group.

Table 2.2 The number of companies developing organ specific tissue-engineered products in each focus country

Germany	UK	Japan	USA	Sweden	Total in the five focus countries
15	5	13	37	3	73

Source: Database of TERM-related firms in five focus countries.

It is obvious in the data that the dynamics in this scientific field and industry is extensive. The figures shown in the text and tables in this report must

therefore be taken as approximation of the actual number of companies and are an indication of the volume of business activities regarding the specified applications. Firstly, there is intense startup activity taking place, especially in the US and UK. Likewise there is much volatility among the firms. In fact, many of the companies listed in the Appendix may not be around anymore due to name changes, mergers and acquisitions or simply going out of business. The most difficult country in which to identify all relevant companies is the US, mainly due to the magnitude of companies there and the above dynamics. Secondly, the activities of the larger, more established companies with many business segments is not easy to discern and it is quite likely that additional companies are active in the field. In fact, whilst large and public companies are involved in TERM, many have core activities in other areas and some may be cautious about giving early signals of their intended product development in what is a new business segment for them.

2.2 The knowledge field of tissue engineering

Within TERM, the overarching competence field is that of tissue science and engineering – or *tissue engineering* for short (abbreviated to TE). The exact description of the field varies, but common definitions are "the application of principles and methods of engineering and the life sciences towards the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve functions",[17] or "the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules".[18] Another commonly used definition is that of the pioneering US Professors Langer and Vacanti, who define tissue engineering as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function".[19] These definitions place TE close to the areas of transplantation and cell therapy, where throughout "several decades, the ability to replace or regenerate damaged, diseased or otherwise compromised tissue or organs, or to replace or augment their function, has rested either with the use of totally synthetic medical devices or with the techniques of organ transplantation".[20] However, a characteristic of human TE is that the engineered products become integrated within the patient, which distinguishes TE from traditional therapies and promises advances in medical technology through the its application. In fact, whilst early definitions are focused on materials science and synthetic biomaterials, more recent advances place more emphasis on cell biology. Today, systems biology is a key competence component underlying this knowledge area.

Within tissue engineering, the "principles are based on the utilisation of three primary components, namely the biomaterial (whether biological or synthetic), the cell and the biomolecules".[21] Thus, it involves the creation of a 3D structure resembling, or even equivalent to, the human body's own tissue. Here, *biocompatible materials* are crucial to build the structure in itself (the *scaffold*) and to organise the growth and differentiation of the *cells* onto that structure. The *cells* used can be the patient's own, or come from a donor. Likewise, tissue can be grown outside the patient and subsequently be transplanted, or it can be grown in situ within the patient. Thus, transplants of cells and tissue are an integral part of TE. While xeno-transplants are excluded from the field in some definitions, they are included in this report. *Biomolecules* include growth, differentiation and angiogenic factors as well as bone morphogenic proteins.

2.2.1 Scaffolds

To create a tissue-engineered product cultured cells or tissue are combined with some form of artificial three-dimensional structure known as a *scaffold* or matrix. Biocompatible materials (often known as biomaterials) are the crucial building blocks for such scaffolds of tissue-engineered products. Biomaterials such as hydrogels, collagen matrices, alginate and lactic acid sheets and matrices are used as carriers, supporting two or three dimensional structures and acting as barriers in these tissue-engineered products.

The structure is used to introduce structure and bear load and should allow for diffusion of cell nutrients or biochemical factors. It will be in place until the implanted cells have multiplied and formed endogenous tissue and a 'natural' endogenous scaffold, in other words the extracellular matrix (ECM). Importantly, each specific type of tissue has a specialised ECM, regulating the function of the tissue. The ECM consists of proteoglycans, hyaluronic acid and structural proteins such as collagen and provides structure for the cells, controls intercellular communication and acts as a depository for growth factors. Current research confirms that the ECM may have functions exceeding that of creating a structure for cells and is also crucial to the signalling system involved. Expansion of this research has been prioritised by several countries and research initiatives, including the MATES strategy in the US.[22]

To avoid the inserted scaffold needing to be removed, it should be biodegradable and there seems to be a delicate balance between the rate of degradation and the tissue formation process. Research groups and firms have experimented with a multitude of materials, both those used for other purposes and those specifically engineered for the purpose at hand. Materials commonly used are collagen, fibrin, hyaluronic acid, polysaccharidic materials, polylactic acid (PLA), polycaprolactone (PCL),

or polyglycolic acid (PGA). Three characteristics are especially important when choosing the material suitable for the scaffold. Firstly, the cell seeding efficiency should be high; this is aided by the pore design and a cell-adhesive surface. Secondly, the degradation mechanism should be suitable in terms of speed and waste products. Thirdly, the matrix needs to function in terms of compatibility with the cells and tissue and not cause any rejection, infection reactions or large scars.

One of the larger problems with a scaffold is the formation of fibrotic tissue. Another major obstacle in engineering tissue thicker than a couple of millimetres is that cells implanted in the scaffold do not survive. Hence, differentiated stem cells or autologous cells in porous scaffolds of larger thickness die upon implantation. The current focus in overcoming this obstacle is therefore on angiogenesis (the growth of new blood vessels) and blood supply.

As an alternative to seeding cells into scaffolding or carrier materials and to overcome the problems with such things as fibrosis, what are known as *cell-sheets* have been developed by for instance groups at Tokyo Women's Medical University and the University Hospital in Zurich. The idea is to reconstruct tissue from entire sheets of cells instead of single cells. One technique is to use culture dishes where temperature-responsive polymers let various cells grow. Cells can then be produced non-invasively as intact sheets simply by reducing the temperature. By the layering of such sheets, one may produce tissue constructs in vitro, or transplant the sheets into the host tissue.[23]

Moreover, as the structure of *hydrogels* is comparable to that of the ECM of various types of tissues, they can be a good type of scaffold material. Recently, the use of micro-engineered hydrogels has been highlighted due to their prospect of overcoming problems in creating vascularised tissues and complex structures. With the prospect of engineering the hydrogel form in detail, it is possible to address micro-vascularisation.[24] Also, by injecting biomaterials which thus create a type of scaffold in situ, problems with unpleasant surgery and cell adhesion are mitigated. The apparent benefit of such a procedure is that one does not have to prefabricate a custom-made scaffold; it will adopt the shape of a tissue defect.

In addition to the choice of material for the scaffold, research groups and firms are involved with various approaches to the production of scaffolds. In essence, the need for complex scaffolds puts the emphasis on new manufacturing processes that may need adjusted regulatory procedures. Thus, careful selection of appropriate manufacturing methods is essential. For example, to increase shape control, CAD/CAM approaches combined with 3-D printing may provide a solution. A different way is to create

textile-like meshes useful for tissue in-growth. Another approach is the 'casting' of the matrix in a mould, but this has the drawback of limited thickness and risk of contamination by the solvents used in the production process. To bypass the solvent problem, gas can be used in the mould to create the porous structure but this introduces problems for heat-sensitive materials. Other approaches include freeze-drying techniques, or liquid-liquid phase separation.

2.2.2 Cells and tissue

As discussed in relation to scaffold, *cells* are key components in the development of TERM products, where cell biology and genetics combined with informatics help explain how cells respond to different stimuli. Understanding of the process by which cells organise into tissue and organs could thereby be enhanced. Thus, cells can be characterised and screened in much less time than previously. In most countries, high-quality, well-integrated research into cell and developmental biology is seen as a crucial success factor for the future of TERM. In fact, the overall US strategy for the TERM area stresses as one of four prioritised goals the need to further understand cell responses and their ability to form various types of tissue.[25] Also, in Japan and the UK for example, there have been substantial efforts in the areas of development biology.

As will be apparent in the discussion of technological choices and business models, the type of cell sets the framework not only for what type of application can be pursued, but also for the regulatory process and market approach. It is therefore important for the reader to distinguish between various cell types and their inherent characteristics.

A common way to classify cells is according to their original source. The cells being used may come from their *own species* or from *other species*, the latter termed *xenogenic* cells. For example, in the development of cardiovascular implants there have been attempts to use cells from various animals. Taking cells from one type of species and implanting them in another raises various safety issues. These include transfer of viruses, unsolved scientific problems of rejection by the body which is currently being addressed by such fields as genetic modification, but also ethical concerns are in focus. The crossing of species borders also poses specific regulatory concerns.

Also, the cell source may be autologous (same individual), allogenic (another individual) or isogenic (cloned). Perhaps the most direct mode is to collect cells from the same individual into which they will be implanted. Such cells are called *autologous* cells and have safety benefits in terms of lower risk of transmission of cancer or other diseases. They also display the

fewest cases of rejection. Such safety characteristics entail a rather direct regulatory path in most countries, often implying a faster and more predictable route to the market. Also, in some countries products where the patient's own cells are used may raise fewer ethical concerns. However, there are a number of market-related problems with autologous cells. One is that the culturing and re-implantation process takes time. Autologous procedures can therefore hardly be used when there is need for immediate treatment in any large quantity; at least not with today's culturing procedures. Also, safety problems may be introduced in the production phase and viability is hard to establish due to difficulties in large clinical trials. In addition, there are patient-related dilemmas in that cell extraction may cause superfluous pain and risk of infection to the patient and that such cells cannot be used when the patient has, say, a genetic disease needing new skin to repair severe burns or ulcers, or other difficulties in submitting a large enough quantity of cells for culturing and re-implantation. Perhaps most importantly for firm choices these products are (currently) not developed for mass markets so they may be less economically interesting.

The other alternative to autologous cells is *allogenic* cells, i.e. cells from a donor (of the same species).[26] This approach is successfully used in the development of, say, artificial skin products, where rejection problems have been under control. However, donor cells may lead to immunology response, cell culturing and legal problems. There are also ethical concerns in some countries regarding passing cells between individuals.

Another distinguishing factor for cells is their *degree of differentiation*, where cells may be fully differentiated (e.g. liver cells or blood cells), undifferentiated (stem cells), or at any stage in between. A stem cell can be defined by its ability to replicate numerous times (by cell division) and that it can differentiate into new types of cells. This latter characteristic is called the potency of the cell, telling us about the cells potential to differentiate into various types of cells. In principle, only the fertilised egg and the cells resulting from the cell divisions following closely after have the full ability to form any type of cell (being totipotent). The cells resulting from cell division from a totipotent cell are pluripotent and can differentiate into the cell types of the three primary tissue layers. This means that with the correct kind of stimuli, over 200 types of cells can be formed from the pluripotent cell. In an adult individual, there are also multipotent (or somatic) stem cells,[27] i.e. cells which, in addition to creating more cells of the same type, can also produce cells with higher differentiation. Multipotent cells can be differentiated into related cells only; in other words, multipotent cells related to blood can only differentiate into other blood-related cells (e.g. white or red blood cells, platelets). Some specific adult stem cells found in, say, umbilical cord blood seem to be pluripotent and may open the way for

harvesting highly potent stem cells without running into the ethical issues related to embryonic cells. In fact, the use of adult stem cells has been in practice for many years in bone marrow transplants in the treatment of diseases like leukaemia and is thus not controversial by nature. Finally, there are unipotent stem cells and while these are undifferentiated, they can only differentiate into one specific type of cell.

2.2.3 Biomolecules

As is obvious from the above definitions of tissue engineering, biomolecules are a crucial ingredient. These biomolecules enhance and control proliferation and are often necessary to integrate the biomaterial with cells and tissue. Such biomolecules include such things as growth factors, differentiation factors, angiogenic factors, as well as bone morphogenic proteins.

Growth factors and differentiation factors are protein-based molecules that kindle cell growth. What they do is to control the speed of cell production and their differentiation. While some growth factors act on several types of cells, many are specifically prone to work for a certain type of cell. This means that some types of growth factors are needed to stimulate the differentiation of blood vessels, whilst others stimulate, say, bone cells. In fact, bone morphogenic proteins are specific types of growth factors that help bone and cartilage to form. Closely related is the process of angiogenesis, the process by which new blood vessels are formed. There is currently a long list of angiogenic factors - growth factors that stimulate angiogenesis - as well as a substantial number of angiogenesis inhibitors.

There is now a multitude, at least 100 or more, growth factors under intense research within the TERM community. For example, in Germany a substantial share of the research effort within TERM is directed towards studying growth factors and their role in tissue engineering. Researchers believe that clues about cell signalling may be a key to spurring the field of TERM and also one way to understand the mechanisms of cancer. Also, as was obvious above, one main issue in TERM is to control the path of cell differentiation and thus researchers are vividly at work to understand what cocktail of factors may yield various outcomes.

2.3 Tissue-engineered applications

Tissue-engineered products are only starting to appear on the market. Some applications aim to be a substitute for structures within the body and a development can be seen here of products such as bone grafts, artificial skin, designed corneas and lenses, ligaments, nerve regeneration and cartilage regeneration. These have generally been the first therapeutic

products on the market. Another set of applications are those aimed at substituting or repairing metabolic functions, including artificial blood, liver-assisting devices, cardiovascular products, pancreatic islet cells, etc. In general, it seems these products take longer to developThe regulatory approval process for such products is currently more complex, and few products are close to market introduction. There are still many scientific challenges to make the dream of tissue-engineered organs come true. Perhaps one of the largest is how to solve vascularisation problems. In the following sections, each of the identified product groups is briefly described.

It is important to note that in the analysis, each company may be found under more than one group of applications since a company may pursue development of a number of products in different application areas. Please note also that, in the tables, the listing of whether the product is in pre-clinical or clinical development or on the market is based on the product which has come the furthest in development in its specific application area.

2.3.1 Skin, cartilage, bone and urological applications

Due to their inherent similarities and because these companies often work on products for more than one of these application areas, firms with applications relating to skin, cartilage bone and urology are grouped together in this analysis. For example, a company using autologous cells to culture epidermal sheets for the treatment of severe burns may also be developing a way to grow cells to replace or repair the urinary bladder or culture cartilage mixed with a collagen gel and shape it into a three-dimensional form to treat damaged cartilage. Also, some companies used decellularised donor skin as bandages to treat severe burns or as a scaffold. In the five focus countries, a total of 32 companies have been identified as active in any of these application areas: 11 in the US, nine in Germany, five in the UK and Japan respectively and two in Sweden (see Table 2.3). Out of the 31 companies, half (15 firms) pursue other tissue engineering applications, mostly related to skin/cartilage/bone/urological, but also a few other applications.

Table 2.3 Number of firms with a focus on skin, cartilage, bone or urological applications and their phase of development

	Total	Pre-clinical	Clinical	Product
Germany	9	1	2	6
UK	5	0	2	3
Japan	5	2	3	0
USA	11	5	3	3
Sweden	2	0	0	2
Total	**32**	**8**	**10**	**14**

Source: Database of TERM-related firms in five focus countries.

Skin has been transplanted since 1889. What has changed is that instead of scraping off skin from one part of the body and transplanting it to another part of the same patient, skin cells are now grown in cell culture media before being returned to the patient. They may be sprayed on or cultured on a matrix which may be biodegradable. Cartilage and bone applications use the same type of techniques, usually combining autologous cells with biomaterials as scaffolds for the cells to proliferate on, but sometimes just using biomaterials as carriers of cells for implantation.

Within this group of skin/cartilage/bone/urological applications are some of the first tissue-engineered products being commercialised or used in clinical practice. Interestingly, none of the firms use embryonic stem cells to develop products for skin, cartilage and/or bone applications. Rather, all but five primarily focus on the use of adult autologous stem cells. For two companies, no information regarding their intended source of cells has been found and three companies use allogenic cells from donors.

As regards origin, the companies seem to have originated from a core competence in either biomaterials or cell biology with about the same number of companies in each category. The companies in Japan and Germany are more likely to have entered the field with a core competence from the biomaterial side than the cell biology side of tissue engineering. For example, Olympus Biomaterials in Japan started as a biomaterials company and moved into the tissue engineering field by collaborating with academic research groups with a stem cell focus. They now plan to manufacture and supply tissue-engineered bones to medical institutes. They manufacture tissue-engineered bones by culturing mesenchymal stem cells extracted from the patient's bone marrow into bone cells on a material based on β-tricalcium phosphate.

In Sweden, Karocell Tissue Engineering started as a company involved in skin banking and also developed a method of removing all cells from donated skin to obtain the extracellular matrix used as bandages. Artecel Sciences in the US is focused on autologous applications in cosmetic

surgery and hematopoietic support. The company also supplies cell banking of adipose tissue. Genzyme is also active in developing and manufacturing autologous cell therapy products such as cultured epidermal autografts and cartilage cells for use in the repair of symptomatic cartilage defects. In Germany, there are a number of companies with skin, cartilage or bone products in clinical use, e.g. Ars Arthro with a 3D mechanically stable transplant based on patient-specific autologous cartilage cells and a collagen matrix and BioTissue with five products to treat skin, oral mucosa, bone and cartilage defects in clinical use. Organogenesis claims it is the only company marketing a commercially available bi-layered bio-engineered cell therapy.

2.3.2 Cardiovascular applications

In the five countries, there are a total of 19 companies with a focus on tissue engineering applications in the cardiovascular area: eight in the US, six in Japan, three in Germany and one in the UK. There are several types of cardiovascular applications. Firstly, it includes the creation of artificial blood vessels. Secondly, stem cells from different sources (often bone marrow cells) are used for myocardial regeneration as a therapy to regenerate infarcted, scarred or non-functioning myocardial tissue into a functioning muscle. Thirdly, another application is to exploit cultured cells to repair or regenerate cardiac valves. One may also use xeno-transplantation (only the use of porcine tissue has been identified) to replace damaged valves.

Table 2.4 Number of firms with a focus on cardiovascular applications and their phase of development

	Total	Pre-clinical	Clinical	Product
Germany	3	1	2	0
UK	1	1	0	0
Japan	6	6	0	0
USA	8	6	2	0
Sweden	0	0	0	0
Total	**19**	**15**	**4**	**0**

Source: Database of TERM-related firms in five focus countries.

The development of tissue-engineered products in the cardiovascular field has not progressed as far as applications for skin, cartilage, bone or urological products. Most products under development are still in the preclinical phase, a few have entered clinical stages and there is no tissue-engineered product on the market. The companies developing tissue-engineered products for cardiovascular applications all seem to have started with a core competence in cell biology. Today, none of the companies are developing products using embryonic stem cells, but rather adult ones.

Most are academic start-ups, although a few large companies broadening their portfolio into this field have also been identified. In fact, in terms of product diversity, some of the companies developing artificial blood vessels are also developing products for skin or cartilage applications and two companies are also developing cell therapies for liver applications.

The US company Genzyme can serve as an example of how tissue engineering is used to repair heart tissue. Genzyme is conducting cell therapy research in novel treatments for heart disease and is exploring the use of adult stem cells in treating a variety of diseases. Its largest cell therapy development effort is the ongoing Phase 2 MAGIC trial (Myoblast Autologous Graft in Ischemic Cardiomyopathy), designed to determine whether cell therapy can be used to reverse damage done to cardiac muscle following a heart attack, or to safely halt a patient's further progression of heart failure. Investigators in the MAGIC trial harvest a patient's own skeletal myoblast cells (autologous) prior to bypass surgery through a small biopsy in the leg. These cells are multiplied in the laboratory over approximately 21 days using a proprietary cell-culture technique. The investigators then inject the cells into the damaged region of a patient's heart during a coronary artery bypass operation. The MAGIC trial builds upon the work of Professor Philippe Menasché (HEGP, Paris, France). Professor Menasché was the first (in 2000) to conduct an autologous intramyocardial graft of skeletal myoblast. His Phase I study of 10 patients demonstrated the feasibility of autologous skeletal myoblast transplantation in severe ischemic heart failure. This multi-centre Phase II clinical trial was designed to assess the safety and efficacy of two doses of autologous skeletal myoblasts, as compared to placebo, in the treatment of ischemic heart failure. The MAGIC trial is conducted in Europe, including centres in Belgium, Denmark, France, Germany, Italy and the UK, with partial funding from Assistance Publique - Hôpitaux de Paris in France.

Another example of heart repair is the Japanese company, Cell Seed Inc. that is developing a regenerative cardiac patch. This requires a patient's own myoblast cells to be cultured in a specially treated cell culture dish creating a viable, beating myocytes cell sheet. This cultured cell-sheet is harvested intact and stacked to the other cell-sheets to achieve a multiple-layered cell-sheet, the "cardiac patch". This "cardiac patch" is a spontaneously pulsatile, contractile cardiomyocyte replacement. Transplanted to damaged parts of the patient's heart, these pulsatile sheets synchronise with the beating heart to provide added cardiac contractile capability.

2.3.3 Neurological applications

The companies with a focus on neurological applications all have their core competence in cell biology and stem cell research. The vast majority of the

companies seem to have emanated from a core competence in cell biology. Thus the focus of their research is on stem cell technologies. In the five countries, a total of 10 companies with a focus on the neurological field have been identified: seven in the US, two in Japan and one in the UK and none in Sweden.

One type of application is stem cell therapies for nerve regeneration and six such companies have been identified. One example of stem cell therapy under development is the use of retinal pigment epithelial cells or dendritic cells for neural regeneration. An example of a therapy under development is the use of epithelial cells. The cells produce dopamine and patients with Parkinson's disease are helped by increased levels of dopamine in the brain. In the treatment, epithelial cells are placed on microcarriers and injected into the brain to provide a continuous localised source of dopamine in brain regions deficient in dopamine for the treatment of Parkinson's disease. One of the companies is the Institute of Gene and Brain Science (GBS) - a venture company supported by the Keio University School of Medicine in Japan – focusing on the amplification of immanent neural stem cell for neurogenesis, which the company claims to have confirmed in spinal cord injured animals.[28]

Table 2.5 Number of firms with a focus on neurological applications and their phase of development

	Total	Pre-clinical	Clinical	Product
Germany	0	0	0	0
UK	1	1	0	0
Japan	2	2	0	0
USA	7	5	1	0
Sweden	0	0	0	0
Total	**10**	**8**	**1**	**0**

Source: Database of TERM-related firms in five focus countries.

None of the companies has a product on the market but one, StemCells, Inc., is in a clinical research phase. The clinical trial is a stem cell therapy to treat a rare neurodegenerative disease, neuronal ceroid lipofuscinosis, using neural stem cells which have been isolated from the human foetal brain, purified and expanded. The disease leads to neuronal cell loss primarily in the brain and affects infants and young children. Also, ReNeuron Group plc in the UK is claiming to be close to clinical trials with a neural stem cell line as a potential stem cell transplantation treatment for stroke. The companies in this category are most often involved in developing stem cell therapies and the primary focus of their R&D is the method for purifying and expanding the cells and then delivering them to patients. A few of these companies are also pursuing other applications, such as stem cell therapies for the cardiovascular, liver and pancreas fields.

2.3.4 Pancreas, liver and kidney applications

Common to the applications for pancreas, liver and kidney is that they are complex three-dimensional inner organs. Moreover, all parts of the organ need to be close to blood vessels for the transportation back and forth of nutrients, oxygen and biomolecules. Companies in this field are aiming to treat patients such as those with a risk of acute liver failure or renal disease and diabetes.

A total of 20 companies in this field have been identified in the five focus countries. Of these companies, 15 are from the US, three are German and one each are Japanese and Swedish; seven of the 20 companies have products in clinical trials.

Table 2.6 Number of firms with a focus on pancreas, liver or kidney applications and their phase of development

	Total	Pre-clinical	Clinical	Product
Germany	3	2	1	0
UK	0	0	0	0
Japan	1	1	0	0
USA	15	9	6	0
Sweden	1	1	0	0
Total	**20**	**13**	**7**	**0**

Source: Database of TERM-related firms in five focus countries.

There is some academic research into constructing three-dimensional tissue (organs) and challenges include the supply and transport of biomolecules as well as the appropriate scaffold design. No firms involved in such endeavours have been identified in the present study. Therefore, as an alternative to building organs, cells may be delivered which produce vital biomolecules. This may be done by designing and transplanting semi-permeable bags in which the cells are deposited, thereby maintaining their function and activity. The required biomolecules can then pass through the membrane at the same time as the risk of immune response or migrating cells is reduced. Firms are more active in this area.

For instance, there has been experimentation in the development of pancreatic applications for many years now. An interesting current example is the Japanese company, Stem Cell Sciences KK which is the only Japanese firm identified in this study as dealing with this application. It is involved in research and development regarding the isolation and purification of pancreatic beta cells. The company also works on precursor and stem cells, based on the specific cell surface markers, to derive insulin-producing pancreatic beta cells from the stem cells. Also, the US company Islet Medical develops thin-sheet bio-artificial pancreas for the treatment of insulin-dependent diabetics, with a sheet surface made of highly purified

and biostable alginate. The patented thin-sheet immunobarrier system is expected to permit transplantation of islets from organ donors without immune suppression drugs by protecting the islets from host rejection, while enabling nutrients such as oxygen and glucose to migrate freely in and out, and allowing insulin produced by the islets to migrate freely out through the immunobarrier. The cells in the islet sheet would respond to changing blood sugar levels with the release of insulin in real time, mimicking the normal function of pancreatic islets. This product is in pre-clinical development.

Regarding applications for the liver, the German company Cytonet AG is an interesting example. The first product it developed was a process for the preparation of primary liver cells from donor organs. The treatment of patients with acute liver failure has already been successful in three cases in which cell transplants were withdrawn from donor livers. Approximately three billion cells were applied into the abdomen. The direct application of the liver cells into the liver through the portal vein is currently being investigated in animal experiments. Cytonet intends to develop a second product for the treatment of severe liver diseases on the basis of liver cell transplants derived from autologous stem cells.

An example of a kidney-related application is the Swedish company Gambro which in 2005 entered a three-year collaboration agreement with the US/German firm Nephrogen LLC to explore the therapeutic potential of adult stem cells collected from blood in restoring kidney function on the indication of acute renal failure. In 2007, the product was still in pre-clinical development. Gambro has now decided not to pursue it anymore and is thus leaving the field of stem cell and tissue engineering.

Almost all of the companies in these fields of application are developing treatments using adult cells, either autologous or allogenic. Most of the companies are academic spin-offs but there are also examples of large mature companies entering this field. Three of the companies are also pursuing applications in other fields including neurological and cardiovascular applications.

2.3.5 Ophthalmic applications

Corneal tissue comprises three layers: epithelium, stroma and endothelium. All of these may have deficiencies, but only epithelium is regenerative at present. Therefore, clinical application of regenerative living cornea is limited to such epithelial pathologies as alkaline injury, impoverished cornea and Stevens-Johnson syndrome. To address such deficiency, the cornea of a patient's non-affected eye can be collected, cultured and grown. Cultured cornea cells are then harvested and transplanted to the patient. If both eyes are diseased and unsuitable for cell donation, an autologous oral

mucous membrane will essentially achieve the same results. This corneal regeneration methodology is still under clinical development.

In this field, only three companies have been identified. Japanese Cell Seed Inc. has an autologous cultured cornea sheet in early clinical trials. Another company in this field is UK CellTran. Also, US ReNeuron is involved in research into stem cell treatment for retinal disease. ReNeuron is also pursuing applications in the neurological field and Cell seed Inc. is looking into cardiovascular applications. The companies aim to use adult cells in their products.

2.3.6 Dental applications

Tissue engineering solutions with stem cells and biodegradable materials can be used for dental applications. Only three companies involved in tissue engineering or regenerative medicine applications in the dental field have been identified within the five focus countries. The companies are Japanese ArBlast, UK Odontis and the US-based Artecel Sciences, all with projects in preclinical trials. For example, ArBlast uses autologous cells from bone marrow, in combination with a collagen matrix, for dental cavities. Odontis is developing a biological replacement tooth product. The clinical application of Odontis' technology will be the culture and implantation of human stem cells to form living, replacement teeth in the patient. According to the company it will still be several years before initial clinical trials in humans. Artecel is the a provider of adipose-derived stem cell banking services but also develops therapeutic products made from adipose-derived stem cell for orthopaedic and dental applications. All three companies aim to use adult cells.

2.3.7 The Swedish position in TE applications

In total, there were three Swedish tissue engineering companies in 2007. As regards the applications relating to skin, cartilage, bone and urology there are two Swedish firms active, Karocell Tissue Engineering and Cell Matrix. Cell Matrix focuses on cartilage cell therapy and the business areas of Karocell Tissue Engineering includes skin and cell banking, expansion of different types of cells such as keratinocytes, melanocytes, fibroblasts, chondrocytes and urothelial cells for autologous applications. Both Karocell Tissue engineering and Cell Matrix have products on the market for research and clinical practice but still they jointly have fewer than five employees and very modest economic returns. This indicates that even though the most mature fields of tissue engineering have products on the market, it is still an industry in its infancy.

In the application area of pancreas, liver and kidney there was one Swedish company active: The large and well established firm Gambro with over

1,000 employees in Sweden. Their product for restoration of kidney function was in pre-clinical development and the company has decided not to pursue R&D within this field.

There are no Swedish firms within cardiovascular or ophthalmic applications and no firms planning to move in this direction have been found. Similarly, there is no Swedish company working on dental applications using tissue engineering In fact, there are only three companies worldwide in this application area.

With only these three companies, the Swedish position when it comes to tissue engineering applications is by no means impressive since two of these companies are very small. These companies are thus unable to serve as engines for the Swedish development, at least for now. Moreover, the third and only large company is no longer pursuing tissue engineering activities.

2.4 Drug discovery as related to TERM

There are at least three ways in which the knowledge base as described above – pertaining to biomaterials and scaffolds, cells and tissue as well as biomolecules – influences the pharmaceutical industry in terms of drug discovery and development. Firstly, the tissue-engineered products may substitute current pharmaceutical treatments. An illustrative example may be the efforts to develop an artificial pancreas to come to terms with the growing problem of diabetes. If successful, a new way to treat diabetes by way of an artificial organ will definitely mean major changes for the pharmaceutical companies as such, as well as for the healthcare sector. This type of company is included in the tissue engineering discussion in section 2.3.

Secondly, growth factors are not only used to enhance proliferation within an ‘artificial organ’, but can also be a crucial means way of stimulating regeneration, by way of a drug. A group of companies involved in developing drugs that affect the regeneration of different types of tissue by means of various growth factors has been identified. These are firms with a core competence in cell biology investigating ways to steer cell differentiation and proliferation. In this study, not all drug discovery and drug development companies in the five focus countries have been reviewed to see if they are involved in applications related to TERM. However, some such companies have been identified.

In fact, quite a few companies have been found which were originally started with the aim of developing cell therapeutic treatments for regenerative medicine purposes but which have now switched focus to drug discovery in order to achieve regeneration. Many of these companies are

developing growth factors. As examples (and not saying anything about the total number of firms of this type in each country), a total of 27 such companies have been analysed in the present study.[29]

Companies developing pharmaceuticals based on growth factors include Cell Concepts, Euroderm, Osteogenetics and Epiontis in Germany, Kaken Pharmaceutical in Japan, Biosurface Engineering in the US as well as Tristem Coorporation in the UK. For example, the Swedish company NeuroNova uses its platform to identify, test and develop substances that stimulate neurogenesis. NeuroNova has two projects scheduled to enter phase I/II clinical trials in 2008. Similarly, the Japanese Institute of Gene and Brain Science (GBS) is developing a growth factor for neural stem cells. German company, Biopharm GmbH is developing a growth and differentiation factor particularly for bone, cartilage and nerve tissue and Osteogenetics Inc. (Germany) and ProStrakan (UK) are focusing on bone morphogenetic proteins responsible for embryonic bone development. AngioGenetics is a Swedish drug discovery companies developing therapeutics to steer cell proliferation within the cardiovascular field. It focuses on drug discovery, development and commercialisation of novel angiogenesis modulating drugs for the treatment of cancer, ischemic heart disease and eye diseases.

Thirdly, another group of firms is developing technology platforms for drug discovery based on the use of stem cells. These use such specialised cells for drug discovery or, perhaps toxicity or metabolic analyses of drug candidates in pre-clinical development. Thus, the applications being pursued are not therapeutic but have the function of 'development tools' in the drug discovery or development process.

As illustrative examples, 27 such companies have been analysed.[30] [31] An example is the US company Novocell which uses human embryonic stem cells and has discovered a cell surface molecule believed to be part of a signalling pathway driving pluripotency. This molecule is also expressed in many primary tumours including breast, colorectal, prostate and ovarian tumours and thus the company is focusing on using it as a target for drug development. Stem cells can also be used for studies of metabolism. One example of a company in that field is the recent spin-off from the University of Wisconsin-Madison – Stemina Biomarker Discovery. Its approach is to offer a 'diagnostic kit' to pharmaceutical companies as well as lab environments concerning its drug candidates, with the potential to reduce development cost for drugs. Other companies using stem cell technologies for drug discovery or development purposes include ReNeuron (UK), Cellartis (Sweden) and Raven Biotechnologies (USA).

Other companies employ stem cell technologies for example in toxicology testing of drug candidates. In fact, toxicology tests can be used as a substitute for animal models and the new products or services thereby come in as a complement to, or a competing solution to, existing products. The potential of the new types of solutions lies in the possibility of quickening development, as well as in its cost efficiency. Moreover, the option to reduce the use of animal trials is naturally highly beneficial.

One company using stem cell technologies is the Swedish/British company Cellartis using human embryonic stem cells (hESC) for drug discovery, toxicity testing and regenerative medicine with the main objective of developing hepatocytes and cardiomyocytes from these cells. The company has developed over 30 well documented cell lines and has recently entered into a collaborative research agreement with Pfizer to develop a screening system for detection of human toxicity. Cellartis received an up-front fee as well as research funding from Pfizer. In addition, Cellartis retains the right to sublicense, manufacture, use and sell the developmental toxicity screening model. Other companies in this field include the German company Axiogenesis and Japan's Effector Cell Institute, Inc.

In summary, there are three Swedish TERM related companies in drug discovery and development: NeuroNova (26 employees); Angiogenetics (1 employee) and Cellartis (35 employees). Of the 27 such companies in the five focus countries developing drugs, two have TERM-related drugs on the market whereas six are in clinical trials. At least one of the two Swedish companies is presently about to enter clinical trials and one has in recent years signed an agreement with a large pharmaceutical company, signalling attractive project development on the international arena. Out of the 27 drug discovery and development platform companies there is one Swedish player (Cellartis). This a small university spin-off company with activities in Sweden and Scotland.

2.5 Development tools and services for TERM

Clearly, in order for the various applications to evolve, a number of ‘development tools’ are needed. This is due to the need to measure new types of indicators and, say, gauge quality as well as appraising safety and speeding up the process of analysis. Importantly, it is also due to the unsolved issues of how to scale-up lab products to a marketable volume. A wide range of enabling technologies may underlie the progress made in creating these various types of tools, indicating that TERM is dependent on an array of competencies.

These tools can have different characteristics. Firstly, there may be need for *complementary products*, such as cell culture media, technologies and

appliances for growth, differentiation, selection and purification of cells. In these areas biomaterials may be an important technological base. For example, hydrogels have been found valuable for *cell culturing*. The company MeBiol Inc (Japan) uses its synthetic hydrogel as a cell and tissue culture reagent for embryonic stem cells, chondrocytes and cancer cells. 3DM Inc. in Massachusetts (USA) develops hydrogels for cell culture purposes.

Secondly, *measurement and monitoring* tools and indicators have to be constructed or adjusted from other related uses. One example is the need to measure the state or quality of cells by the use of biomarkers. Various molecules can be utilised to give information on the standing of the cultured cells and their stage of differentiation.

Thirdly, to meet the strict requirements for *clinical tests* in order to prove safety and efficacy, firms need to design methods and indicators (as discussed above) for such analysis, as well as designing the study outlines including recruitment of test populations.

Fourth, firms and research groups alike often must design new *production technologies*, manufacturing techniques and equipment. This may include the various types of manufacturing techniques for scaffolds as discussed above, techniques to proliferate cells using bioreactors or other ways to speed up and scale up production, as well as methods to store and preserve cells and tissue. In particular, a key issue is how to scale up production from a laboratory setting to full-scale, volume manufacturing. In this process various 'test beds' are essential. These test such things as whether quality parameters remain stable and in alignment with GMP standards.

There is undoubtedly a growing need for specialised development tools and services for TERM. This is an area where the borders between the firm, institute and university-based research groups become blurred as several research groups work on providing various types of tools and test beds. Also, as this market grows so does the number of firms following such business logic. In fact, several companies that initially aimed for therapeutic development are now focusing on the niche of tools, thereby addressing a more direct market need and products earlier in the value chain.

One company focusing on the growing market of development tools is UK-based ReInnervate. As a spin-off from Durham University, it develops biomarkers for indication of phase and quality of cell differentiation. By employing proteomic technologies, it can identify biomarkers specifically suitable for various types of tissue development. While these products are not yet on the market, the company's business concept is licensing both the technology and the specific biomarkers. The company also develops a cell

culture device for the study of in vitro cell differentiation. Interestingly, ReInnervate explicitly states that in the long run they may move into therapeutic development. The market for biomarkers as a development tool seems to be rapidly growing.

BD Biosciences in the US is another tools company, developing such products as tools for cell analysis, for example flow cytometry systems where cells tagged with fluorescents pass through a laser point and can thereby be characterised and sorted. Using this fast method, a larger population of cells can be analysed.

In the Swedish arena, there are several interesting examples or firms as well as research institutes and university research groups providing development tools and services for TERM. A new initiative from a university-based setting is the centre of excellence BIOMATCELL - Center of Biomaterials and Cell Therapy - with funding for 10 years from VINNOVA and support from regional players such as universities, institutes, life-science firms and venture capital companies. The Centre is intended to develop new materials for implants and prostheses individually adapted to patients so as to speed up the healing process. New methods to evaluate the performance of these materials before and after being implanted will also be developed. Knowledge concerning biomaterials and stem cell technology will thus be combined in the R&D efforts of the centre.

Among the Swedish companies in this field is Cellartis which, as mentioned, is using human embryonic stem (hES) cells for drug discovery, toxicity testing and regenerative medicine with the main objective of developing hepatocytes and cardiomyocytes from these cells. The company has entered R&D collaboration with Swedish Vitrolife regarding R&D on cell culture media, Swemed Lab International AB for the development and marketing of cell culture tools and with GE Healthcare for cell separation media.

2.6 Biomaterials companies related to TERM

As was described in the discussion on tissue engineering above, biocompatible materials are an integral part of that field. Additionally, the field of biocompatible materials is naturally important in its own right. They are integral in various forms of implants, be they orthopaedic or dental. What is of importance in relation to TERM is that the competence area of biomaterials – as it is traditionally understood in terms of biocompability of materials for implants – is increasingly intertwined with the competence areas of cell biology and tissue engineering. According to interviews, several researchers and company representatives expect that the traditional biomaterials-related industries such as orthopaedics and dental implants will

change as a result of recent discoveries and products pertaining to tissue engineering.

Among the products developed by the 148 analysed biomaterials companies are biocements and bone-anchored metals with dental, orthopaedic, craniofacial and spinal applications, as well as hearing aids. Other biomaterial products include porcine heart valves, metal pacemakers and plastic stents and catheters. Biomaterials such as hydrogels and collagen are used for cosmetic dermatology as dermal fillers and collagen and synthetic polymers are used to replace or restore cartilage and tendons. Biomaterial companies also develop products for coating medical devices to make them more biocompatible, often for temporary insertion into the body.

Today, the majority of the biomaterials applications or companies do not have any clear connection to the TERM area, although there may potentially be great promise in such interrelation. There are however some exceptions where knowledge of cells is integrated with that of biomaterials.

Firstly, biomaterials are used in scaffolds for tissue engineering and a number of firms are focusing on such development. In addition, a related type of application is as carriers of cells in cell-therapeutic applications. Here the tendency appears to be for cell biology firms to use an existing biomaterial (for example a polymer) for their specific cell-therapeutic needs. There may also be biomaterials firms dedicated to developing new materials or modifying existing ones to carry or package cells when delivering them into the body in cell-therapeutic products. These categories of firms are analysed in section 2.3.

Secondly, biomaterials can be carriers of drugs. Injectable hydrogel materials have been developed for use within drug delivery.[32] Some examples of companies using hydrogels for drug delivery purposes include BioArtificial Gel Technologies in Canada, Controlled Therapeutics in Scotland and Hydromer in the US.

Thus, regenerative medicine may increasingly be defined to include the wide array of applications, with blurred borders between implant products and ‘artificial organs’. This is particularly important in the context of a Swedish analysis. In fact, Sweden has long assumed a stronghold within the biomaterials field and it is important to understand how this position will affect and be affected by the tissue engineering area.

2.7 Swedish firms

The analysis shows that Sweden has a number of established companies in tissue engineering, drug discovery using stem cells, drug discovery to stimulate regeneration of cells as well as tools for tissue engineering and

tools using stem cells for drug discovery and development. Apart from these companies, Sweden also hosts companies developing products in other fields related to TERM and the results are summarised in the table below (firms developing biomaterial products are not included but are listed in the Appendix).

Table 2.7. Activities of identified Swedish companies *

Area	No. companies
Tissue engineering (combination of cells and biomaterials and possibly growth factors)	3
Cell therapies	2
Drug discovery using stem cells	2
Tools for using stem cells for drug development	1
Tools for cell handling	3
Drug discovery and development to control regeneration of cells	2
Total number of companies in the above mentioned areas	**8**

Source: Database of TERM-related firms in five focus countries

** Companies developing biomaterial products, wound healing solutions and tools for transplantations (e.g. tissue typing) and surgery are not included*

The table illustrates that Sweden apart from having a few companies actually developing tissue-engineered products, also has a number of companies involved in developing products in fields related to tissue engineering.

In Sweden, about 20 firms developing biomaterial products have also been identified. These include companies such as Q-Med, which for instance uses modified hyaluronic acid as dermal filler; Artimplant, with its degradable implants that regenerate body functions for treatment of osteoarthritis in hands and feet, shoulder and other soft tissue injuries as well as dental applications; Nobel Biocare and AstraTech with bone-anchored titanium alloy dental implants and Cochlear Bone Anchored Solutions AB (formerly Entific Medical Systems) with bone-anchored hearing aids; Bone Support which develops bone cement products etc. Thus, the commercial knowledge base in relevant areas is substantial.

One area for biomaterial products with a major commercial market is the dental field. To solve dental deficiencies, the industry for dental applications is currently dominated by the use of stable implants and cavity repair materials, using materials like e.g. titanium alloys, ceramics and bio-cements. This is of particular interest in regard to Sweden as Nobel Biocare, a pioneer and market leader in the field, is Swedish. While there are many firms active in the field, the international market for titanium implants is dominated by a few players, Swedish Nobel Biocare and Swiss Straumann

being the largest. According to data from Nobel Biocare, the total dental implant market is about EUR 1.4 billion which corresponds to about 11% of the total dental products market. Five companies jointly hold over 85% of the total world market. At the same time, in some countries there are many small players focusing on the domestic market, Italy for example.[33]

There are also a number of start-up companies entering TERM-related fields in Sweden. Arterion is a small academic spin-off company (with three employees) which commercialises artificial blood vessels consisting of microbially derived cellulose for revascularisation of patients with cardiovascular disease. Celltrix (two employees) focuses on reconstructive cosmetic surgery and is aiming to launch its first product in 2008. The product is a new type of dermal filler consisting of macroporous microspheres of gelatin.

In summary, Sweden has a definite strength concerning stable biomaterials products, with almost 15 companies, SMEs as well as large firms. There are also some five established firms, mainly SMEs, using biodegradable biomaterials apart from Q-Med which had almost 500 employees in 2007. Two recent start-up companies have entered that particular sub-field. As regards tools for cell handling, there are three Swedish firms, two of which originate from the in vitro fertilisation field. Two companies are developing tissue-engineered products and they are both small start-up companies. Only two firms focus on drug discovery for TERM purposes and one firm develops tools to use stem cells for drug discovery and development. These three firms are small start-up companies and have yet to show commercial success. Thus, to sum up the characteristics of the Swedish firm population, besides the commercial strength in biomaterials there are eight companies in total and these are commonly small, often academic, spin-offs with a wide variety of TERM-related applications.

3 The path to market

As TERM products have the potential to address a number of diseases like diabetes or Parkinson's, many analysts judge the overall market for TERM products to be quite large. While such analysis is at best uncertain, there is general agreement that the field has high growth potential. However, as yet this is more vision than reality for many companies. This chapter explores some of the factors influencing the firm's and product's path to market, starting with an overview in section 3.1 and then dwelling on each of the following aspects: dependence on scientific development, legitimacy and reimbursement, business models and critical mass and clusters.

A likely prerequisite for applications being early adopted in clinical practice is that researchers in a country are part of the development of the field. Research taking place is also a prerequisite for companies to have access to a test bed for developed products and services and leads to patients having access to the latest treatments. To have national research environments involved in the field also gives companies more easy access to such environments for collaboration concerning identifying clinical needs and requirements as well as the development of products and services.

3.1 Market-related hurdles

Only a few of the 'less complex' products relating to skin, cartilage and bone are on the market, as are specialised cells for such things as toxicology tests within the pharmaceutical industry and a number of research and development tools. In fact, only in some applications have the firms ventured as far as clinical trials; most development projects are still in an early phase. Thus tools for R&D, cell banking and to some extent supplying stem cells are among the applications so far most successfully commercialised. Among the tissue-engineered products on the market or in clinical practice are those relating to skin, cartilage and bone. Most other applications such as cardiovascular, neurological, kidney, pancreas etc. are still under development and few products under development have entered clinical trials. This may be due in part to technological hurdles leading to miscalculations, the heavy regulatory burden placed on the firms or uncertainty regarding reimbursement, but may also be due to lack of legitimacy and financing.

Some geographical markets pose more substantial difficulties for firms to reach the market than others. Such difficulties may include cumbersome regulatory requirements, or – as will be discussed in a later chapter –

heterogeneity between the regulatory practices of various countries. Specific country difficulties may also involve ethical concerns among the general public, strongholds of an incumbent industry or a policy that excludes reimbursement. The Japanese market may serve as an example as it is only now moving into a commercial phase with products approaching the customers. As yet, the Japanese tissue engineering companies do not have any products on their home market and no foreign companies have received marketing approval. The Japanese company, J-TEC has been through a lengthy approval process and plans to launch its cultured skin product for burn treatments in mid-2005. J-TEC produces the artificial skin by sampling skin tissue from the patient and culturing it with mouse cells in cow embryo blood plasma to produce transplantable sheets. The company claims it takes three weeks to produce the sheets. Interestingly, J-TEC has opted for an in-house scheme and handles R&D as well as manufacturing and distribution. However, not until August 2007 did the Ministry of Health, Labour and Welfare (MHLW) approve the manufacture and sale of their autologous cultured skin tissue. Awaiting marketing approval from the Pharmaceutical Affairs and Food Sanitation Council in October 2007, J-TEC can still rejoice in being the first company with a TERM product approaching the Japanese market.

In order to understand the firms' situations, this chapter will discuss some of the specific hurdles firms may meet en route to the market, and will build on secondary sources as well as extensive interview material.

Firstly, scientific and technological uncertainties are high within TERM and the path to market is subject to the paths the scientific development takes. This can be illustrated by the situation of stem cells. The emphasis here will be on the specific case of stem cells where the path to market will be designed and based on scientific realities, and on public and political acceptance of these technologies. Such concerns have led to the question of type of cell source being high on the agendas of many countries, leading to differing circumstances for firms located in these countries or regions. Understanding national differences and their implications is of strategic importance, since to some extent the type of cell source guides market opportunities and the specific path to market taken by a firm.

Secondly, political acceptance and receptivity are key issues. While the reasons for a lack of acceptance may differ between different cultural settings, it leads to similar types of constraints in terms of things like lagging reimbursement systems. There seems to be a general understanding that one aspect which will change the scene is when technological uncertainties are removed. For example, it may be that when a proven life-saving therapy is brought out, acceptance will be forthcoming from the general public and from policymakers concerning that particular application.

Until then, firms bear a heavy load of proving the worth of new technologies and products. They must seek out strategies to overcome acceptance problems. However, it is not necessarily the case that such a breakthrough for one application leads to increased acceptance for other applications.

Thirdly, in this early phase much experimentation takes place with different business models; balancing high-potential products with more readily available returns. The choice of business model also involves determining the company's role in the value chain, what competencies to develop in-house and how to solve the need for externally provided development tools, production technologies and equipment. The specific demands of production and distribution also come into the equation.

Fourthly, the path to market is partly guided by the firm's location. This is due to the issues of acceptance, reimbursement, legislation etc., as above, as well as the resource network. Recruitment of speciality skills, access to custom-designed development tools, knowledge of new scientific discoveries, financial potential and possibilities for innovative collaboration may all be dependent on where in the world the firms choose to locate.

3.2 Stem cells and the market path

It is crucial to stress that within TERM, the path to market is still largely dependent on scientific development. This can be illustrated with the situation of stem cells. For example, many products will be intimately dependent on the scientific development of stem cell research and the choices the firm takes in this respect. This is a very vibrant research field with several competing approaches and it shows much promise. There are a number of central milestones in the history of stem cell research – from the groundbreaking findings by Altman and Das in the 1960s about neurogenesis in adults, to discoveries of stem cells in bone marrow, cord blood and primary teeth and the revelation of some of the mechanisms behind cancer. One predominant event was Professor James Thomson and his team at University of Wisconsin-Madison being the first group to derive a human embryonic stem cell line in 1998. Also, Advanced Cell Technology's generation of stem cells by cloning the first human embryo in 2001 by was a major event. Of similar importance have been recently claimed discoveries of new types of stem cells: In 2005 by a group at Kingston University in the UK and in 2007 by Professor Atala in the US. Also in 2007, research on mice proved that embryonic conditions can be attained by using ordinary skin cells. However, despite these impressive results, many scientific issues still remain to be deciphered, including ways

to purify and differentiate stem cells and industrial issues such as how to ensure growth and scale-up from the lab into full-volume production.

A stem cell line is a collection of stem cells cultured from the same source, kept undifferentiated and thereby retaining their ability to differentiate into new types of cells.[34] Much research is underway on creating stable stem cell lines. For example, it is not yet clear if the way to keep stem cells undifferentiated is to give them certain 'signals', or whether the main answer lies in the different types of division processes the cells undergo (symmetric versus asymmetric divisions). The research on embryonic stem cells (i.e. cells derived from an embryo) is conducted either on cells from mice (mES) or from humans (hES) and it is important to point out that the conditions for culturing these two types of cells are quite different. They require different feeders and growth factors. Based on such differences, there is a debate as to what extent experiments on mouse cells truly can be used to increase knowledge concerning products aimed at humans.

The safety issues of rejection, introduction of tumours or other malignant tissue is very important in this debate. Nevertheless, if the high hopes for stem cells prove valid, many inherent safety and ethical issues may be solved. For example, using cells that can be differentiated into other types of cells is one way of handling the problem of a rather tedious process of culturing autologous cells. A future ability to extract autologous cells from fat or bone marrow (mesenchymal stem cells) and differentiate these into another type of cell - perhaps cartilage cells - would provide a way to bypass the safety issues of allogenic cells and yet still have sufficient rapidity of treatment.

Also, the ethical debate surrounding embryonic stem cells (hES) comes from the fact that these are harvested from early-stage human embryos (the blastocyst), roughly four days old when there are approximately 50-150 cells in the inner cell mass. The objection is that the embryo is destroyed in the process and that embryos *could* be created for research purposes. Such concerns are ethically and morally defensible, but may not be consistent with the widespread and, in many societies accepted, use of in vitro fertilisation (IVF) where embryos are created and later discarded. Stem cells are often sourced often from such surplus IVF embryos. The proponents of stem cell research argue in favour of avoiding human suffering by curing diseases and stress the use of embryos created for in vitro fertilisation treatments. However, a solution to this ethical dilemma may be forthcoming, with hES lines possibly produced in the future without damage to the embryo.

Another apprehension is the issue of cloning and that stem cell research possibly may lead to such applications. The production of *new* hES lines is

prohibited in some countries and regions due to those ethical concerns and in other cases research on *existing* cell lines is also deemed unlawful.

Clearly, the issue of cell sources is being considered at national level. For example, the Japanese focus on cells is mirrored by a centre (in Kansai) specifically devoted to supplying national players with cells of various types, stressing the specific Japanese situation where cultural/religious values discourage cell and organ donation as well as xenogeneic therapy. Clearly, the exact choice of cell source is crucial since various types of cells have different characteristics and are suited to different applications. The source used influences the opportunities for, and time to, regulatory approval as well as which markets may be feasible for the final product. There are different regulatory and ethical debates in different countries, for different applications and for different markets. The issue of availability and choice of cells is determined not only by technological factors but also by laws, cultural and ethical views on cell and organ donation. Ultimately, it is determined by the application in focus and involves issues of production, logistics and scale as well as market approval and reimbursement policies.

Approaches to the question of choice of cell source have varied between countries. In the US, restrictive laws have led to national research funding not being focused on embryonic stem cells, while some state funding sources have taken different viewpoints on this matter (for example, California). However, this has not prevented private donations to embryonic stem cell research. Partly in response, but also to some extent as a research avenue in its own right, exploration on the use of adult stem cells has been expanded. There are currently reports that some adult stem cells may actually be pluripotent and that bone marrow stem cells for example have differentiated into cardiac cells. However, many questions remain on where adult stem cells can be found, what gives them plasticity or how various adult stem cells differ from one another. Thus, in practice various research groups and companies have worked on extracting stem cells from a number of different source materials. While embryonic stem cells have only been isolated from the inner cell mass or the blastocyst, embryonic germ cells can be extracted from later-stage foetuses. The problem with embryonic germ cells is their longevity, but on the other hand these cells may be less prone to transferring cancer. Umbilical cords have been used in producing multipotent stem cells and there are several companies focusing on cord blood banks. The manufacture of blood cells derived from bone marrow is well established and research shows this source may also lead to other types of cells.[35] Also, adult stem cells have been isolated from such things as skin, fat and muscles and been used to produce bone, cartilage and other types of tissue.

The type of cell source used will determine many of the market possibilities. Industrial activities include autologous, allogeneic as well as xenogeneic cell sources. Due to issues of cell and tissue transportation, autologous therapies might be thought of as geared to service applications and therefore to regional or national markets rather than international ones. By contrast, products based on allogeneic therapies (based on donated cells) can more readily be produced for mass-markets. However, for safety and ethical reasons the regulatory procedure for allogeneic treatment is complex, time-consuming and rather uncertain. Thus, many companies have chosen a business model based on autologous therapies. In analysing the tissue engineering firms, the figures indicate that German and Japanese firms almost solely focus on autologous therapies (see Table 3.1). Thus, there may be a focus on services and regional markets.

Table 3.1 Number of firms among the 73 TE-companies focusing on autologous and allogeneic therapies

Country	Autologous therapies	Allogeneic therapies	No information
Germany	12	2	1
UK	3	3	0
Sweden	3	0	0
USA	14	22	5
Japan	13	1	0

Source: Database of TERM-related firms in five focus countries.

According to interviews, the focus on autologous applications apart from the lower risk of immunological response is due to the burden of clinical trials being smaller than for allogeneic therapies and customers' preferences for using their own cells. However, interviews also reveal a move towards allogeneic approaches. By contrast, in the US, both types of products are researched and produced. In fact, Table 3.1 reveals that US companies are the ones most prone to pursuing allogenic therapies. This may be due in part to the role models of early companies such as Organogenesis and Advanced Tissue Sciences (now closed), which to some extent both sprang from university research and focused on allogenic approaches to 'artificial skin'.

3.3 Legitimacy and reimbursement

As illustrated for stem cells, a key issue affecting the path to market is what may be called *legitimacy* – or *public acceptance* – and political receptivity. Admittedly, the legitimacy issue differs between different cultural settings and different governments. For instance, in a number of Asian countries such as China and Singapore, stem cell technology receives government funding and the legitimacy seems to be high. This is also true in countries

like Israel. Elsewhere, in the Scandinavia countries for example, official support is strong, but there has been little to back up the words in terms of major investment.[36]

The fact that legitimacy is a major concern in the TERM field can be illustrated by such things as the specific questions relating to the stem cell area, as above. Naturally in the US, there is frustration in the stem cell field that the potential of stem cells for treatment of a wide range of diseases has not been fully explored, largely for political and religious reasons. Amongst the interviewees, there is a consensus that an associated lack of funding has slowed the scientific and technological breakthroughs. Respondents on the US scene also feel that the restrictive funding for embryonic stem cell research has led to a lack of competence-building, especially on the academic arena. Importantly, the perceived government position has also slowed the appeal of the field for large, well-established firms. For example, in large pharmaceutical companies there is little incentive for the strategic senior leadership to invest seriously at this stage of development. Also, a lack of political and public legitimacy has led to there being less appeal for venture capitalists or institutional investors, who see a long road before exit is possible.

What is thought to change the landscape of, say, the stem cell field is evolution of the technology itself. When a therapy becomes available for a disease for which there is no alternative treatment, it will presumably raise serious ethical questions. Political refutation of the technologies or products is then less possible. In the interviews, respondents point out that essentially the same progression will change the landscape for companies, venture capitalists or institutional investors. Thus, companies believe that much of the burden of evidence currently rests with them. They must bring data back from phase I and II trials and demonstrate safety and efficacy. In essence, this means the burden of proof rests with those few companies who can raise enough capital to push a project or two to that point.

This discussion of legitimacy and the burden of evidence as a key factor in the firms' path to market are closely related to the theme of reimbursement. Admittedly, a major problem with the innovative treatments developed within the TERM area is the structure of financial incentives for firms and other players to invest. Firms have no incentive to develop high-cost medical treatments if they are not reimbursed. In fact, many state this as one of the most crucial factors affecting the possible future commercial success of TERM companies. The willingness of insurers to pay for new treatments is essential, especially since the cost of the new treatments is often expected to be higher than traditional ones.

Reimbursement is clearly a problem, as the national health insurance system in most countries has yet to approve wider payment of TERM-based treatments. The fact that reimbursement rules differ between countries is also a considerable obstacle to reaching a large market. In fact, it seems likely that in Europe at least, reimbursement issues will remain within the responsibility of nation states. It is generally thought that companies must show substantial clinical benefits in order to attract wider use of their products. From one point of view, such a system is fair to all parties as patients and taxpayers should be able to trust that there is ample evidence not only of safety and efficacy, but also of efficiency. From another as stated above, the full burden of evidence rests with companies which must produce convincing clinical data. This makes research and product developments in this field a very risky venture.

There are several strategies for companies, as well as venture capitalists and other investors, to tackle the lack of reimbursement. The most obvious is shying away from applications that currently have a functioning treatment and where there are no obvious benefits of an innovative, TERM-based, treatment. Instead, the development efforts could be directed to products for which there is a clear demand, for a large enough patient population. For example, one of the Japanese firms, ArBlast, has one of its focuses on dental applications and addresses the generally poor dental status in Japan where gingivitis is a major problem among the adult population. This company is now developing products for reconstruction of gums and (jaw) bone for these patients. Likewise, one may target markets where there are large segments of wealthy patients that can become key customers. Ethically, there may be considerations for a specific firm or country in relation to strategies where only the needs of the wealthy come into focus.

Another strategy is to actively lobby and build legitimacy for the new solutions. In addition to lobbying policymakers and the public, legitimacy can be attained by such means as close cooperation between firms and leading clinical researchers. In interviews, this is mentioned as a key element in gaining acceptance from both the medical profession and insurers. Acceptance also has to be earned from the general public. Many say it is currently easier to gain acceptance for therapies that save life, but a number of TERM products may not address issues of survival so much as quality of life. Thus, for some products to gain a market, quality of life has to be seen as a value worth paying for in its own right.

3.4 Business model experiments

In this emerging field there is much experimentation with different types of *business models* and speculation about which of these will be successful on

the market. There are a number of strategic issues. Firstly, the choice of business model essentially involves a balance between products with high potential but a long and risky path to market and products that are closer to the market but may not have the same potential in terms of economic returns or breakthrough treatment possibilities. From the interviews, it is clear that many companies go through these types of strategic choices once or twice. A few companies seem to have based their businesses on such an unyielding concept. With a solid set of resources in terms of IP base, human resources and so on, they can finance their quest for a high-risk application with a long path to market. Other firms initially focus on a rather distant, high-return application, but redefine their market and position over time. The reason for this may simply be that their understanding of the market increases and they see their part in the value chain more clearly. Still other companies just run into technological problems, run out of money, come up against regulatory obstacles or other problems and need to go for the easy pickings to sustain themselves. Admittedly, in addition to breaking new technological ground, there are many uncertainties facing TERM companies. For example, the size of the market is often unclear in regard to which customer groups would benefit from the therapy, which markets would approve of the ethical issues, which types of patients would be reimbursed and in what markets. Not infrequently, the market has turned out to be smaller than initially expected. There is also considerable ambiguity as to who is the buyer; the patient, the physician or the hospital, and this often varies across geographical markets.

Naturally, it is true that many companies foresee such business hurdles from the start and choose instead to base their initial operations on consulting or less complex products. This means they can build a solid business model, with the company more or less self-financing and avoiding dependence on venture capitalists for example. It also means that a number of companies are developing regenerative therapies alongside more mundane technologies such as cell culture media and equipment. The interpretation of this is that the business models include alternative ways of generating cashflow should the more high-risk therapeutic products encounter obstacles en route to market.

From a national perspective, this means the firms need all the help they can get in terms of removing uncertainties. In fact, the scientific and technological uncertainties are already a big enough challenge to any firm. Thus, a clear route is needed.

Secondly, the choice of business model is a strategic decision regarding the company's role in a value chain and what competencies should be developed in-house. This also raises the issue of a need for various kinds of development tools and production technologies and equipment. In Japan for

example, specialised equipment is under development by several companies or academic institutes to facilitate multi-sample parallel production under current Good Manufacturing Practice (cGMP) standards. Actually, as most TERM products are still in their infancy, there is a need for many complementary products and services in order to develop them. Such complementary companies are yet to emerge in many locations, leaving the TERM-firms with the need to develop such things as internal methods for scaling up production, suitable cell culture media, etc. This was the case with California-based company Geron Inc. which, due to a lack of knowledgeable process suppliers, had to invest heavily in such things as cell manufacturing techniques whilst going ahead with their own product development. Thus, they had to 'invent every step of the way', which explains their large number of patents pending or issued.

Thirdly, the market path will be highly influenced by the production and distribution matters at hand, with autologous and allogenic products clearly placing quite different demands on the firms. As regards manufacturing, due to the special regulatory requirements which must be fulfilled in order to manufacture products for use in humans, there is still some uncertainty as to where and by whom tissues and cells can be produced. Some experts interviewed foresee the most likely producers to be either companies specialising in tissue engineering or some larger hospitals with appropriate GMP facilities. It may be that material for autologous grafts will be collected at clinics, transferred to cell and tissue processing centres (companies or hospitals) for amplification or modification and subsequently brought back to the clinic for the patient to be treated. Several of the companies have services like this as important parts of current or future business. For allogenic grafts on the other hand, the companies may produce ready-made products based on their in-house material. Also, in terms of distribution an autologous application therefore often requires a presence in the local market, whereas allogenic products generally have more of an off-the-shelf character, allowing more wide-spread distribution.

3.5 The need for critical mass and clusters

In an area like TERM, it is evident that much of the scientific development, innovation processes, regulatory processes, ethical debates, marketing and distribution are international in character. This implies that knowledge and resource flows occur over national and regional borders and policies and strategies need to take the global arena into consideration. However, considering the evidence from a variety of countries and sectors it is also obvious from the literature that globalisation definitely does not mean distance no longer matters.[37] It is not the case that knowledge flows freely over long distances, or that players always connect to the 'best in class',

regardless of location. On the contrary, national, regional and even highly local links and connections seem to be important if knowledge is to be disseminated and shared and learning is to take place. There are those in the scientific literature on clusters that argue the current industrial development is due to the combination of strong national/regional environments, or clusters, and direct global communication pathways between players in them.[38]

Thus, there has been much focus in recent decades on policy measures supporting national and regional development programmes and acknowledging these spatial and dynamic processes. The policy focus on building sustainable clusters is particularly apparent within biomedicine and modern biotechnology.[39] Likewise, industrial players as well as research groups have independently discovered that they learn more and better when connected to a strong cluster or regional innovation system.

It is important to stress the difference between 'co-location' or agglomeration and 'clustering'. There is more to the clustering phenomenon than mere 'co-location' of a variety of actors in the same geographical place. Clustering also includes co-location of related knowledge areas, links between actors, knowledge flows, mobility of people, learning etc. This section analyses the patterns of co-location in the TERM area and in the concluding chapter the issue of clustering receives further attention. The geographic distribution of the 73 tissue engineering companies in the five focus countries was analysed in order to address this question.

Figure 3.1. Geographic distribution of the 73 companies developing tissue-engineered products in the five focus countries

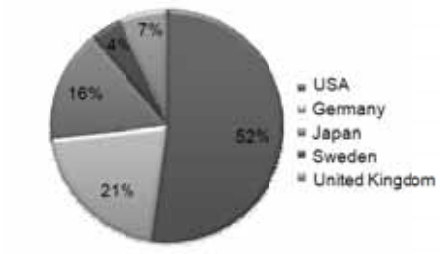
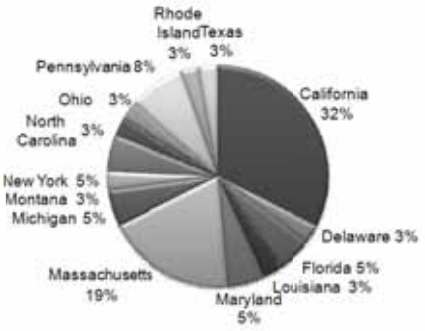


Figure 3.2. Geographic distribution of the 37 companies developing tissue-engineered products in the US[1]



[1] *One California-based company has a branch in Massachusetts but is here placed in CA*

Figure 3.3. Geographic distribution of the 15 companies developing tissue-engineered products in Germany

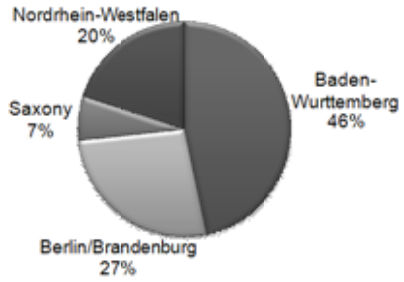


Figure 3.4. Geographic distribution of the 15 companies developing tissue-engineered products in the United Kingdom

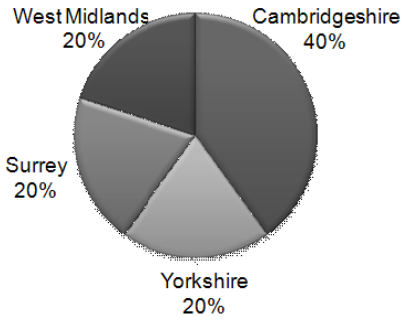


Table 3.2. Geographic distribution of 11 of the 13 companies developing tissue-engineered products in Japan[1]

Japan	**11**
Osaka/Kobe/Kyoto	5
Tokyo [2]	5
Yamaguchi	1

Table 3.3. Geographic distribution of the three companies developing tissue-engineered products in Sweden

Sweden	**3**
Stockholm	1
Gothenburg	1
Lund	1

[1] *Two large Japanese companies with many business areas have not been distributed geographically since it is unclear where in Japan the TE-applications are located*
[2] *Two of the Tokyo companies have branches in Kanagawa and Yokohama respectively*

The analysis illustrates that the tissue engineering firms are located in larger city regions, and in close proximity to universities and other public and private research organisations, clinics, firms, service providers, consultancies, etc. (see figures and tables). In fact, the 37 US companies developing tissue-engineered products are distributed across 14 states with a denser population in California and Massachusetts than the other states. Most are located in proximity to the larger cities and some within dense regions where 'clusters' can be found. In fact, California and Massachusetts are also the location of many other life science companies as well as prominent life science academic centres.

In Sweden, the three companies are found in the three regions with the most life science companies and the largest life science academic centres. In Germany, the densest population is found in Baden-Wurttemberg with seven companies. In United Kingdom, the five companies are evenly distributed across five regions. Japan has five companies in the metropolitan

region of Keihanshin encompassing Kyoto, Osaka and Kobe and five in Tokyo. In general, most companies seem to be located close to prominent academic life science centres where there is also a significant population of other life science companies.

Co-location does not automatically lead to clustering, however. To come into industrial practice the research needs to be interactively linked to everyday clinical realities, something made easier by the co-location of research and healthcare organisations such as university hospitals. Often, the integration may take place on an individual and group level when medical doctors work in 'both worlds'; caring for patients one day and standing in the lab the next. The experiences learned from closeness to patient needs and scientific solutions must be connected to resources and knowhow in business development and industrial dynamics. This has been done in many different ways in different parts of the world, including setting up incubators at universities or firms, inviting venture capitalist competence, etc. Moreover, the process of building viable clusters involves building a skilled work force and a flexible, highly mobile labour market, assuring legitimacy for the cluster with the general public as well as financiers, policymakers and many others.

Accordingly, due to issues such as the regulatory issues discussed above, the location of firms seems highly influential in deciding their path to market. However, it is also related to the available resources and knowledge flows. In fact, there are two especially important issues related to geographical location:

Firstly, there is a question of why firms locate in a specific country, region or city, either as young start-ups or later in their lives. In particular, the US firms point out the benefit of having investor banks and other financiers that are technically trained and well-versed in the specific technologies and industrial settings. Also, interviews show that geographical proximity to universities, research institutes and other science-based companies is of major importance to TERM-related firms, particularly if they are to attract good staff. Scientist like to be located where they can associate with other scientific talents. As regards recruitment, the California-based firm Geron notes that while the talent pool grows each year, five years ago there were precious few people who knew anything about working specifically with embryonic stem cells. As always in biology, a combination of art and science is involved and the staff need a lot of know-how. In the US, this is further challenged by the fact that academic scientists have been unable to get grant funding and have therefore not developed the art of the science. Geron also states that the labour market is highly globalised and that in their case, they have more non-Americans employers in the company than they do Americans. The recruitment path is very much through referrals,

indicating that there is a global *buzz* between players in various settings such as conferences, etc.

In terms of location of subsidiaries, there are naturally a number of specific reasons in each case. Nevertheless, interviews hint that US firms are positioning themselves outside the country due to the attractiveness of sites with high politically receptivity which makes their specific technologies legitimate (perhaps even resulting in grants) and gives them access to scientific talent. For Japanese firms, the possibility of clinical trials is attractive, especially as the national regulatory authorities have been fairly restrictive on this matter for reasons of safety and ethics. Interestingly, some Japanese respondents pointed to the language barrier as a major obstacle to foreign establishment or collaboration.

Secondly, there is the question of what role location has in choice of partners or preference of subsidiary location. Importantly, academic research plays a dominant role in the firm development. In most cases, the industrial development projects actually originated in academic research and most of the companies engaged in the field actively cooperate with academic scientists and medical centres. This is true for most biotech-related areas of course and not specific to the TERM field. However, in some countries, the field may actually be opening up new avenues of labour organisation and collaborative patterns. This is true in Japan, where such a close cooperation between industry and academia is quite different from the way Japanese pharmaceutical companies usually work, where in-house R&D still dominates. By contrast, within TERM many research centres actively pursue cooperation with industry. One such example of academic-industry cooperation is the Division of Tissue Engineering, established in 2001 at University of Tokyo Hospital (Medical School) and supported by donations from seven companies, including chemical, pharmaceutical and tissue engineering firms.[40]

4 Regulation for product market approval in the EU

A number of different types of regulations shape the emerging field of TERM in various ways.[41] These range from market approval to antitrust or pro-competition regulation, environmental and safety regulation, ethical approval, reimbursement and intellectual property rights. As a way to dwell on the types of issues involved, this section will focus on regulatory issues related to clinical trials and market approval in the EU – generally for the TERM area and in some sections specifically for the stem cell one. This is a particularly interesting example as several EU countries have had a lack of clear regulation covering TERM products. This has resulted in a patchwork of different regulations and has made any cross-border activities difficult. Specific examples of the situation in Germany and the UK will be given as well as how the new EU regulations will affect the players.

4.1 The need for harmonised regulation

An increasing number of tissue-engineered products and therapies are under development globally. However, introducing these new types of products onto the market has been a delicate matter due to the lack of clear-cut regulatory practice *in* many countries and harmonised regulation *between* them. Tissue-engineered products are classed as neither medicinal products nor medical devices since they differ from these traditional medicinal products and thus fall outside of existing EU regulation. In fact, these products cannot come under pharmaceutical legislation because they cannot be considered somatic cell therapy. Similarly, they cannot be considered medical devices because they include tissues and cells which are clearly beyond the scope of the relevant directive.

Europe has long been missing a harmonised framework for regulating market approval for tissue-engineered products. Today, such regulations are being shaped. 'Existing' European Community legislation has indeed governed various regulatory aspects for TERM-related products, that is to say those products falling *within* the legislation for pharmaceuticals or medical devices. Areas covered include patenting of biotechnological inventions, the authorisation of pharmaceutical products, the use of genetically modified micro-organisms and marketing of products consisting of, or derived from, GMO. This existing regulatory framework was the result of gradual development over the past 25 years, but with major developments in recent years. However, existing European directives have

not been sufficient as, say, TE products involve complex processes for manufacturing and the requirements of the Directive are not strict enough. Thus, whilst there are a number of regulations that can be partly applied, they rarely match the product entirely.

The objectives for a single, integrated and tailored regulation have been:[42]

- To guarantee a *high level of health protection* for European patients treated with advanced therapies
- To *harmonise market access* for advanced therapies by establishing a tailored and comprehensive regulatory framework for their authorisation, supervision and post-authorisation vigilance
- To *foster the competitiveness* of European undertakings operating in this field
- To *provide overall legal certainty*; whilst allowing for *sufficient flexibility on a technical level*, in order to keep the pace with the evolution of science and technology.

4.2 Shortcomings of the existing regulation

As stated in the previous section, due to the TERM products' similarity to products from other areas whilst still having very distinct characteristics, challenges have arisen concerning the regulation of these products. There is thus a problem of limited applicability of the existing key directives to TERM products.

Firstly, the *Medicinal Product Directive* has been amended and extended several times, but still does not sufficiently cover tissue engineering products. A medicinal product is defined as "any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product".[43] The medicinal product regulation is often referred to as an "old approach", meaning that such directives attempt to pre-define nearly all characteristics of a given product by directly determining technical specifications.[44]

In particular, TE products have a device-like action inside the body and thus cannot be seen within the scope of medicinal products. In fact, most of the pharmaceutical products affect the body on a biochemical level and have a so-called systemic effect, meaning that after their absorption they are transported by the bloodstream to the intended place. Contrary to this, most of the TE products aim to act at the place where they are implanted or applied and thus have no systemic effect. While the medicinal product

regulations cover "biomolecules that are added to stimulate the cellular part of a tissue engineered product to meet the principle intended function", overall it is not designed and does not provide sufficient coverage to meet the characteristics of TERM products.[45]

Secondly, the other alternative was the *Medical Devices Directive* that has been in force since 1995.[46] This defines a medical device as:

> *"any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of:*
> *- Diagnosis, prevention, monitoring, treatment or alleviation of disease,*
> *- Diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,*
> *- Investigation, replacement or modification of the anatomy or a physiological process,*
> *- Control of conception,*
> *And which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means".*[47]

Products regulated under this directive range from breast implants to syringes and pacemakers. However, the Directive excludes cells and tissues of human origin. Instead, these are dealt with in tissue-banking, blood-products and cell banking legislation. The only exception that includes products incorporating human cells and tissues is made when a substance derived from human blood or plasma forms an integral part of the device or when a device utilises human tissue that has been rendered non-viable.[48] As a consequence of this, similar TERM products have been differently regulated in the past in the various member states. This also means there were different safety requirements and patients did not have equal access to TERM products. Thus, Article 5 of the Medical Devices Directive specifically excludes products that incorporate human cells and states that the Directive does not cover "transplants or tissues of human origin or products incorporating nor derived from tissues or cells of human origin".[49] Thus, the matrix or scaffold used for the creation of an artificial extracellular matrix can be classified as a medical device, but when cells are added the product is not covered by the medical device regulation.

Thus, the different characteristics that constitute a TE product (cells, biomaterials, scaffold and biomolecules) are to some extent all covered in the existing regulation. However, none of these regulations takes into

consideration the simultaneous presence and working of the various components, including the interactions that might occur between them. Therefore, the need for a regulation which would cover these aspects has long been expressed.[50] This need was also confirmed in the interviews.

4.3 A centralised authorisation procedure for medicinal products?

Due to the situation of harmonised legislation having long been missing at EU level, a number of country-specific approaches have been taken to the regulation of TERM products. Due to the country-specific approach in Europe, companies have only had access to one geographical market in case of a successful approval; most often their national market. They have needed specific approval to go onto each new market and not infrequently have the different markets had (slightly or very) different requirements. As a result of this varied classification and authorisation of tissue-engineered products across EU member states, cross-border cooperation and marketing has been constrained, as has patients' access to new treatments. There is also the suspicion that this undermines the development of the industry.[51]

Related to the existence of country-specific approaches is the debate as to what extent all parts of a harmonised regulation should be fully in the hands of the EC and to what extent countries should keep some national authority over certain aspects. Another related issue is the most suitable procedure - national or centralised. Since 1995, the European system for authorising medicinal products offers two different procedures, the so-called "centralised" procedure and the "mutual recognition" procedure.[52] The *"centralised procedure"* covers applications made directly to the European Agency for the Evaluation of Medicinal products (EMEA). While this procedure is obligatory for products derived from biotechnology, it is not compulsory for other innovative medicinal products. In practice, the procedure works by a company that intends placing a medicinal product (eligible for the centralised procedure) on the market sending an application directly to the Agency for assessment by the *Committee for Proprietary Medicinal Products* (CPMP). This procedure results in a Commission decision, binding on all EU member states, to authorise the product. Products that are centrally-authorised can be marketed in all member states.[53]

In contrast, the *"mutual recognition" procedure* applies to most of the conventional medicinal products. The application is sent to the member states that the applicant selects and the procedure is managed through mutual recognition of the national marketing authorisations.[54] [55]

In the process of deciding on a legal framework for TE products, many stakeholders have supported one which is partly or entirely based on the centralised authorisation procedure.[56] However, possibilities for the establishment of a simple and effective authorisation procedure are also being considered in order to meet the specific needs of small and local players.[57]

4.4 Regulation of the stem cell area in the EU

In recent years, there has been a growing interest in the use of embryonic stem cells as a universal source of starting material for cell and tissue engineering. It is believed that these progenitor cells can differentiate in vivo, or be differentiated in vitro, into basically any cell type of the human body. The research on human embryonic stem cells is still in its infancy and many pitfalls will probably appear on the way to the clinic and ultimately the patient. As regards regulation of this highly potent but also ethically controversial area, the European Group on Life Sciences (EGLD) has agreed that:[58]

1 The EU should continue to support research with all sources of human stem cells, including human embryonic stem cells.
2 Reproductive cloning should be prohibited.
3 Derivation of human embryonic stem cells from nuclear transplants (so-called therapeutic cloning) has not been achieved and appears to raise considerable difficulties. Research into additional strategies to overcome immune rejection is therefore to be strongly encouraged.
4 Although EGLD respects the special moral status of the human embryo even prior to implantation, it agrees on the use of spare human embryos for the preparation of embryonic stem cell lines. Research on human embryonic stem cells should be carefully regulated, peer reviewed, scientifically sound, directed towards substantial goals and ethically controlled.
5 Publicly and privately funded research should be subject to the same regulations.
6 A European registry of human embryonic stem cell lines should be established.

The opinion of EGLD is also that the current research on human stem cells, be they from differentiated tissue or from embryo, is scientifically sound and medically promising and should be actively developed and supported.

The legal situation for stem cell research is not regulated as such at the national level. Concerning embryonic stem cell (hES) research, one therefore has to refer to the general legislation on embryo research and there is a variety of different situations in the member states. Ireland is the only

country where the right to life of the embryo us equal to that of the mother, whilst some other countries do not have any legislation on embryo research at all. This is the case for Belgium and the Netherlands, but embryo research is nevertheless carried out in these countries. In contrast, in other countries lacking legislation, such as Portugal and Italy, there is no hES research.[59] Some other countries (such as Germany and Austria) have legislation prohibiting any research involving human embryos, whilst France, for example, prohibits embryo research in most cases but allows for some exceptions. Finally, in some instances research is permitted under certain conditions that are clearly specified (Sweden, Finland, the UK and Spain).

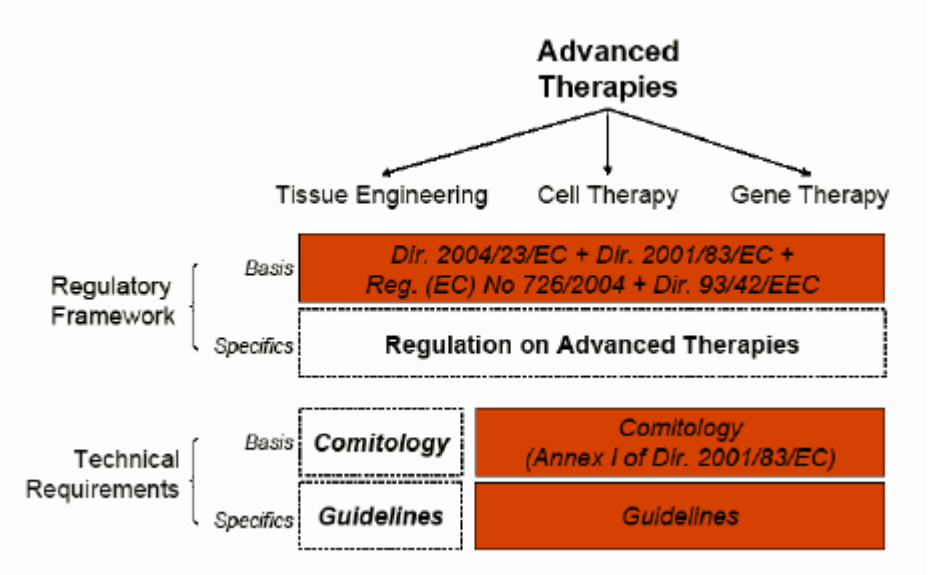
In many countries, the regulatory situation for stem cell research is under development. Some countries are preparing legislation which allows research on stem cells derived from supernumerary embryos, in other words, residual after in vitro fertilisation (the Netherlands for instance), other countries are drafting legislation where creating embryos by nuclear transfer for stem cell research purposes is possible (Belgium, the UK).[60]

Thus, there is currently no coherent Europe-wide legislation in the field and different EU member states have adopted different legislation in this area. Due to the lack of a coherent European-wide legislation for stem cell research, there are currently totally different approaches, attitudes and opinions throughout the different member states, expressing very different views on the subject, ranging from the view that all cloning technologies should be permitted and funded to the opposite view that no cloning technologies should be permitted or funded. Despite the advantages of a common regulatory framework, the question has been raised whether one should actually try and find a common European position or rather allow member states to develop country-specific legislation which corresponds with the demands of their individual cultures.[61]

4.5 The new regulation

Due to the problems described above, the European Commission has been working towards a new regulation for these products in recent years and released a proposal on a European Regulation on Advanced Therapies in November 2005. The efforts of both the European Commission and various European regulatory authorities signalled their belief in these innovative products and the benefits they expect for patients. On 25/4/07, the European Parliament voted on the European Commission's proposal for the *Regulation on advanced therapy medicinal products*. Following the opinion of the European Parliament on 25th April, the Council of Ministers approved the regulation on 31/5/07 and it will come into force from December 2008.

Figure 4.1 Elements of the new regulation



Source: EC (2005: 15). Existing elements are highlighted, elements that had to be developed are in white, dashed boxes.

This new European approach consists of addressing all advanced therapies (gene therapy, somatic cell therapy, tissue engineering) within a single, coherent framework, taking into account their regulatory and technical specifics (see Figure 4.1).[62] Thus, the chosen approach is of "advanced therapies", meaning that all advanced therapies based on genes, cells and tissues are integrated in one framework. Adopting this approach allowed a focus on the crucial regulatory and technical specifics of this emerging industrial sector whilst avoiding an entire re-draft of existing and applicable regulatory options, as in some of the other suggested approaches. Thus, instead of drafting a completely new legal framework for TE products, the European Commission has designed a more global and integrated approach building on existing legislation, as illustrated in the above figure.

Areas kept under the responsibility of the national member states include issues of reimbursement and ethical issues. In particular, for the use of embryonic stem cells, the regulation is neutral and member states are free to make their own choices regarding the use of and research on embryonic stem cells. A key element of the new regulation is the setting up of an interdisciplinary Committee for Advanced Cell Therapies (CAT) under the EMEA.

It is too early to speculate on the effects this new regulation will have on players in the field and further research will be required when the regulation comes into force in 2008. The specific needs of the various stakeholders in the field (which is dominated on the industry side by small or medium-sized firms) have been taken into account by the provision of specific incentives

for them.[63] However, during interviews conducted in 2006 with firms in the field, various concerns were expressed regarding the new regulation. One manager argued that the regulation, *"will dramatically affect the firms in the field, some of them will just fail."* In fact, some voices have expressed concern that the new regulation, *"will assure quality of the products. It is a high quality standard. But this is just a market clearance, not all companies will manage to fulfil the requirements".* Thus, difficulties that will arise from the new regulations relate to a high administrative and research burden which may pose a severe threat to many of the small firms in the field. It remains to be seen whether the challenges will be too high, or whether the positive aspects can balance this.

The new regulations will undoubtedly contribute to the market being more uniform market than previously. Hence, as some respondents add, "*there will be a strong advantage through this now. The different regulations, is a major disadvantage as we have it in Germany at the moment*" and, "*These are tremendous hurdles concerning the current market in Europe… There are for instance language problems … so if we have a European regulation on the legal side and product assurance it will be easier for cross border activities."*

4.6 The German situation

In Germany, tissue-engineered products are classified in principle as a medicinal product and fall under either the Medical Product Law or the Medical Drug Law. Tissue-engineered products are included in the definition of "somatic cell therapies". Thus, there has been no regulation specifically designed to handle TERM products, but rather the existing regulation has served as the general framework. As TERM products and therapies do not always fit perfectly into such existing regulation, TERM products have had to be managed and regulated on a case-by-case basis, yet within the framework of the existing regulations. This means it has been decided which specific law to apply in which product case, be that the Medical Product Law or the Medical Drug Law.

There are also specific rules applicable to some products. For example, the growth of autologous cells for tissue regeneration is currently excluded from a specific approval procedure. On the other hand, growth factors are seen as a biotechnological medical drug, requiring approval.[64]

Thus, the situation in Germany is different than on the EU level, where there was no regulation covering TE products. This difference is now changing with the new regulation on "advanced cell therapies" proposed by the European Commission. In order to avoid disadvantaging firms which produce TERM products, an exception for market approval for these

products has been added until the EU law comes into force (at the beginning of 2008). When the new regulation is in force, German companies will have to conform to the new requirements, the main change being that market approval will be required for TERM products. This includes following good manufacturing practice. For example, stem cell specimens are regarded as medical drugs in Germany. This means that for an organisation to be allowed to prepare and store umbilical cord blood, it has to have a manufacturing license in accordance with the Medical Preparations Act and meet the legal requirements.

Research on embryonic and adult stem cells is carried out worldwide. Major differences exist, however, in the regulatory and legal environments, as seen above. One critical issue in Germany in terms of regulation is that research on embryonic stem cells is very restrictive. Under the current regulation, German researchers only have permission to work on stem cells harvested before January 1st 2002.[65] According to some, this regulation may lead to an isolation of German research in the field if the scientists do not have the same access to stem cell lines as their colleagues in neighbouring countries. As noted by some well-known scientists, such as Professor Hans Schöler, Chair of the Managing Board of the Stem Cell Network, these older stem cell lines are contaminated and they are of reduced value for research purposes.[66] Still, any infringement on the stem cell act is prosecuted. For firms, these restrictions have meant managing and overcoming regulatory problems. For instance, one company interviewed explains that, "…in our case, we wanted to make quality control on embryonic stem cells…. And to tell our partners abroad to only ship us the DNA of the embryo stem cells… then they are not living anymore, if its only the DNA then they are not considered as embryonic anymore…. So for us these regulations are not very restrictive. This is actually more a concern of our partners abroad…I think it is more of a psychological concern of them… with good communication it can be compensated…".[67]

Thus, in Germany, discussions on the Stem Cell Act of 2002 are taking place. After five years of experience with this regulation, the German National Ethics Council has published an opinion on the current regulation with human embryonic stem cells (17th July 2007). The conclusion is that the current Stem Cell Act needs to be reformed and the majority of members of the Council argue for making stem cell research easier and allowing for import of newer stem cell lines. The German Research Foundation (DFG) and most of the members of the German Ethics Council (GNEC), together with leading research politicians have now argued for this. Their recommendation is to control both the import and use of human embryonic stem cells on a case-by-case basis.

Specific recommendations by the German Research Foundation (DFG) have been made in connection with discussions for a change of this regulation:

- The current regulation should be repealed and German research should have access to new stem cell lines produced and used abroad, as long as these are supernumerary embryos (derived from in vitro fertilisation)
- The introduction of cell lines should be permitted if they are to be used for diagnostic, preventive or therapeutic purposes
- The threat of penalties for German scientists should be removed and the scope of the law limited to German territory, i.e. meaning that there will be no threat to German scientists participating in international collaborations.

4.7 The UK situation

There has been no specific regulatory framework for tissue engineering and tissue-engineered products in the UK.[68] Gene therapy and somatic cell therapy medicinal products have fallen under medicinal legislation. However, tissue-engineered products have fallen outside devices legislation and some even fall outside medicinal legislation. However, some may fall within the definition of somatic cell therapy medicinal products. The Medicines and Healthcare products Regulatory Agency's (MHRA) Medicines Borderline Section determines whether a particular product is medicinal or a borderline product (for example, cosmetics or food supplements).

In this situation, regulation has been in the form of 'codes of practice' for human-derived therapeutic products and the use of stem cells. In fact, since there has been no Europe-wide regulation, a voluntary interim code of practice for manufacturers has been published in the United Kingdom. These codes of practice guide practitioners until the EU regulation is in effect. The Code of Practice for the Production of Human-Derived Therapeutic Products has been established in order to provide guidance for organisations that produce healthcare products containing material of human origin.[69] The objective of the Code of Practice is to create an outline of the principles and systems securing safety and quality of products. The Code mirrors the current scientific situation and the professional standards that are accepted by commercial organisations, institutes and health service establishments. Furthermore, these are being developed in a practical way. As such, the Code is highly important to organisations wanting to supply the UK Health Service, such as specialised hospital units, manufacturers and others. The Code of Practice is continually updated and addresses important regulatory issues dealing with establishing good standards for the selection of donors, retrieval of tissues, testing, processing, storage and delivery. It attempts to bring together the professional expectations of the Medical

Devices Agency of the Department of Health, the Medicines Control Agency, professional organisations, commercial producers and specialised hospital units, thus securing the interests of all stakeholders.

For the field of stem cell research, the Human Fertilisation and Embryology Authority (HFEA) has the responsibility for legal control of research involving human embryos, including human embryonic stem cell lines. Current legislation includes the Human Tissue Act of 2004 and in August 2007 a Joint Committee on human tissue and embryos created a draft of the "Human Tissue and Embryos (Draft) Bill". A 'Code of Practice for the Use of Human Stem Cell Lines'[70] was also established in order to provide guidance for organisations working with stem cell lines. According to UK legislation once established, embryonic stem cell lines are not embryos. Following this, the British government decided that research involving established stem cell lines does not need the same level of regulation to which embryo research is subject under the HFEA. However, a critical issue is the fact that production of embryonic stem cell lines involves the destruction of human embryos and, as such, control of the process was recommended in form of a steering committee to ensure that research is conducted within the ethical framework required by HFEA regulations. Such control mechanisms governing research as well as the Code of Practice are voluntary. Even so, they are conditions of statutory regulation in the UK and there is an expectation by government that they will be adhered to.

4.8 Implications for Europe

The present study argues that Europe has long been missing a synchronised agenda for regulation of market approval of tissue-engineered products. Accordingly, various countries have put their custom-designed approaches into practice, implying that companies had excessive costs in adapting their applications to different markets with dissimilar requirements. In addition, possibilities for cooperation and marketing between countries have been inhibited. It is not far-fetched to think that this situation has weakened the development of the field in Europe and may have led to fewer products being placed on the market.

This analysis illustrates that TERM products are not easily classified in traditional regulation for pharmaceuticals or medical devices and links to the category of biologics as used in the US system. The EU position stresses a recognition of new types of products, combining biological material and chemical structures. Importantly, both scaffolds and stable biomaterials are highlighted as being of crucial importance, further linking the particularly important (to Sweden) field of biomaterials to tissue engineering.

Today, a common regulation has been shaped and will apply from 30th December 2008. This new regulation may prove a crucial step for Europe to be able to continue to take a prominent position in this field. This regulation for advanced therapy medicinal products embraces products based on genes, cells and tissues. It involves a centralised marketing authorisation procedure which gives the successful applicants direct access to the entire European market. With the pooling of experts within the European Medicines Agency (EMEA) it also builds a common understanding of the emerging field as a whole. Importantly, specific emphasis in the regulation has been placed on aiding small and medium-sized enterprises. One concern raised from various stakeholders involved in the review process is the balance of regulatory flexibility in this field, where scientific development is ongoing and product standards are hardly set and predictable. Indeed, reducing uncertainty is crucial from both the researchers' and firms' perspectives.

5 Policy initiatives and research environments

As has been discussed earlier in this report, the geographical dimension plays a major role in the evolution of TERM.[71] In fact, it is important to develop strong regional or national research and innovation environments and to be skilled in linking such activities to the global knowledge development. This section analyses the type of national or regional initiatives relating to TERM put into practice in the focus countries of this study (Germany, the UK, Japan, the US and Sweden). Data has been collected from the various federal, state or regional agencies mentioned, as well as from research reports.[72] The lack of analogous data prevents direct comparison of the volume of financing between countries. The comparability is also reduced by such things as national differences in the R&D financing systems and the degree to which data is presented on a detailed project or area level. When identifying centres, projects and initiatives, they include overheads, basic funding, salaries etc to differing extents. This not only differs between countries but also within a country depending on the initiative and funding organisation. As will be made clear in this chapter, despite these differences and difficulties in comparing national efforts, significant investments are made into the TERM area in all the focus countries. An overview of some of the major research environments in the field is also given, but not with the aim of providing full coverage. Rather, this chapter strives to give a flavour of the profile and size of the initiatives and environments, and links to the following chapter which asks what the leading countries and universities are in terms of scientific output (based on a bibliometric analysis).

5.1 Germany

5.1.1 Major initiatives in Germany

In Germany, the federal and regional strategies for TERM include both direct funding for research projects, as well as support to create a critical mass of research in geographical clusters. The Federal Ministry for Education and Research (BMBF) is responsible for the implementation of public funding programmes and allocates resources directly to project initiatives, as well as to regional agencies.

Firstly, the government position in initiating clusters of excellence through the German Research Foundation (DFG) has been crucial to the

geographical clustering of TERM-related research activities. In a situation which does have strong research, but nevertheless lacks links and critical mass, a call for grants was announced in 2005. The aim of this public initiative was to establish one specific research centre focusing on TERM. Several such clusters have now been created based on this funding and additional financial sources. At the Centre for Regenerative Therapies (CRTD) at the University of Dresden, the staff of 100 people and its network of some 70 labs focus on stem cell physiology and manipulation, as well as integration of biomaterials and cells and the suppression of immunological rejection. The Centre has received EUR 67.5 million for the period 2006-2017. Another cluster of excellence is the Hannover-based 'Centre for Regenerative Biology and Reconstructive Therapies' (ReBirth), with a EUR 1.5 million grant for the period 2006-2010. As a spin-off from the DFG calls, the Translational Center for Regenerative Medicine (TRM) in Leipzig was founded in 2006 with EUR 23 million in funds from the Federal Ministry for Education and Research, the Free State of Saxony and Leipzig University. With EUR 50 million from BMBF for 2007-2010, the Berlin-Brandenburg Centre for Regenerative Therapies (BCRT) was also established as a joint initiative by the major research hospital Charité and Germany's largest research organisation, Helmholtz Association.

Secondly, specific programmes aiming to promote the field of TERM have been initiated in some regions in order to offer funding for both research organisations and industry. Via the BioRegio programme, 25 bioregions in Germany were federally financed by BMBF. In relation to TERM, the BioRegioSTERN has a particular focus on regeneration biology.[73]

Thirdly, in addition to these TERM-specialised centres, many regional biotechnology groups are often located close to either scientific institutes (such as Max Planck institutes) or university-based medical schools.

5.1.2 University and institute-based research in Germany

A recent study on regenerative medicine in Germany shows that of 222 identified researchers in the field, about half work at (university) hospitals, 30% at universities and 20% in private research institutes. Research areas in which these interviewees work are musculoskeletal (26%), nervous system (17%), cardiovascular system (16%), gastrointestinal system (9%), skin (9%), cellular system (8%) and 14% cover various other areas.[74] The main TERM work in Germany is based on technologies applying growth factors (24%), multipotent adult stem cells (22%), biomaterials (18%), various autologous cells (17%) and pluripotent stem cells (7 %). A small amount of this will be research projects with human embryonic stem cells, as the Robert Koch Institute has only given 19 approvals for use of these so far.

In Germany, there are a large number of university groups active in the field. At the *University of Leipzig***,** The IZKF, an interdisciplinary centre for clinical research was founded in Leipzig in 1996. This was at the University of Leipzig belonging to the Medical Faculty. Funding came from the "Health Research 2000" government programme run by the Federal Ministry for Education, Science, Research and Technology. Through its projects, IZKF is currently financing over 50 scientists and another 30 principle investigators are leading IZFK projects within their institutes and clinics. Research projects of the IZKF Leipzig have the overall theme of "Cell-Cell and Cell-Matrix Interactions for Diagnostic and Therapeutic Strategies". The IZKF Centre is also interacting with BBZ, the association of six biotech professors in Leipzig. Another very important piece of this new infrastructure was the new Fraunhofer Institute for Cell and Therapy and Immunology (IZI), founded in Leipzig 2005. The research is application -orientated, in keeping with the way this is done at all Fraunhofer institutes. Part of the funding also comes from industrial partners. Focusing on translational medicine, this is a very important player as it can be seen to serve as mediator between biomedical research and the clinic. The Center for Biotechnology and Biomedicine Cell Techniques and Applied Stem Cell Biology at the University of Leipzig is led by Prof. Bader and currently has a staff of 17 researchers and scientists, as well as nine technical engineers and assistants. The focus at the Centre is on neurosciences, cardiology, liver and skin.

The Centre for Regenerative Therapies (CRTD) at the *University of Dresden* focuses on five research areas**:** haematology/oncology/immunology, diabetes, neurodegeneration/degeneration of the retina, hard tissue replacement and cardiovascular diseases. The Centre has a faculty from the Technical University of Dresden and its director is Michael Brand. The Centre comprises 33 professors and doctors from the Medical faculty, eight from the Biology department, five from Bioinformatics and nine others from various departments. In addition, The Max Planck Institute of Molecular Cell Biology and Genetics contributes 10 scientists and six other scientists come from various research institutes in the region.

The Berlin-Brandenburg Center for Regenerative Therapies has a centre of excellence in Regenerative Medicine. It includes researchers from several universities and research institutes in the Berlin area and is led by the Dept. of Medicine – Charité – at the University Medicine Berlin and the joint medical faculty of the Free University and Humboldt University Berlin. The Centre is directed by Professor Hans-Dieter Volk and involves 41 scientists.[75] The Centre focuses on research and clinical programmes related to musculoskeletal and immunological applications, which are the key

strengths of regenerative medicine at the Charité as well as being closest to clinical translation. In addition, the Centre also focuses on regenerative therapies concerning the cardiovascular and nervous system and on liver-related applications. The programme is divided into five medical research fields linked to overlapping platforms on basic, bioengineering and translational research.

The *University of Tübingen* is known for its specific expertise in regeneration biology. Research is in the area of biomaterials within bone and cartilage products. The Centre for Regenerative Biology and Medicine is a joint centre between the university hospitals and the School of Medicine. The Centre focuses on regeneration biology and regenerative medicine from basic research to clinical application. In particular, the research in tissue engineering focuses on cultivating new tissue from a patient's own autologous cell material and developing transplants for application in orthopaedics, urology and dermatology. A research group focuses on regenerative therapies in the field of artificial skin/wound healing, cardiovascular regeneration, regeneration of bones and cartilage, regeneration of muscles, neural regeneration, oncology and regeneration of inner organs. Another strand of research takes place at the Department of Radiation Oncology where researchers study regenerative medicine as applied to treatment of radiation injury. Irradiation of tumours in the head and neck area can lead to alteration of tissue and cause ulceration due to the death of epidermal cells. At the University Clinic for Paediatrics and Youth Medicine, a technique known as haploidentical stem cell transplantation is used for treatment of leukaemia. This group is led by Dr Rupert Handgretinger.

Medimplant Hannover is a competence centre for cardiovascular implants and a key player in the field of medical devices for cardiovascular products. Based on its long-standing expertise in transplantation medicine and on extensive activities in cell therapy and TERM, the *Hannover Medical School* has recently funded a centre for basic and clinical research in the area of Regenerative Biology and Reconstructive Therapy, with the acronym REBIRTH. This excellence cluster has been selected for funding through an initiative of the German federal and state governments to promote science and research at German universities. At REBIRTH, research projects are conducted that identify and evaluate cellular and molecular targets that stimulate regeneration. Study focuses on intrinsic pathways and milieu-dependent mechanisms which control epigenetic reprogramming, cell expansion, differentiation, migration and disease-specific regeneration. REBIRTH is organised into four research and training areas:

- Regenerative biology, covering stem cell biology, organogenesis and ageing
- Reconstructive therapy in preclinical models and enabling technologies
- Translation: imaging and vigilance, process development and clinical trials
- Human resources: training programme, gender equality and diversity

Key scientists from the seven partner institutes work together in all these four areas. The seven major players in the field of biomedical sciences and related enabling technologies connected by REBIRTH are the three partner universities of Hannover Medical School (MHH), the University of Veterinary Medicine (TiHo) and the University of Hannover (UniH), plus the Fraunhofer Institute for Experimental Medicine (ITEM), MHH's new joint venture with the Helmholtz Centre for Infection Research (HZI), known as the "Centre for Experimental and Clinical Infection Research", the Institute for Animal Breeding (FAL) and the final crucial player is the Max Planck Institute for Molecular Biomedicine (MPI) in Münster. This is a key player in the basic science of stem cells. REBIRTH is coordinated by Professor Axel Haverich, a leader in transplant surgery and a pioneer in the search for innovative treatments.

At the *University of Veterinary Medicine* (TiHo) in Hannover, two centres were established to promote biomedical research focusing on infection biology and neurosciences: the virtual Centre for Systems Neurosciences (ZSN) and the virtual Centre for the Biology of Infections (ZIB). These centres offer international postgraduate training programmes leading to a PhD. Other important research at universities takes place at the Hannover Medical School, a competence centre for cardiovascular implants focusing on medical devices for cardiovascular products. The University of Hannover (UniH) is also involved in TERM research.

The Department of Cardiac Surgery at *The Medical School of the University of Rostock* is led by Professor Gustav Steinhoff and has achieved success in the area of cardiology. Projects include the development of cardiac stem cell therapy with bone marrow stem cells and protection of chronically injured myocardium by transplantation of genetically modified human stem cells. The focus is on cardiology and gastroenterology.

The Bioprocess and Biosystems Engineering Institute at the *Technical University in Hamburg* is led by Professor An-Ping Zeng and has five PhD students and one senior research associate. The focus is on tissue engineering methods for the development of artificial cartilage

At the Institute of Experimental and Clinical Pharmacology at the *University Medical Center Hamburg-Eppendorf* Professor Zimmermann

leads a group focusing on cardiac tissue engineering and has a group consisting of three PhD students, one scientist and two guest scientists.

The tissue engineering group at *The University of Regensburg* is led by Professor Minuth. The focus of this group is on the differentiation of tissue and evaluation of the characteristics in maturing tissue constructs. Another key researcher at Regensburg is Professor Strehl who focuses on human embryonic stem cells in relation to drug discovery and securing soft tissues to bone.

In Germany, the institute-based research takes on a significant role, as a complement to the university-based research. The *Max Delbrück Center for Molecular Medicine*, in Berlin-Buch, has 61 scientists and the research focus of the centre is organised through three programmes; Cardiovascular and Metabolic Diseases, Cancer Research, Function and Dysfunction of the Nervous System. The research programme on Signalling Pathways, Cell Biology and Cancer is led by Professor Achim Leutz and includes two teams focused on stem cells. Dr Frank Rosenbauer leads the Stem Cells and transcription factors research while Dr Daniel Besser leads the group focusing on the signalling Mechanisms in Embryonic Stem Cells. At the Cardiovascular and Metabolic Diseases Research Programme, Dr M. Cristina Cardoso leads a research group that works on molecular and cell biology of the (Epi)genome. The focus of this group is the molecular mechanisms regulating the establishment and maintenance of terminal differentiation and tissue regeneration.

The Fraunhofer Institute has several centres involved in TERM, including Cell Therapy and Immunology (IZI) in Leipzig, Experimental Medicine (ITEM) in Hannover and for Biomedical Technology in St. Ingbeerg. In addition to these TERM-specialised centres, there are many regional biotechnology centres.

The Max Planck Institute of Molecular Cell Biology and Genetics is divided into 24 research groups and includes research on a broad range of topics such as cancer and stem cell biology and the application of functional genomics in mammalian cells, cell biological mechanisms in developing tissues and tissue formation for regenerative and molecular medicine. Other focuses at the Institute are applications for blood vessels (artherosclerosis and cancer) as well as pancreatic islets. This centre has 78 researchers and 120 junior researchers.

There are also some research centres in Köln, Bonn and Aachen with particular competences in the area of stem cell research which have established a competence network on stem cells.

Clearly, there are a number of important research groups and initiatives in Germany. In fact, there have historically been some distinguished regional clusters or groups and academic and institute-based research within TERM is diffused throughout different locations in Germany, where the various areas have specialised in different applications. Experts in the area of bones have resided in Berlin, whilst TERM in the area of neurosciences, cardiology and liver is specifically present in Leipzig. Importantly, there have been some important regional initiatives in Germany shaping the prerequisites of the field.

Firstly, the region of *Saxony* is increasingly known for its focus on bio and on TERM and was also one of the winners in the centre formation. State initiatives are mostly concentrated on the two major cities, Leipzig and Dresden, with particular emphasis on molecular bioengineering and regenerative medicine. An attractive player located in this region is the new Fraunhofer Institute of Cell Therapy and Immunology (IZI) in Leipzig. IZI is the first special Research Center for Regenerative Therapies in Dresden, funded by the German Research Society (DFG, Deutsche Forschungsgemeinschaft). The various activities within biotech are coordinated under "Biosaxony". This was launched in 2000 and received EUR 200 million from the Saxon State Ministry of Economics and Labour. The aim was to build up a biotech-targeted infrastructure, including research and application-orientated development in the sector. Right from the beginning, the aim of the Biosaxony concept was to have and develop a very clear focus. One was a geographical one. The two largest cities in Saxony, Leipzig and Dresden, were important and already had very high levels of biotech competence. The other was thematic, with the choices being regenerative medicine and molecular bioengineering. It was natural to keep this thematic focus as medicine and medical research has been a strength in Saxony. The specific decision of thematic focus was made based on a thorough examination of existing local and regional strengths and the aim of furthering this research, which is or aims to be interdisciplinary and application-orientated.

The new infrastructure in connection with the launch of Biosaxony included the building of two bio-incubators in Leipzig and Dresden. In each city, six new biotech professorships were established in the bio-incubators.[76] This combination, of science and business in one location, or rather in one and the same building is rather unique in Germany and was meant to initiate interactions between science and industry. Application-orientated research and branches of biotech are also explicitly addressed in the professorships that have been selected. At the same time, the focus on molecular bioengineering and regenerative medicine has been kept. In Leipzig, there

has been established a Chair for Regenerative Medicine and in Dresden a new research group for Tissue Engineering has been set up.

The RegMedNet initiative served as a mediator, with the explicit aim of bridging research between scientists and clinicians. Also crucial to the regenerative medicine biotech profile of Biosaxony was the establishment in 2002 of the Max Bergmann Center of Biomaterials Dresden (MBC).

As stated earlier, a call for funding by the German Research Foundation (DFG) was announced in 2006 to expand and increase the regional strengths in TERM and build major clusters in the field. The aim was to establish a research centre focusing on RM.[77] Three centres, Dresden and Leipzig (in Saxony) and Berlin got into the final round of applicants, and in 2006 the University of Dresden and its Centre for Regenerative Therapies (CRTD) was awarded a 10-year grant. The financing of this *Centre of Excellence* is an active step on the part of government to promote RM and create critical mass. Since Berlin and Leipzig had also submitted very good proposals, there were two other players which decided to support these proposals and hence also promote these initiatives in RM. Thus, what was initially a government action was followed up by other players enabling the establishment of two more centres. These were the Fraunhofer Institute which decided to fund the Centre in Leipzig; the Berlin Centre was then supported by the Helmholtz Association, also a federal player.

A specific feature of these three centres is that many competences are captured within the walls of the centres and also, importantly, united in specific buildings, truly forming *centres* as opposed to the more loose collection of TERM activities within a region. These may be the very seeds needed to build major clusters. Overall, the various biotech centres receive extensive support from regional governments. For example, the BioRegio programme discussed above show an attempt by government to apply public policy as a catalyst to stimulate innovation. Typically these support programmes include free consulting services on business plans for entrepreneurs, subsidies for costs in connection with patenting, low-cost lab space and market analysis.

5.2 The UK

5.2.1 Major initiatives in the UK

In the United Kingdom, major research initiatives relating to TERM have been launched during the last few years. Of the eight research councils in the UK, three support TERM-related research. Firstly, *the Biotechnology and Biological Sciences Research Council* (BBSRC) is the major funder of basic and strategic biological research in the UK and one of its focuses is

stem cell biology.[78] In addition to universities, it sponsors several research institutes such as the Roslin Institute (cloning and epigenetics) with approximately GBP 5.7 million (EUR 8 million) and the Babraham Institute (cell signalling and epigenetics).[79] [80] Secondly, the *UK Medical Research Council* (MRC) focuses on molecular and cellular medicine which receives 38% of the resources. Funding amounted to over GBP 500 million (EUR 677 million) during 2005/06, amongst other things making it the largest non-commercial funder of clinical trials in the UK.[81] [82] [83] Thirdly, the *Engineering and Physical Sciences Research Council* (EPSRC) has one programme partly relating to TERM: The *Life Sciences Interface Programme* focused on interdisciplinary research.[84]

Since the UK government perceives TERM as a strategic field to develop, this has resulted in relatively major resources being devoted to this field compared to other European countries. In particular, the area of stem cells receive a lot of attention as can be seen in the 'UK Stem Cell Initiative' (UKSCI), launched in 2006 by the Department of Health and the Department of Business, Enterprise and Regulatory Reform. The perceived importance of the field is expressed in the recent doubling of public funding on this initiative for stem cell research. In fact, from mid-2004 to mid-2006 the UKSCI received GBP 26 million (EUR 35 million) per year but this sum was increased to EUR 71.5 million annually for the period from mid-2006 to mid-2008.[85] It was set up to develop a ten-year vision and strategy for UK stem cell research, to be implemented between 2006 and 2015. In this process, the UKSCI consulted widely with academia and the private sector. The aim is to establish a public-private consortium that will use stem cells to enhance drug discovery and development. There is also a wish to facilitate cross-fertilisation between scientists, engineering experts and private industry and provide a platform over the next decade for a sustained programme of public dialogue on stem cell research. Another key goal is to secure the necessary *resources* needed for the UK Stem Cell Bank, as well as supporting basic stem cell research and *centres of excellence*, cell production facilities and clinical research and the translational stem cell research and clinical trials.

Partly as a result of such initiatives in terms of cluster building and critical mass, in 2007 the *Scottish Centre for Regenerative Medicine* (SCRM) at Edinburgh University received GBP 59 million (EUR 80 million) in support to build the Centre with an estimated completion date of 2010. The funding comes from BBSRC and MRC combined with a number of other financiers. The Centre is part of the UKSCI strategy, but has additional financing and a clear focus on stem cell research. Another centre of excellence has been set up at the University of Cambridge, the *Wellcome Trust Centre for Stem Cell Research*. In 2006, the Wellcome Trust provided GBP 10 million (EUR

13.5 million), the Medical Research Council contributed GBP 1.5 million (EUR 2 million) and the Wolfson Foundation GBP 1.5 million (EUR 2 million) to this centre.

As stated above, another important initiative, funded jointly by BBSRC and MRC, is *the UK Stem Cell Bank,* set up to assist the scientific and clinical community in assuring the quality of human stem cell lines used in research and therapy. The bank is governed by the National Biological Standards Board (NBSB) which is a non-departmental public body (NDPB).[86] The bank constitutes an important resource for conducting research in the TERM area. Access to cell lines is a critical resource for the research community and the bank develops important safeguards, thus ensuring that cell lines are handled and stored under properly controlled conditions and undergo stringent safety and quality control testing. The bank constitutes a key asset to UK researchers "*by providing high quality starting materials to facilitate the development of stem cell therapy, and acting as a centralised resource for researchers, the UK Stem Cell Bank should reduce the demand for surplus embryos to be used for the development of stem cell lines".* [87] It was established in January 2003 with a grant of GBP 2.4 million (EUR 3.2 million) from the MRC and BBSRC and in December 2005 received an additional GBP 9.4 million (EUR 1.2 million) to build, equip and run a permanent UK Stem Cell Bank.[88]

There is also the *UK Technology Programme* as set up by the Department of Trade and Industry (DTI) to support business. This comprises two types of activities; collaborative R&D and knowledge transfer networks.[89] One such R&D project is that of stem cell technology; in 2004, the DTI gave funding of GBP 4.9 million (EUR 6.6 million) for three projects.[90]

In addition to central funding, a set of *non-governmental* foundations and trusts play an important role for biotech in general and TERM. Firstly, the charity organisation *UK Stem Cell Foundation* (UKSCF) was established in 2005. Relying on financial backing from individuals, trusts and companies, it focuses on supporting the advance of stem cell research into medical practice and pursues direct funding of UK clinical projects with a high potential for practical results. The target of the foundation is to raise GBP 100 million (EUR 135 million) in endowments. The foundation is partnered by the MRC, London Developmental Agency, Scottish Enterprise and HM Treasury. Secondly, as stated above the Wellcome Trust has co-funded a centre for stem cell research in Cambridge.[91] In addition, during 2004 and 2005 it gave EUR 16.4 million in funding to stem cell research[92] and in conjunction with the Juvenile Diabetes Research Foundation (JDRF) has funded research into human pluripotent stem cells, with each granting up to GBP 3 million (EUR 4 million) over five years in funding. Thirdly, the Wolfson Foundation is a major contributor to TERM research and supports

stem cell research in Cambridge, as noted above.[93] In September 2007, the new Wolfson Centre for Stem Cells, Tissue Engineering and Modelling (STEM) opened at Nottingham with GBP 4 million in funding from the Wolfson Foundation, MRC, BBSCR and the Wellcome Trust.

Importantly, in terms of collaboration between the various research groups as well as between academia and industry, there are several research networks within TERM. The stem cell area has been organised into four regional networks: the East of England Stem Cell Network, the Scottish Stem Cell Network, the Northeast England Stem Cell Institute and the London Regenerative Medicine Network. Perhaps the most influential of these is the *London Regenerative Medicine Network* as founded by Dr Stephen L. Minger (the director of the Stem Cell Biology Laboratory at King's College London) and Dr Chris Mason (Group Leader of the Stem Cell and Regenerative Medicine Bioprocessing Unit at University College London). Recently these four networks were assembled at national level into the UK National Stem Cell Network which aims to bring new coordination and coherence to national and regional stem cell research efforts. Another network is *BRITE-Net*, the British Tissue Engineering Network, set up to promote communication between the different disciplines involved in tissue engineering and, as such, help create a national identity in this field.[94] BRITE arranges seminars, meetings and workshops, thus linking the different research environments together.[95]

5.2.2 University and institute-based research in the UK

It is safe to claim that TERM research clearly holds a strong position in the UK universities and research institutes. More than 20 universities in the UK are involved in TERM-related research and the UK boasts some of the most excellent TERM-related research centres in the world. The leading UK centres for stem cell research include the Institute for Stem Cell Research at Edinburgh University, the Centre for Stem Cell Biology at the University of Sheffield and Dr Stephen Minger's group at King's College London. The related fields of biomaterials and medical devices also have a strong scientific base in the UK and there are interdisciplinary research centres in biomedical materials at Queen Mary (University of London) and in tissue engineering at Liverpool/Manchester universities. In addition, many universities in the UK have international reputations in the area including University College London, Imperial College London, Leeds, Sheffield, Nottingham, Strathclyde, Cambridge, Southampton and Sussex. The following sections provide an overview of some of the most important university centres and institutes in the UK.

Edinburgh University hosts the Scottish Centre for Regenerative Medicine (SCRM) which is directed by Professor Ian Wilmut. The SCRM has 20

research groups involving over 150 scientists, graduate students and support and ancillary staff. SCRM focus on two major research themes. Firstly, in understanding stem cells and their niches they focus on embryonic stem cells, including the fundamental mechanisms underlying the control of pluripotency, the regulation of lineage commitment and the control of ES cell differentiation. Also, there is work on the identification and characterisation of defined tissue progenitor/stem cell populations, the regulation of the postnatal stem cell compartment by the niche and the identification of cancer stem cells, with particular focus on neural, haematopoietic, thymic epithelial and liver stem/progenitor cells. Secondly, in the sub-area of stem cells and regenerative therapies, research includes drug screening and disease modelling as focused on neurological, haematopoietic (blood), liver and bone and cartilage repair

Another key UK research centre, also at Edinburgh University, is the *Institute for Stem Cell Research* (ISCR). ISCR has 11 research groups involving a total of 73 researchers. The focus is on development of medical therapies based on stem cell research for the treatment of human diseases, such as cancer, liver disease, Parkinson's disease, diabetes and spinal cord injury. ISCR is a coordinating partner in EuroStemCell, an EU-funded FP6 integrated research project,[96] as well as the Genome Engineering Group led by Andrew Smith which is a member of ESTools (also an EU-funded research project).[97] The institute recently received GBP 1 million (EUR 1.35 million) in funding from The Medical Research Council to develop a new centre of excellence in stem cell research, with the goal of speeding up the development of stem cell therapies from laboratory to clinic.

Kings College is a leading player in the field of regenerative dentistry and in stem cells. Firstly, *the Stem Cell Biology Laboratory* at the Wolfson Centre for Age Related Diseases (CARD) is led by Dr Stephen Minger. The laboratory has 28 researchers and focuses on the derivation, propagation, characterisation and assessment of the therapeutic potential of a wide range of stem cell populations. This includes cells from early embryos, as well as cells obtained from foetal and adult tissues. This group was the first in the UK to grow human embryonic stem cells. One bottleneck in this research has been the shortage of high quality human cell lines as well as a lack of related expertise. The laboratory combines the expertise of the Stem Cell Biology Laboratory and the Assisted Conception Unit at Guy's Hospital as a mean of overcoming this shortage. This has resulted in the development of three novel human embryonic stem cell lines, including the first line human ES cell line carrying a known genetic disorder, Cystic Fibrosis. This has local ethical approval and has been developed under licence from the HFEA. Furthermore, these cells have been stored in the UK Stem Cell Bank and as such are made available to researchers throughout the world. In terms

of therapeutic focus, Dr Minger's lab concentrates on such things as Cellular replacement strategies. These can be applied clinically to patients with Parkinson's disease, but this is not currently feasible due in the main to scarcity of transplantable tissue which must be obtained from early first-trimester human embryos. One of the major projects in the laboratory is determining the extent to which neural stem cells can be utilised for repair of the human central nervous system. Research is also undertaken to investigate the extent that neural stem cells in the adult human brain are influenced by various neurodegenerative processes, pharmacological interventions and vascular changes.

Secondly, in the field of regenerative dentistry, the Dental Institute at King's College London is the largest dental research centre in the UK. Professor Paul Sharpe has made advancements in the dentistry field which have led to the creation of a commercial spin-off company, Odontis Ltd. The focus is the creation of a biological replacement tooth product (BioTooth^{TM}). This is based on tooth development initiated in stem cells and fully formed teeth can be created in developmental models. The tooth is formed in the embryo which may lead to the development of a tooth for recreation in the mouth of an adult patient.

The *Trust Centre for Cell-Matrix Research* is located in the Faculty of Life Sciences at the University of Manchester. The Centre currently has 22 independent investigators and a total of 170 research staff. The focus of research is on four different tracks. Firstly, in matrix assembly the aim is to determine the blueprints on which the long-range architecture of tissues is established. Secondly, adhesion signalling aims to define currently elusive mechanisms whereby adhesion contacts integrate the ECM with the cytoskeleton and associated cellular signalling machinery. Thirdly, research into cell fate determination aims to investigate the responses of cells to dynamic 3D ECM and the link between the composition of an ECM and its instructive properties. Finally, tissue regeneration research aims to exploit advances made in the fundamental research programmes to regenerate functional tissues and thereby treat human diseases and degenerative conditions. In January 2004, the Centre relocated to the new Michael Smith Building, which was partially funded by a GBP 15 million (EUR 20 million) grant from the Wellcome Trust and the UK government.

The UK *Centre for Tissue Engineering* at the universities of Manchester and Liverpool (UKCTE) has 50 researchers and focuses on applications in cartilage, bone, cornea and skin. The research is divided into three themes. The Skin and Laminar Structures group is headed by Professor Mark Ferguson and focus on developing tissue-engineered skin products as an effective and economic treatment for victims of trauma, burns, surgery, as well as accelerating the healing of acute and chronic wounds in the elderly.

The Cartilage, Intervertebral Disc, Compressive and Tensile Structures group is headed by Professor Tim Hardingham. The focuses of this group are on investigating the expression of SOX genes in human chondrocytes during the loss of phenotype in cell culture and identifying the key interactions in the initial assembly of ECM by chondrocytes which lead to new strategies for generating cartilage matrix in culture for tissue engineering. Finally, the Vascular and Tubular Structures group is headed by Professor Cay Kielty and focuses on developing small-diameter vascular prostheses for coronary and other revascularisation procedures.

Regenerative medicine, tissue engineering and associated disciplines at *Imperial College* span many departments in the faculties of medicine, natural science and engineering. The leader of the stem cell research theme is Professor Malcolm Parker from the *Institute of Reproductive and Developmental Biology* and 19 researchers are involved. The research started in the *Tissue Engineering and Regenerative Medicine Centre*, which was led by Dame Julia Polak. The research is now distributed at different units across Imperial, such as the unit for *Stem Cell Bioprocessing* which is a collaboration between Professor Dame Julia Polak and Dr A. Mantalaris. Dr Mantalaris is a systems engineering expert on bioreactors and cell encapsulation technologies. This project targets the transfer of laboratory-based practice of stem cells and tissue culture to the clinic as therapeutics, with the means of applying engineering principles and practices. *The Stem Cell and Regenerative Medicine Group* is based at the Hammersmith Hospital Campus and is directed by Professor Martin Wilkins. This group focuses on repairing lungs using murine embryonic stem cells. The group working on regenerative strategies for the liver is located at Hammersmith Hospital and focuses on the therapeutic potential of adult stem cells to improve liver function. Another research avenue is using stem cells to carry anti-cancer reagents to kill residual cancer cells following debulking surgery, or in patients for whom other treatment modalities have failed. *The Bone Group* is based at South Kensington's Department of Materials with Dr Molly Stevens and at the Department of Chemical Engineering with Dr Sakis Mantalaris. *The Stem Cell Imaging* group is led by Kishore Bhakoo and has 10 additional researchers.

At University College London (UCL), there are four different units involved in TERM research. Firstly, *the Institute of Ophthalmology* has 44 researchers, 56 PhDs and post-docs and receives GBP 20 million (EUR 27 million) in funding. The institute focuses on the pathological features in numerous forms of blindness and investigates the cellular and molecular mechanisms that control vascular growth in the retina in the hopes of a better understanding of this process. Achievements have been made in cell biology, developmental biology and genetics, such as investigations of

development of retinal circulation and neuronal development. Secondly, the *Tissue Repair & Engineering Centre (TREC)* is led by Professor Robert Brown, who is also the co-ordinator of the *London Tissue Engineering Consortium* and the *British Tissue Engineering Network* (BRITE Net). TREC is focused on research into cyto-mechanical control of tissue organisation and matrix material growth and currently has nine researchers and three PhDs and post-docs. Funding is in the range of GBP 2 million (GBP 2.7 million), including two EU consortia and strong European and US collaborative links. Thirdly, the *Centre for Stem Cell Research* involves 96 researchers and spans several faculties. The overall focus is on stem cells and tissue engineering, regeneration and repair. Research on stem cells includes identifying genes that define stem cell properties, functions and modes of action and finding endogenous stem cells in embryos and adults. They are also working on defining culture conditions that favour the isolation and maintenance of stem cells as well as studying factors that control stem cell properties and instruct cells to proliferate or differentiate along specific pathways. Finally, *the Eastman Dental institute* currently has 100 researchers and one of their main focuses is on biomaterials and tissue engineering. Their research tries to understand the fundamental phenotypic and functional responses of both soft and hard tissue cells to novel biomaterial compositions.

There are two leading research centres located at the *University of Sheffield*, the *Centre for Stem Cell Biology* and the *Centre for Biomaterials and Tissue Engineering*. The latter has 37 researchers and their focus is related to applications in tissue engineering such as cartilage, bone, cornea and skin and clinical prosthetics. These are important aspects for clinical applications, as well as providing proof-of-concept for engineering more complex tissues. The centre is also involved in artificial replacements for natural tissues damaged or lost through injury or disease. There is ongoing clinical research at Sheffield into the manufacture of custom implants for dentistry and maxillofacial surgery and modelling of the performance of heart valves, stents and other medical devices. The Centre for Stem Cell Biology focuses on developing human ES cell technologies and resources central to the future development of clinical applications of stem cells in regenerative medicine.

Also, the *University of Cambridge* has created *the Cambridge Stem Cell Initiative* under the direction Professors Roger Pedersen, Azim Surani and Austin Smith. The initiative is multidisciplinary and includes researchers from the School of Biological Sciences, School of Clinical Medicine and Department of Veterinary Medicine. It links together basic and clinical scientists aimed at biomedical translation of stem cell and regenerative

medicine research. The focus is creation of a bridge between the biology of stem cells (basic research) and practical therapies in regenerative medicine.

Some additional groups are also in place at UK universities:

- *The University of Leeds:* The Institute of Medical and Biological Engineering conducts research in the field of Tissue Engineering.
- *Cardiff University*: The Biomaterials and Biomechanics Research Centre (BBRC) carries out research in biomechanics and biomaterials within the dental school.
- Interdisciplinary research centres in biomedical materials at *Queen Mary* have a platform of four research programmes: bone and joint replacement materials, orthopaedic systems, dental application and tissue engineering.

There are also two research institutes of importance to the TERM area. Firstly, the *Babraham Institute* (BI) is a key UK research institute sponsored by the Biotechnology and Biological Sciences Research Council. BI is focused on understanding the mechanisms of cell communication and gene regulation in order to understand the basis of human disease, such as cancer, Alzheimer's, foetal abnormality and rheumatoid arthritis. BI currently has 32 project directors, 160 research scientists and laboratory support staff and 70 PhD students.

Secondly, the Roslin Institute focuses mainly on research related to animals, but also conducts some research on stem cells for humans. The resources embrace a staff of 250, including students and visiting scientists. Research relevant to TERM is currently focused on *stem cells and cellular differentiation*, such as developing methods for differentiation of hES cells into specific lineages, understanding the intercellular signalling mechanisms involved in allowing hES cells to multiply indefinitely in the laboratory and isolating new hES cell lines.

5.3 National and regional initiatives in Japan

5.3.1 Major initiatives in Japan

Presented in December 2002, the Japanese Biotechnology Strategy Guidelines stated a focus on understanding the biological basis for generation and regeneration, including research into cell and developmental biology. Clearly, from the government's point of view, the emerging TERM area provides a new field in which Japanese science may be able to compete with that of the US and Europe. Japanese S&T policy was slow to react to the changes that the rapid development of "-omics" created in the 1990s. Here, Japan definitely lagged behind the US and also to some extent Europe, despite being well advanced in the 1980s. Accordingly, the

combined Japanese initiatives are impressive and in the strategy it is clear that Japan aspires to be a global leader in the development of technologies for large-scale cultivation and transplantation of cells/tissues.[98] A number of choices have been made:

- Establishment of a stem cell bank
- Support for clinical applications
- Development of practices for product management and evaluation of results
- Research into gene and cell therapy, an important aspect being the ability to handle immune rejection.
- A focus on restoring function rather than producing organs de novo
- Treatment of neurodegenerative disorders
- Due to the limited number of possible organ or tissue donors, a focus on techniques for propagation and cultivation of cell/tissue material
- Development of medical equipment to restore function – i.e. the area of artificial organs and sensory system

One key concern in the strategy is the process of industrialisation, where one mentions development of complementary equipment – such as, e.g., cell culture equipment for TERM – as well as evaluation methods for tissue compatibility and for quality control/assurance. Another area is the clarification of intellectual property issues, specifically those not affecting the individual doctor's right to perform adequate medical procedures. Another problem mentioned by some players is a lack of the knowledge and human resources needed to develop the area. There is a clear need for new combinations of knowledge in order to fully explore this field. Previously, there was no university curriculum merging biology, medicine and engineering at undergraduate or masters level and this is considered by some to be a competitive disadvantage compared to the US or Europe. Efforts are now under way to rectify this shortfall. Many of the new centres being formed do include groups from different scientific fields but it remains to be seen whether this leads to new approaches to the challenges of TERM.

There are a number of large, government-instigated research initiatives in Japan relating to TERM. Firstly, the Millennium Project ran from 2000-2004 with the goals of strengthening Japanese S&T in the 21st Century and specifically relating to TERM focused on treatment for bones, blood vessels, etc. Under the Millennium Project, the Government has spent close to JPY 11 billion (EUR 66.5 million) on projects in TERM. These funds are provided through MEXT, METI and MHLW with the ministries taking responsibilities for different activities.[99]

Secondly, one important initiative is the RIKEN Centre for Developmental Biology (CDB), launched in 2000 as part of the Millennium Project.[100] The initial investment for buildings and facilities was around EUR 35 million and the budget for 2004 was EUR 31 million (JPY 5.2 billion), with a total staff of 387. The new institute was located in Kobe to help revitalise the region after the 1995 earthquake which had devastated Kobe City and its economy.

Thirdly, another large-scale programme, "Realisation of regenerative medicine" was initiated in 2003 and is one of several national so called "Leading projects".[101] The total budget was set at EUR 139 million (JPY 23 billion) over 10 years and the main focus is developing medical treatments based on the use of stem cells of various types.

Fourthly, the 21st Century COE programme was launched by MEXT in 2002 and ran until 2004, financing five-year projects. It addresses the need to strengthen leading scientific environments at universities across Japan.[102] Whilst it covered many disciplines, several COEs within TERM have been established. The effort has now been followed by a 'Global COE Programme', linking Japanese educational and research centres closer to global excellence.

Fifthly, the Research Institute for Cell Engineering (RICE) was founded in 2004 at the AIST Kansai Center and deals with cell engineering, integrating cell biology with materials engineering, nanotechnology and IT. It involves 200 people as part or full-time staff.

Finally, the Ministry of Health, Labor and Welfare (MHLW) invests significant funds for TERM through several of the national medical centres and their research institutes and in the form of grants to scientists at universities and institutes. Since the MHLW funding is mostly in the form of individual "grants-in-aid", a large number of research groups are involved. MHLW's budget for TERM for the period 2001-2004 was over EUR 24 million (JPY 4 billion).[103] The areas of research funded involve skin, cornea, bone, cartilage, blood and blood vessels, bone marrow, nerve cells and technologies for improvement of implantation and transplantation (rejection). Research to regenerate more complex tissues such as liver and pancreas are also covered by this funding source. Projects from basic research as well as clinically-orientated applications of TERM are funded. For the latter, the less complicated tissues such as cornea, skin, bone and cartilage seem to be in a rather advanced state and in clinical testing. Potential risks involved in the application of TERM are also being studied in several projects funded by MHLW.[104]

5.3.2 Industrial and regional support programmes

As regards industrialisation of research there are a number of initiatives. While there are no specific programmes focused on TERM under the auspices of Japan Science and Technology Agency (JST), individual projects linked to this field can be found, for example in the nanotechnology field, as well as projects dealing with technologies for cell and tissue engineering, or novel biomaterials.[105] For example, the "Regenerative Cell Therapy" project was funded by JST, 2000-2004. This particular project focused on the development of new regenerative cell therapies and associated analysis and monitoring procedures including advanced imaging technologies. The project was managed by the Foundation for Biochemical Research and Innovation - FBRI and involved both organisations from Kobe and elsewhere in Kansai.

Also, as the main goal of the METI-funded R&D is development of new technologies that may improve the competitiveness of Japanese industry, its focus has been mostly geared towards the "engineering" side of TERM and projects with a significant share of industrial involvement. While large companies from traditional sectors such as materials, steel, optics and electronics are participating actively, the financial support is especially important for SMEs. Total spending by METI in 2004 was EUR 11 million in various projects. One example of a project within the TERM area is the "Development of a Physical Function Substitute or Restoration System", with a total budget for 2004 of EUR 4.2 million, including the development of an artificial vision system, a totally implantable artificial heart for clinical use, biocompatible materials and technology assessment of biocompatible implant materials. The synthetic blood substitute project was given a EUR 2.2 million budget in 2004. There is also work on an automated large-scale system for cell/tissue culture under GMP conditions for TERM, as well as development of culture devices for cells and tissues under GMP standards for clinical use with a budget of EUR 3 million for 2004.

The regional development of the Kobe/Kansai region – the Kobe regenerative medicine initiative - is an important part of the research-orientated and industrial support to the TERM area in Japan. The development has mainly been supported by public spending and financial incentives for companies located in the Port Island area. In fact, the development of Kobe, including the Port Island, as a major cluster for biomedical industry involves giving generous benefits to companies establishing themselves there. The Kobe region has only limited previous industry in this sector. In 2004, around 70 companies had located to Kobe and 13 of these were foreign firms. These represent both large global corporations (GE, Schering) and smaller biotech companies, mainly from the Pacific Rim (US, Korea, Australia). The foreign firms are engaged in

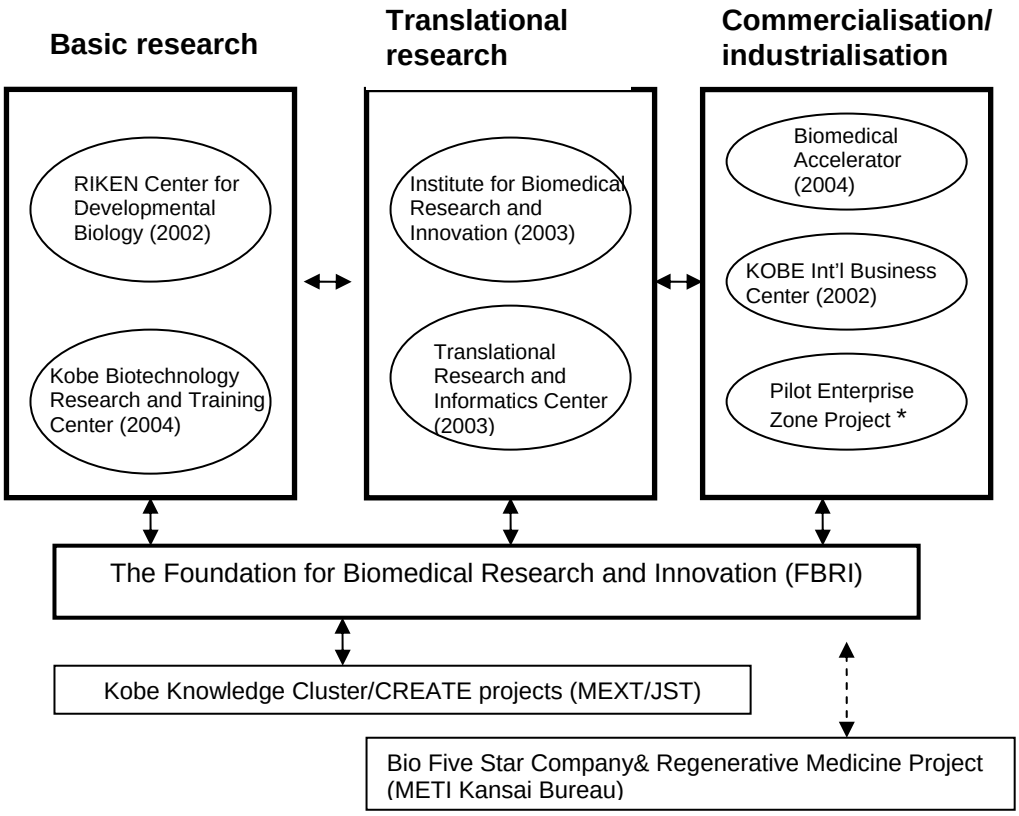
both R&D, manufacturing and production. Thus, to rapidly establish a new industry Kobe has chosen a comprehensive "entrepreneurial zoning regulation". This includes tax reduction on real estate and property (50% of normal), subsidies for job creation (up to JPY 1.2 million (EUR 7200) per position if a Kobe resident is hired), market surveys, office rental (foreign firms get extra subsidies), construction of facilities; monetary support including loans to stimulate firms' business setup – an 80% limit of a total investment of JPY 1-1.5 billion (EUR 6-9 million) for core facility, fixed interest loans etc., and interest subsidy on loans for construction of facilities.

One example of a specific initiative is the *Kansai Bio Five-Star Company & Tissue Engineering Project*, which is being run by the Ministry's Kansai Bureau and the non-profit Kinki Bio-Industry Development Organisation. It aims to strengthen regional innovation systems in several areas.[106] The project aims to create new industries and developing existing ones from the seeds of cutting-edge biotechnology research. It also encourages partnerships among private companies, public bodies and academia for the purpose of launching venture companies and developing global markets for small and medium-sized technology companies. The project works to link biotechnology projects conducted by biotech researchers, companies, institutes and local governments. Participants include nine local governments, 36 universities, 14 public research institutes, 20 business incubators and 24 investment funds, several TLOs, etc. According to official sources, 220 companies are taking part in the initiative but it is not clear if they all are active participants or not. The project's initiatives can be roughly divided into three categories:

- Facilitation of networking among biotech companies and researchers in Kansai (main focus at present)
- Data collection, provision of support for public assistance and facilities utilisation
- Linking of biotech institutes in Japan and overseas

Also, the *Kobe Medical Industry Development Project* is a comprehensive new investment for the development of the medical industry and in particular TERM. From an outsider's point of view, the goals are very bold when it comes to regional development and growth.[107] The initiative comprises a number of new facilities, investment funds, business support and incentives for enterprises.

Figure 5.1 Structure of the biomedical complex created in Kobe



Source: Fridén (2005).

In terms of physical infrastructure, the *Institute of Biomedical Research and Innovation*, IBRI,[108] is the central facility of the Port Island development. It is described as a core facility for bridging the gap between basic research and clinical application. The three main areas of IBRI are research and development of medical equipment, clinical applications of TERM and support for clinical research into pharmaceutical products (clinical trials). This "translational research" centre occupies a 20,000 m^2 building housing both research labs and a clinical department; a sort of advanced "mini-hospital" with 60 beds. Furthermore, the Institute also houses the "Cell Processing Centre" (CPC) for tissue engineering. The CPC is a specially designed laboratory to facilitate R&D and manufacturing of medical products, tissue and organs based on human cells. One of the CPC's main roles is to support the application and industrialisation of TERM and for this purpose, the labs complies with GMP standards required for clinical research. Part of the CPC facility is rented out to private companies and there are currently four cell processing labs. Candidate cells and tissue engineering products developed by AIST RICE (former TERC), RIKEN CDB or other public or private organisations are propagated at the CPC

before going into clinical trials/applications. Companies utilising CPC are Kirin Brewery (hematopoetic), Olympus Corp. (bone), Terumo Corp. (myocardium) and ArBlast (alveolar bone). An important area is the development of new biomedical imaging techniques. IBRI therefore hosts facilities with state-of the-art medical imaging (and radiation treatment) equipment, such as PET, CT-Linac and MRI.

Another initiative is the MEXT-supported *Clinical Research Informatics Centre* (Translational Research Informatics Centre, TRI), started in 2003 with four explicit aims:

- Supporting the clinical (practical) application of new areas such as TERM and genome-based medicine.
- Cooperating with local medical community to enhance early-stage diagnosis and efficient treatment of, say, lifestyle-related diseases for the citizens of the region
- Planning and managing genome analysis and clinical trials, including data management and evaluation
- Promoting the creation of bio-ventures and supporting the development of existing medical ones. This part involves development of novel methods of data analysis and management (such as clinical data, post-genomics medicine) as well as human resources development (training).

The Kobe Biotechnology Research and Human Resource Development Centre (Kobe BT Centre) opened in 2004 and is also supported by MEXT and operated in association with Kobe University. The main focus is on training and research in the biotechnology areas. The research activities presently involve three groups, including regenerative medicine-related research (scaffolds). The research groups come from Kobe and Kyoto Universities. Training courses in biotechnology, biotech-medical engineering, bioinformatics and clinical genome informatics are also given. Kobe University Incubation Centre (located in the same building as Kobe BT Centre), is a facility established by Kobe University to support venture businesses created by their faculty and/or students.

The so called *Knowledge cluster initiative* was started by MEXT in 2002 with the aim of developing internationally competitive, knowledge intense, regional innovation systems.[109] The clusters are centred on local universities and public research institutes with the cooperation of regional government and R&D-based industry. One of the projects, Kobe Translational Research Cluster, is almost entirely focused on TERM and several other knowledge cluster projects have some activities relating to this field. Thus, on an overall level, the Kobe Translational Research Cluster aims to create a life sciences super-cluster in the Kansai region, involving industry, academia and institutes.

Inaugurated in June 2004, the *Biomedical Accelerator* (BMA) is a business support facility for Kobe. The BMA also functions as a core facility of the Kobe Medical Industry Development Project to assist bio-ventures and companies in industrialising their research findings. Facilities include rental laboratories for general biotechnology and cell culture (GMP), an animal facility and imaging equipment (MRI). Kobe Healthcare Industry Development Center (HI-DEC) is an incubator providing support for and leasing business facilities to small and medium-sized venture companies and university professors developing novel technologies and products. There is also the Kobe International Business Center that has an important role in inviting foreign firms and Kobe International Business Center (KIBC), an "incubation centre" for foreign firms.

As regards financial support, the mission of Kobe Biomedical Venture Fund is to support venture business in biotechnology, medicine and healthcare in seed, early and middle stages of development. The appraisal of investment objects is done in cooperation with the Foundation for Biomedical Research and Innovation (FBRI) through a technology assessment committee and the investors include several large banks and financial institutes, biomedical companies and local/regional government through FBRI. The funds totalled JPY 6.3 billion (EUR 38 million) in 2004.

There is also a set of networks and platforms aimed at facilitating the regional development. For example, the Kansai tissue (engineering) initiative – kTi - is an organisation for mutual information exchange and cooperation established to build liaisons among researchers involving tissue and cell engineering in the Kansai region. kTi consists of researchers from major research institutes in Kansai.

Despite all these schemes, it will still be a challenge to get the traditional industries of steel and materials, mechanical manufacturing and shipbuilding to benefit from the large-scale initiatives. In METI's "Nakagawa Report", named after the government minister who commissioned it, high-tech areas like nano and biotechnology are envisioned to act as an engine in the development of traditional industry. In Kobe, initiatives to engage SMEs from traditional industrial areas in the development of medical technology have attracted some attention from local industry. In 2005, the Kobe Machinery & Metal Firms Association, in collaboration with the Institute of Biomedical Research and Innovation, Kobe University and Kobe City College of Technology had engaged 73 companies in a total of 28 projects. Achievements include: Non-magnetic surgical instruments (for use in open MRI); container for radionuclide made of acrylic resin; positron probe (for detection of tumours); measurement system for radiation levels in blood for PET/SPECT. These products (or prototypes) are not for a mass market and the value of the participating

businesses may be limited for some time to come. Efforts have been made to expand onto an international market, which is sometimes a new concept for these companies, having previously acted as subcontractors for large corporations.

Clearly, the methods and models used in Japanese S&T and industrial policy, with a detailed plan of highly focused initiatives, has a long history in Japan. This was the hallmark method of the former Ministry of Industry and Trade, MITI (now METI). In the more internationalised economy with more focus on a global knowledge intensive market, the top-down implementation may not always be sensitive enough to rapid changes in markets and technologies. Furthermore, local strengths and weaknesses may not be appropriately addressed if decision-making is centralised. In fact, although the Kansai area has a very strong life science base in both research and industry, Kobe lacks an industrial tradition in the biomedical areas. A real challenge for Kobe will be to attract the required human resources and competencies, both from Japan and internationally, in order to develop a sustainable and competitive cluster both from a scientific and a business perspective.

5.3.3 University and institute-based research in Japan[110]

As has been apparent in the above presentation of Japanese government initiatives (section 3), there are a number of strong research groups and environments in Japan, some of which will be highlighted in this section. In 2004, the *RIKEN Centre for Developmental Biology* (CDB) in Kobe led by Professor Masatoshi Takeichi had 29 laboratories, including seven research groups, 20 research teams and two support labs. An important feature of the Centre is the rather "flat" organisation (by Japanese academic institute standards) where relatively young scientist are promoted as group leaders. Several of the leading scientists at the Centre are from Kyoto University and links with other Kansai area universities are also strong. The Centre has also made it a key strategy to recruit internationally. Generally, the CDB's research is focused on understanding the basic mechanisms of differentiation and development. Several groups focus on stem cell biology, of both embryonic and adult origin. The main research areas of the institute are mechanisms of development and regeneration and clinical issues. Professor Shinichi Nishikawa at RIKEN CDB is also project director of the ten-year project "Realisation of regenerative medicine". The programme is divided into three sub projects. One is a stem cell bank organisation, involving a system for collection, storage and distribution of human stem cells used for research purposes. The two main sources of cells are blood stem cells from umbilical cords, collected and stored at five different sites and human neuronal stem cells, collected by Keio University. The stem cell

bank is coordinated from the Institute of Medical Science, University of Tokyo and involves research centres and hospitals from different areas of Japan.[111] Another project is the stem cell technology development project, coordinated by Professor Yoshiki Sasai of RIKEN CDB in Kobe and focusing on elucidating the basic mechanisms of stem cell biology in order to extend the future possibilities of regenerative medical treatment.[112] Finally, there is the project for development of clinical applications based on stem cells, as coordinated by Professor Hideyuki Okano at Keio University, Medical School.[113] The focus of translational research is to develop therapies for conditions such as spinal cord injuries, retinal diseases, vascular diseases, diabetes, inner ear injuries etc. Research includes establishment of omnipotent stem cell lines, control of stem cell specialisation, blood stem cells, etc.

A leading research centre at the University of Tokyo is the Center for Experimental Medicine at the Institute of Medical Science, where Professor Nakauchi is head of the Laboratory of Stem Cell Therapy. He has long worked on hematopoietic stem cells and strives to understand cells' self-renewal processes. He is also the leading Japanese researcher in terms of publishing in the field of stem cells. Another interesting research theme at the University of Tokyo is Organ Regeneration. This was started in March 2004 under an initiative to promote international scientific cooperation, and involves collaboration between Professor Makoto Asashima, Graduate School of Arts and Sciences at the University of Tokyo and Professor Douglas Melton, Howard Hughes Medical Institute, Harvard University. The Japanese side uses a unique method to study the organogenesis of heart, liver and eye using undifferentiated cells in vertebrate models (mainly amphibians), whereas the US side studies regeneration of various complex organs such as the pancreas.

Also, at the *Tokyo Institute of Technology*, the Department of Biomolecular Engineering is researching technologies for regenerative medicine and interesting work relating to cancer research in biomaterials has been conducted by such people as Professors Tagawa and Akaike. The late Professor Hirai at the Cell Therapy and Transplantation Medicine, *University of Tokyo Hospital* worked on stem cell transplantation for pancreatic cancer and haematological diseases. In fact, there is also a rather large division of tissue engineering researchers at the University of Tokyo Hospital which functions as a translational research centre and aims to reach clinical applications within a few years. Based on work with human embryonic stem cells, the focus is on corneal, vascular, renal, bone and cartilage regeneration. There is work in such areas as clinical applications of a new scaffold material and use of cord blood for renal regeneration.

At *Tokyo Women's Medical University*, the Institute of Advanced Biomedical Engineering & Science conducts research directed at the fields of biomaterials, artificial organs, tissue engineering and regeneration, drug delivery systems (DDS), genetic medicine and advanced surgical techniques.[114] The Institute also hosts a 21st Century COE, the Center for Tissue Engineering and Regenerative Medicine. This is led by Professor Teruo Okano, one of the leading figures in regenerative medicine and founder of one of the new venture companies, Cell Seed.

Nagoya University hosts one of the Japanese pioneers in regenerative medicine, Professor Minoru Ueda at the Department of Oral and Maxillofacial Surgery, Postgraduate School of Medicine.[115] His research focuses on tissue engineering related to maxillofacial surgery and dentistry. Professor Ueda has also been heavily involved in research cooperation with industry and is co-founder of several venture companies based on his research (for example, J-TEC, ArBlast).

Kyoto University has a strong programme in regenerative medicine, both in basic and clinical science. Firstly, the Institute for Frontier Medical Science, Kyoto University was established in April 1998 and aims to regenerate tissues and organs. With RICE and the facilities in the Kobe Medical Industry project, it is probably among the largest centres for regenerative medicine in Japan.[116] A number of fields are integrated under the auspices of the institute, including medicine, developmental biology, cell and molecular biology and engineering (including biomaterials) and the research covers a wide range if models, technologies and diseases. The director is Professor Norio Nakatsuji, one of the leading stem cell experts in Japan. Secondly, at Kyoto University Hospital the Center for Cell and Molecular Therapy focuses on clinical application or cell therapy and regenerative medicine. One main activity is running the cGMP facility for cell and tissue culture and the Centre was involved in the first successful pancreatic islet transplant from a living donor.[117] Thirdly, the Translational Research Center runs several projects in regenerative medicine, including liver, retina, pancreatic beta-cells and cardiac stem cells. Project directors are usually invited from the outside and the Centre provides space, lab staff and expertise in clinical trials.[118] Fourthly, under the 21st Century COE Programme, the Center for Integration of Transplantation Therapy and Regenerative Medicine aims to constitute a regional centre of excellence for the education of young investigators, such as graduate students and post-doctoral fellows. The project management team includes several leading transplantation and regenerative medicine professors at Kyoto University (and Hospital). The programme leader is Professor Koichi Tanaka, a well-known transplantation surgeon. Fifthly, it is also interesting to note that the researchers from Kyoto University have an influence throughout Japan, with

several of the leading figures at RIKEN CDB being from Kyoto University, including the director.

An interesting research centre is *RICE,* focusing on the understanding of the functions of cells and tissues. Examples of research areas are bone and cartilage regeneration, neural cell culture and new biomaterials. In order to develop technologies that can be used commercially, they often partner with different companies. RICE is expected to play an important role in the development of the Kansai region into an internationally competitive hub for TERM in Japan. There are seven research groups, all related to the TERM area and dealing with tissue engineering, cell operation, neuronics, cell dynamics, the artificial cell, biomolecular engineering and functional proteins.

At *Keio University*, there is a designated 21st Century COE headed by developmental neurobiologist Professor Hideyuki Okano. It focuses on basic study and clinical application of human stem cell biology and immunology and works on approaches based on the development of experimental animal models.[119] Activities within the regenerative medicine section include development of stem cell isolation and culture technology and elucidation of the basic biological properties of stem cells, stem cell biology research using disease models, establishment of preclinical testing and maintenance of a cell processing centre. Professor Okano also participates in the Leading Project for Realisation of Regenerative Medicine.

The National Cardiovascular Center in Osaka is an example of a national medical centre involved in TERM. It has a larger programme in the field, mainly focusing on heart muscle and blood vessel regeneration and combining hospital and medical research facilities.[120] *Osaka University* is also one of the leading medical research institutes in Japan and pursues activities in regenerative medicine in several departments. Professor Ryuichi Morishita at the Department of Medicine, Division of Gene Therapy Science is a renowned researcher and entrepreneur in Japan. Research includes some aspects of regenerative medicine and his research into growth factors has been spun off as a company, AnGes MG. The company was the first biotech company to have a successful IPO. He is also a leader in the development of the Osaka region life science industry and serves as an expert on government panels.[121]

There are also a number of other national institutes. The MEXT-supported National Institute for Material Science (NIMS) under the leadership of Professor Tsukuba pursues R&D relating to biocompatible material, scaffolds and regenerative medicine. There is ongoing research cooperation between NIMS and Professor Bengt Kasemo at Chalmers University of

Technology.[122] Also, the R&D Centre for Artificial Skin at the School of Allied Health Sciences at *Kitasato University* in Kanagawa started research and development of artificial skin in 1985. The culture skin developed at the Centre is manufactured and transported to 30 university hospitals in Japan.[123]

Two additional examples of Century COE programmes are firstly, Professor Susumu Ikehara's group at Kansai Medical University, working on a novel strategy for the treatment of intractable diseases, from animal models to humans and combining cell therapy and transplantation research (Century COE programme). The second is the Cell Fate Regulation Research and Education Unit at Kumamoto University, studying organogenesis and stem cell differentiation and led by Professor Tetsuya Taga at the Institute of Molecular Embryology and Genetics – IMEG.

5.3.4 Breakthrough in iPS cell research attracts political attention

In November 2007 two research groups, one at Kyoto University and the other at University of Wisconsin, reported breakthroughs in stem cell research.[124] Both groups had managed to reprogram ordinary human skin cells into stem cells which in turn could be differentiated into numerous types of cells, including nerve and heart cells, in a fashion similar to that of embryonic stem (ES) cells, but without the ethical concerns associated with the latter. In both cases, the reprogramming was accomplished through the insertion of only four genes, two of which were the same, using retroviruses as carriers. The term for stem cells produced in this way is induced pluripotent stem (iPS) cells. While a vast number of problems remain to be solved before iPS cells could be used for therapeutic purposes, applications in drug discovery and toxicology are thought to be feasible in the near future. Scientists are hoping it will be possible to avoid the use of viruses for gene insertion, and instead switch on the few crucial genes by influencing gene regulation in the cell through insertion of fitting small molecules.

The breakthrough in iPS cell research has energised stem cell research internationally and caused many stem cell scientists to focus on iPS cell research.[125] Not surprisingly, the fact that a Japanese group crucially contributed to the breakthrough has also created great excitement in scientific as well as political circles in Japan. Professor Shinya Yamanaka, leader of the group at Kyoto University and a very modest person, has become something of a national hero.[126] In terms of medical therapies and commercial gains for Japanese industry, it seems that unavoidably high expectations of future results have been created. The pressure on both scientists and policymakers to ensure that Japan is reaping the benefits of its initial leading position in iPS cell research is therefore great.

The Japanese government reacted very rapidly to the breakthrough by Professor Yamanaka and his group.[127] Budgets for iPS cell research were

drastically increased. Some adjustment seems to have already been made for the final months of the fiscal year 2007 (to end of March 2008), but the main increase came in the budget for fiscal year 2008. In this year, the national "project for realisation of regenerative medicine" entered its second five-year period and as a result of the excitement over iPS cell research the budget was increased from JPY 970 million in FY 2007 (8 M€) to JPY 2 billion in FY 2008 (20 M€).[128] The increase corresponded more or less to a new part of the project specifically supporting iPS cell research. The largest part was used for funding core centres of excellence at Kyoto University, University of Tokyo, Keio University and RIKEN Center for Developmental Biology (CDB). The Principal Investigators for the iPS centre grants at each of these centres are Professor Shinya Yamanaka, Professor Hiromitsu Nakauchi, Professor Hideyuki Okano, and Dr. Yoshiki Sasai. Each organisation receives between JPY 100 and 500 million per year over five years (0.84-4.2 M€). An additional 11 grants of JPY 10-50 million per year were awarded to other universities or research institutes.[129][130] One, divided among four organisations, concerns the development of a stem cell bank for research purposes. Five projects involve the development of technology for manipulating iPS and other stem cells. Another five projects focus on research for the development of therapies for specific diseases.

To promote iPS cell research, Kyoto University established the Center of iPS Cell Research and Applications (CIRA) in January 2008 with Professor Yamanaka as its Director.[131] CIRA forms part of the Institute for Integrated Cell-Material Sciences (iCeMS) which was set up as recently as October 1, 2007. [132]

Even before iPS cell research helped reinvigorate research into the stem cell and regenerative medicine fields in Japan, the establishment of iCeMS represented a boost to the field. It is one of five centres, two of which are in the life sciences, under the World Premier International Research Center (WPI) Initiative launched by MEXT.[133] Their purpose is to become truly world top-class research centres capable of attracting the very best scientists from all over the world. A stated target is that each centre should have at least around 30 highly recognised principal investigators and around 30% of these from outside of Japan. In total, a research centre may have around 200 researchers. An additional requirement is that the WPI-centres are to be given a high degree of autonomy and be allowed to experiment with new types of management structures and employment practices. The expectation is that any organisational innovations created in the centres will gradually affect the entire host university and possibly others too.

In FY 2008, the special funding of the five centres amounted to a total of JPY 7.1 billion (60 M€), which translates into an average of JPY 1.42 billion per centre (12 M€). As is common practice in Japan, salaries for university teachers employed by the host university as well as many other expenses will be covered by the basic funding of the universities. However, salaries for researchers newly recruited to the centre from outside may be covered by the centre grant. The centres are established for an initial period

of 10 years with a possible extension of another five. The research agenda for iCeMs is much broader than iPS cell research or stem cell research more generally. It aims to create "the science and technology of meso-control, based on the atomic and molecular interactions occurring in the scale of 5-100 nm, as the cells have designed themselves during evolution". However, the fact that iPS cells are very much at the core of the institute's activities is evident in the statement that "the key cell paradigm at the iCeMS is pluripotent stem cells."[134]

Another major new initiative, launched in response to the breakthroughs by Professor Yamanaka and others, was two new competitive research programmes started by Japan Science and Technology Agency, both starting in 2008. The programme "Fundamental technologies for medicine concerning the generation and regulation of induced pluripotent stem (iPS) cells" under the CREST framework provides grants amounting to JPY 150-500 million over five years. "Understanding life by iPS cells technology" is a PRESTO programme, which gives grants of JPY 30-40 million over three years to individual young investigators.[135] Ten grants were awarded in each category in April 2008.[136] The total budget for the two programs was JPY 700 million for FY 2008. In addition, a special grant of JPY 300 million per year (duration not certain) was given to Professor Yamanaka.

From the very beginning, government policies have stressed the need to effectively utilise the leading position in iPS cell research which Japan has achieved through the work of Professor Yamanaka and his group, for the development of practical applications and associated commercial developments. On June 25, 2008, a new company was formed, iPS Academia Japan. Its purpose is to manage patents and other intellectual properties relating to iPS cells, initially those produced at Kyoto University but perhaps later also including IPR from other research organisations in Japan.[137] Patent specialists were dispatched from JST to Kyoto University at an early stage. Likewise, the Japanese Patent Office (JPO) has been engaged in providing services such as analysing the global development of patenting and scientific publications in the iPS cell research and related fields.

MEXT has taken the initiative to create an "all Japan network" of research groups working on iPS cells.[138] Researchers and research organisations becoming members of this network have to sign an agreement concerning the handling of IPR. The basic principle is that intellectual property created by members of the network shall be made available free of charge inside the network for research purposes. One of the ideas behind creating the network has been to make it possible to manage IPR in a comprehensive and integrated way across a growing number of Japanese research organisations involved in iPS cell research. Distribution of iPS cells is one issue that would be facilitated by common principles for Material Transfer Agreements (MTAs) among the members. Whether the network has actually materialised or not according to the intentions expressed in various policy documents is unclear as there does not yet seem to be any public website for the network.

The first clear sign of involvement of Japanese industry in the development of iPS cell technology and its applications came through the announcement of a new five-year cooperative project between the four core iPS cell research centres and three companies: Astellas Pharma, Takeda Pharmaceutical and Shimadzu. The project is one of 24 selected "advanced medical development special zones" announced by MHLW on 18 November 2008.[139] Under the scheme relevant ministries and agencies are supposed to combine their various instruments, including regulatory measures, to support development projects carried out jointly by leading research groups and companies in Japan in a particular field. Another six of the 24 selected projects also concerned regenerative medicine.

Although the recent discussions in Japan concerning iPS cell research have tended to focus on exchanges among Japanese actors, foreign research organisations and companies certainly will not be totally excluded. The extent to which Japanese organisations will be favoured over foreign actors remains to be seen. Clearly, one objective of government policy is to utilise the strong research position which has been achieved to promote the development of Japanese industry. On the other hand, it should be pointed out that CIRA at Kyoto University (the core centre of iPS cell research in Japan) is a part of iCeMS and, with four other WPI-centres, is supposed to lead the way in showing the world how Japanese research can be fully integrated in the global and open system of science. How this balancing act will work out will be very interesting indeed to follow.

5.4 National initiatives in the US

5.4.1 Major initiatives in the US

Cumulative federal investment in TERM from 1988 to 2001 amounted to about USD 250 million (EUR 174 million),[140] but as shown below the level of financing has boomed in later years. In fact, as was noted as early as 2002, moving "from a few modest NSF grants in the mid-1980s, followed by major funding from NIH and NIST, the field has spawned a burgeoning industry that has enjoyed over USD 3 billion in funding over the past decade, much of it from private sources".[141] Even though it is true that many countries see the US as a pioneer in the field, according to a report by the *Department of Health and Human Services* further product development in TERM has been hindered by a lack of fundamental research in TERM; a form of research not undertaken by the private sector. Another problem identified is the isolation of the different scientific fields working with TERM research such as biologists, clinicians, engineers, biochemists, materials scientists and other related fields. TERM is a field requiring cooperation and communication among these different disciplines. This problem has been addressed by the establishment of a so called 'roadmap' by the National Institute of Health (NIH) and the *Multi-Agency Tissue*

Engineering Science (MATES) working group.[142] In fact, the NIH developed such a roadmap for medical research in order to cope with the high levels of complexity connected to biomedical research in general. The purpose of the roadmap was to identify the major opportunities and gaps in biomedical research that "no single institute at NIH could tackle alone but that the agency as a whole must address, to make the largest impact on the progress of medical research".[143] A key focus was on removing disciplinary barriers and enable cooperation. The roadmap did not have a particular focus on TERM research but several of the topics included related research.[144] A key part of the national strategy was the establishment of the above-mentioned *Multi-Agency Tissue Engineering Science* (MATES) *Working Group,* involving several of the federal agencies in tissue engineering and enabling them to "stay informed of each other's activities and coordinate their efforts in a timely and efficient manner".[145] Accordingly and in keeping with similar efforts in other fields, the MATES working group is a key tool in avoiding wasteful duplication of efforts and achieving a balanced portfolio of research activities. The MATES is a key forum where different agencies negotiate regarding strategic funding decisions on TERM.[146]

Another important strategic initiative is the *National Tissue Engineering Center* (NTEC) as established by the US Congress in order to design and deliver regenerative tissue engineering therapies to the *Department of Defense* and to assist in the development of a national tissue engineering strategy. NTEC is administered by the *Pittsburgh Tissue Engineering Initiative* (PTEI), founded by Peter Johnson in 1994. PTEI started as a loose network that funded various activities to generate support for tissue engineering research in the Pittsburgh area. These were technology development grants, summer research internships, biotech exposure and a guest speaker programme. PTEI has also supported the establishment of a group of firms and as such the Pittsburgh area has become a key node.

Several federal agencies have been involved in providing financing to the TERM field: NIH, the National Science Foundation (NSF), the National Institute of Standards and Technology (NIST), National Aeronautics and Space Administration (NASA), the Department of Defense (DOD), the Department of Energy (DOE) and the Department of Veterans' Affairs (DVA). There are several different estimates of the total financing and these vary in terms of definition of the field. In estimating the financing of tissue engineering from 1993-2000 (Table 5.1), the conclusion is that the total federal funding was approximately USD 108 million (EUR 75 million), with the share of NIH funding totalling 62%. In that analysis, tissue engineering was defined in a narrow sense, excluding such things as gene therapy/gene transfer, scaffolding, cell culturing, cell adhesion, DNA delivery, stem cell

technology, functional tissue engineering (such as mechanical properties of tissues) and tissue preservation.

Table 5.1. Research 1993-2000, from different agencies [USD 1,000s, rounded]

	1993	1994	1995	1996	1997	1998	1999	2000
NIH	2,317	3,892	9,519	13,259	5,625	16,761	6,797	8,917
NSF	588	1,218	1,364	934	1,858	4,429	6,421	5,993
NIST	0	0	620	0	3,612	2,454	2,749	600
NASA	0	0	1,033	1,274	1,394	776	1,147	496
DOE	0	0	0	0	0	0	0	50
DVA	0	135	295	89	204	340	449	388
DOD	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
TOTAL	**2,905**	**5,244**	**12,831**	**15,557**	**12,693**	**24,760**	**17,563**	**16,445**
NIH share (%)	79.8	74.2	74.2	85.2	44.3	67.7	38.7	54.2
NSF share (%)	20.2	23.2	10.6	6.0	14.6	17.9	36.6	36.4

Source: Viola et al. (2003).

Another calculation focuses on NIH funding only, as the single largest federal financing agency. It supports research in its own laboratories as well as research by scientists in universities, medical schools, hospitals, research institutes and abroad. The research areas are cut differently compared with the above table on tissue engineering and relate to regenerative medicine and stem cell research respectively. Between 2003 and 2009, NIH estimates a total funding of USD 4,083 million for regenerative medicine and USD 4,290 million on stem cell research (see Table 5.2).

Table 5.2. NIH funding for Regenerative Medicine and Stem Cell Research, 2003-09 [USD millions, rounded].

	2003	2004	2005	2006	2007	2008	2009	2003-2009
Regenerative Medicine	570	585	591	614	575	574	574	4,083
Stem Cell Research	517	553	609	643	657	656	655	4,290

Source: NIH (2007a) (Note that figures for 2008 and 2009 are estimates from NIH).

Interestingly, within the stem cell area the largest share of research is devoted to non-embryonic research and there is also proportionally greater focus on non-human stem cell research (see Table 5.3).

Table 5.3. NIH funding for various types of Stem Cell Research, 2004-09
[USD millions, rounded]

	2004	2005	2006	2007	2008	2009	Total 2004-2009
Human Non-Embryonic	203	199	206	203	203	203	**1217**
Non-Human Non-Embryonic	236	273	289	306	305	306	**1715**
Non-Human Embryonic	89	97	110	106	105	105	**612**
Human Embryonic	24	40	38	42	42	41	**227**
Involving Umbilical Cord Blood/Placenta	19	18	19	22	22	22	**122**
Involving Umbilical Cord Blood/Placenta -- Human	16	15	16	19	19	19	**104**
Involving Umbilical Cord Blood/Placenta -- Non-Human	3	3	4	2	2	2	**16**

Source: NIH (2007a) (Note that figures for 2008 and 2009 are estimates from NIH).

The National Cancer Institute is part of the NIH and makes agreements for the purpose of creating interaction between its own scientists and university researchers. Another key institute of the NIH is the *National Institute of Biomedical Imaging and Bioengineering* (NIBIB). This focuses on the development of biomedical technologies and integrating the physical and engineering sciences with the life sciences to advance basic research and medical care. The different research programme areas include biomaterials and tissue engineering. In 2006-2007, NIH announced eleven different grants relating to TERM.[147]

Another key player in the US research system is the *National Science Foundation (NSF)* which is responsible for 13% of federal biomedical research. The NSF Directorate for Engineering plays an important role in the field of TERM, having provided support to a broad range of players and programmes. In the period 1998-2001 a total of 92 awards for TERM were funded.[148] [149] The largest share was in the form of awards supporting three centres: The Georgia Tech/Emory Center for the Engineering of Live Tissues, the University of Washington Engineered Biomaterials (UWEB) ERC and MIT's Biotechnology Process Research Center (BPEC). Another major share of the funding was given as awards for individual investigator research. The third largest share went to career development awards.

As regards the NIST, it generally targets the development of standards, measurement and technology and relates to TERM in at least three ways. Firstly, NIST engages in improved technologies for quantitative measurement methods in biological samples, such as tissues and cells. Secondly, another responsibility of NIST is technologies for cell, tissue and medical imaging. Thirdly, within the Advanced Technology Programme there is a sub-programme focused on tissue engineering, with 26 active or

completed projects involving EUR 36 million (USD 51.1 million) in ATP funding.[150] [151]

NASA also has two units involved in TERM: the NASA/NIH Center for Three Dimensional Tissue Culture and the Biotechnology Cell Science Program. The NASA/NIH centre uses the technology of NASA's rotating wall vessel bioreactor to facilitate mutual leverage of research across agencies. It thus provides facilities for scientists to launch pilot projects using the bioreactor, as well as continuing those projects with small grant proposals.[152] The NASA Biotechnology programme focuses on the effect of space and planetary environment stressors on humans on the cellular and tissue levels and the selective pressure of space on cells and tissues that have evolved in the 1G environment of Earth.[153]

In addition to federal financing, several foundations and philanthropists also act as key sources of funding for TERM research, particularly embryonic stem cell research. Table 5.4 aims to capture the majority of such private donations and shows a total of USD 200 million (EUR 130 million) in 2006. For example, the *Whitaker Foundation* supports TERM research through a series of grant programmes in biomedical engineering at various academic institutes in the United States and Canada. One of the key activities related to TERM has been the establishment of the *Whitaker Institute for Biomedical Engineering* at UCSD, with tissue engineering as a main focus area.

Table 5.4. Overview of private donation for TERM in 2006 [USD millions].

Donor	Sum	Recipient	Field
The Whitaker Foundation	n.a.	Universities & institutes	Biomedical Engineering
Michael Bloomberg	$100 m	Johns Hopkins University	Stem cell research
Tashia and John Morgridge	$50 m	The University of Wisconsin	Interdisciplinary research centre on stem cell research
15 California philanthropists	$46 m	CIRM	stem cell research
Li Ka Shing Foundation	$40 m	The University of California, Berkeley	Stem cell biology, in June 2005
Eli Broad	$25 m	University of Southern California	New research facilities
Dagmar and Ray Dolby	$16 m	UCSF Institute for Regeneration Medicine	RM
Sue and Bill Gross	$10 m	UC Irvine	Stem cell research centre
The Kozmetsky family	$1 m	The Burnham Institute for Medical Research	ALS studies involving stem cells

Source: CIRM (2006) and The Whitaker Foundation (2007).

5.4.2 The specific situation for stem cell research

There has been a particularly vibrant and polarised debate on the regulation of stem cell research in the US. On the national level, a milestone in the position of the US was the 1995 law signed by President Clinton, restricting federal funds from being used for embryonic stem cell research in which embryos were created or destroyed. This law is further strengthened by the restriction on federal funds for research into existing available stem cell lines, as presented by President Bush and the Bush veto in 2006 of a suggested change to the restrictive 1995 law. As an alternative to the hES, federal funding of USD 350 million (EUR 250 million) was channelled into research on adult and xenogenic stem cells between 2001-2006.

On the state level, some have contested the federal laws. California has been an active opponent to the Clinton/Bush law. As early as 2004, there was a suggestion under the name of Proposition 71 to allocate USD 3 billion (EUR 2100 million) to human hES research over a 10-year period. Today, the largest funds for hES research are in California, with the California Institute for Regenerative Medicine providing USD 45 million (EUR 32 million) for research. The background and process on Proposition 71 is therefore of particular interest in understanding the TERM field in California and the US as a whole.

In essence, the California Stem Cell Research and Cures Initiative is legislation set up in 2004 to secure funding for hES research in California. The proposition includes USD 3 billion (EUR 2100 million) for stem cell research funding in California over a ten-year period and means that the right to do stem cell research has been added to the State Constitution. However, it is important to note that the Proposition also means funding for human reproductive cloning is forbidden and a ban on human reproductive cloning has been added to the California Constitution. The funding would come from the sale of general obligation bonds to a value of USD 3 billion, and would actually be paid back over a period of 30 years.

The result was that almost 60% of voters approved the initiative. Californians as such are more positive towards hES than the current administration. They believe that the potential of the technology far outstrips the increased costs inflicted on citizens and that the ethical issues are manageable. Still, the Proposition was highly controversial and characterised by lawsuits, obstacles from conservative lobby groups and support from state politicians and private financiers. In fact, during the period there were over 170 bills across the country related to stem cell research (both for and against).

The California Institute for Regenerative Medicine (CIRM) is the organisation in charge of the grant allocations. Their resources were stalled

by lawsuits from opposing organisations until mid-2007. CIRM is currently the largest source of funding for human embryonic stem cell research in the world. The size of the grants allocated are over USD 208.5 million (EUR 148 million) and, including the round scheduled for December 2007 amounting to USD 227 million (EUR 161 million), the total funding from CIRM will be over USD 430 million (EUR 306 million).[154]

In a way, the Proposition was designed to assure public and peer acceptance. For instance, it requires that research from the funds is conducted safely and ethically and within strict rules that protect patient safety, rights and privacy. The allocation of research funds is also to be distributed through a peer review process so that allocation is fair and effective. Furthermore, the public will be informed about the activities supported by the proposition and decisions will be made through audits, open meetings and public hearings.

Opponents of hES have continuously contested CIRM in court. The opponents of the Proposition have used economic as well as ethical and scientific arguments to prevent its passage. Firstly, it is argued that the USD 3 billion targeted at hES research will lead to an increase in bond debt on California's already immense debt burden. It is also considered wrong that they propose to support research with taxpayers' money which ultimately goes into the hands of big pharmaceutical companies and venture capitalists. However, advocates of the Proposition claim that hES research has the potential to reduce future healthcare costs to the State by several billion dollars as well as create new incentives in California's economy that will lead to the creation of new jobs and increased tax revenues. Secondly, the arguments from the opponents include a moral debate and the fact that hES is perceived as taking one human being's life in order to save another. The fact that hES is conducted on embryos that are 5-7 days old has triggered the opposition of different religious and anti-abortion groupings, including the Roman Catholic Church. President Bush, amongst others, supports this view and has successfully blocked any attempt of easing hES funding restrictions. Thirdly, opponents have claimed it is unnecessary to destroy human embryos as, they claim, adult and cord blood stem cells actually show greater potential in the treatment of diseases. This argument has its scientific pitfalls. Fourthly, the opponents claim that the Proposition would fund a huge, new bureaucracy whilst existing programmes for health, education and public safety are being cut. Thus, they argue, Proposition 71 and the funding of hES is not the most effective way to improve healthcare in California. Fifthly, the Proposition would mean that the public would have no insight into what was being funded. This is because grants under it are being recommended by a subgroup and not members of the bodies.

The Proposition has received support in California including from a large coalition of patient advocates and medical groups. [155] This comprises such bodies as the Juvenile Diabetes Research Foundation, the Christopher Reeve Paralysis Foundation, Children's Hospital of Los Angeles, former Secretary of State George Shultz, the California Medical Association, several Nobel Prizewinners and Governor Arnold Schwarzenegger. Support has also come from philanthropic bodies with the CIRM for example securing USD 14 million in bond anticipation notes purchased by six local philanthropic bodies. This was a direct action to secure that stem cell research in California would continue despite the delay created by legal action from opponents.

In the period to August 2007, grants of over USD 208.5 million (EUR 148 million) have been approved by the ICOC and in August 2007, CIRM launched their largest grants amounting to USD 227 million (EUR 161 million) that is available for the creation of new stem cell labs. [156] Calls were at the time of writing this report out for centres of excellence, faculty awards, training, etc.[157]

5.5 Sweden: Biomaterials and TERM

5.5.1 Major initiatives in Sweden

Swedish governmental agencies have not formulated an overall strategy and programme for the TERM area. However, TERM projects and centres are financed by public and private organisations through the general research and innovation funding system of Sweden as described below. Thus, funding of a few centres of excellence and one cluster in the field is currently in place. Also, quite a few TERM projects are given funding through grants to individual researchers. It is difficult to tell what share of the total grants to the TERM field in Sweden the mapping of funding below has captured and it is important to note that the funding listed does not include the basic funding that the research groups receive through the government grant to universities. Note also that the Swedish figures include the area of biomaterials; this was not the case for the other countries analysed.

In the light of the very recent Swedish research and innovation bill presented in October 2008, the overall situation for TERM may be changing. In this bill, stem cells and regenerative medicine was identified as one of 24 strategic areas.[158] It received an earmarked budget of SEK 65 million (EUR 6.5 million) corresponding to 3.6% of the total budget allocated to the strategic R&D investment areas planned for the period 2010-2012. Nevertheless, how the budget will be distributed and to what initiatives is still unclear.

There are three main funding organisations in Sweden involved in the TERM area: the Swedish Foundation for Strategic Research (SSF), the Swedish Governmental Agency for Innovation Systems (VINNOVA) and the Swedish Research Council. SSF was founded in 1994 with capital from the former wage-earner funds and founding capital of SEK 6 billion (EUR 600 million). The objective of SSF is to support research into natural science, engineering and medicine that strengthens Sweden's competitiveness. The SSF's Governing Board is appointed by the government and currently (spring 2008) some 20 strategic research centres and over 200 research projects are funded. Up to and including 2007, SSF has approved research support totalling about SEK 10 billion, of which SEK 2 billion has not yet been disbursed. VINNOVA is a state authority which finances needs-driven research and provides funding to develop effective innovation systems based on an interaction between academia, business and the public sector. The total annual budget of VINNOVA is about SEK 2 billion (EUR 200 million) and is used for many different types of programmes and initiatives including project grants to universities in collaboration with industry, financing to support SME R&D, centres of excellence and cluster development. The Swedish Research Council provides support for basic research in all academic disciplines through a peer review process and the total annual budget is about SEK 3.6 billion 2008 (EUR 360 million).

The project provided grants for *biomaterials* and *tissue engineering* research from these three organisations totalling about SEK 250 million (EUR 27.5 million) during 997-2005. This funding was supplied separately by the organisations through their normal processes of deciding what to fund. Of this SEK 250 million, two thirds was allocated to five selected research groups as presented in the table below (Table 5.5). In 2007, the research programme "Medical technology for better health" jointly financed by the Swedish Research Council, VINNOVA and SSF, funded two TERM-related projects. These were Professor Gatenholm's project for biosynthetic blood vessels and Professor Ramstedt's for new anti-bacterial surfaces; total funding of SEK11.4 million (EUR 1.3 million).

Table 5.5. Biomaterials and tissue engineering research funding from the Swedish Research Council, VINNOVA and SSF

University/City	Research area	Group leader	Amount SEK m (EUR m)
Chalmers University of Technology/Gothenburg	Chemical physics	Bengt Kassemo	70 (7.7)
Linköping University/ Linköping	Ortophedics	Per Aspenberg	35 (3.8)
Royal Institute of Technology/Stockholm	Biopolymers	Ann-Christine Albertsson	25 (2.8)
Chalmers University of Technology/Gothenburg	Biopolymers	Paul Gatenholm	20 (2.2)
Uppsala University/Uppsala	Clinical Immunology	Bo Nilsson	15 (1.6)

Source: VINNOVA, the Swedish Research Council and the Swedish Foundation for Strategic Research.

As regards *stem cell* research, the Swedish Research Council funded about 270 projects involving stem cell research during 2002-2007. The research teams which received the largest grants are presented below and their funding amounted to SEK 113 million (EUR 12.4 million). The corresponding listing from SSF totals SEK 21 million (EUR 2.3 million).

Table 5.6. Stem cell research funding from the Swedish Research Council (VR) and SSF

University/City	Group leader	Time period	Financier	Amount SEK m (EUR m)
Lund University /Lund	Patrik Brundin	n.a.	VR	30 (3.3)
Karolinska Institutet /Stockholm	Stein Eirik Jacobsen	n.a.	VR	25 (2.8)
Lund	Stefan Karlsson	n.a.	VR	13 (1.4)
Karolinska Institutet /Stockholm	Jonas Frisén	n.a.	VR	12 (1.3)
Uppsala	Rolf Ohlsson	n.a.	VR	12 (1.3)
Lund University /Lund	Olle Lindvall	n.a.	VR	11 (1.2)
Lund University /Lund & Gothenburg University /Gothenburg	Henrik Semb	n.a.	VR	10 (1.1)
Karolinska Institutet /Stockholm	Ernest Arenas	2001-2007	SSF	10 (1.1)
Karolinska Institutet /Stockholm	Jonas Frisen	2005-2008	SSF	5.5 (0.6)
Karolinska Institutet /Stockholm	Edward Smith	2005-2008	SSF	5.5 (0.6)

Source: The Swedish Research Council and the Swedish Foundation for Strategic Research.

In 2006, the stem cell research environments at Lund University and Karolinska Institutet were awarded a grant of SEK 20 million for a research programme on Parkinson's disease by the private Knut and Alice Wallenberg Foundation.

In 2007, researchers at Umeå University were rewarded a large research grant of SEK 77.5 million from the Swedish Research Council for a new laboratory in molecular medicine. The recipient of the funding, Umeå Centre for Microbial Research (UCMR), comprises researchers in microbiology, molecular biology, chemistry and physics. Research focused on conditions for hES cells (cell cultures, growth factors) to form insulin-producing beta cells.

In addition, SSF, VINNOVA and the Swedish research foundation funds research environments through different grants to centres of excellence, some with an emphasis on basic research and others including applied research and collaboration with industry. Supporting centres of excellence has increased in the Swedish research and innovation funding system but there has been no major shift towards this. For example, in 2007 the Swedish Research Council devoted 4% of its budget to centres of excellence. As described above, the strategies and selection processes of the three funding organisations differ somewhat and this is reflected in the selection of centres of excellence to support. The centres selected for funding by SSF in TERM-related fields totalled a funding of SEK 217 million (EUR 23.9 million). Their selection was based primarily on a peer review process of scientific excellence. Another important selection criteria was the added value the centre would give as opposed to individual project grants. Also evaluated in judging applications is the importance of the centre to industry and society. The Swedish Research Council selected TERM-related centres based on a peer review process of scientific excellence, but in this case the university management had to choose which centres were allowed to apply for centre funding. This implies that the choice of which exact areas would be supported had to be seen as strategic issue for the university as a whole. In total, the Swedish Research Council gave centres SEK 125 million (EUR 13.8 million) in funding for TERM-related fields. At the Swedish Governmental Agency for Innovation Systems (VINNOVA) the strategy has been to develop research and innovation environments where industry takes an active part in the development of the centre and, in evaluating applications, to choose research projects with the potential to contribute to economic growth. Different types of centres are funded by VINNOVA, and by VINNOVA in combination with other research funding bodies. The table below also lists TERM-related cluster initiatives and excellence centres funded by VINNOVA. The total funding of these centres was SEK 230 million (EUR 23 million), excluding Swedish Brain Power, to which VINNOVA contributes SEK 25 million.

Table 5.7 TERM-related centres funded by SSF, VINNOVA and the Swedish Research Council (VR)

University/City	Initiative	Time period	Financier	Amount SEK m (EUR m)
Karolinska Institutet /Stockholm	Development Biology	2003-2008	SSF	79 (8.7)
Lund University /Lund	Lund Center for Stem Cell Biology and Cell Therapy	2003-2009	SSF	59 (6.5)
The Royal Institute of Technology /Stockholm	Biomedical functional polymers	2003-2007	SSF	14.5 (1.6)
Chalmers Univ. of Tech. /Gothenburg	n.a.	2003-2007	SSF	14.5 (1.6)
Karolinska Institutet /Stockholm	Developmental Biology for Regenerative Medicine	2006-2016	VR	100 (11.0)
Gothenburg University /Gothenburg	Biomedical development in Western Sweden	2004-2014	VINNOVA	60 (6.6)
Stockholm University /Stockholm	EXSELENT - zeolites	2006-2016	VINNOVA	100 (11.0)
Gothenburg University + others /Gothenburg	BIOMATCELL - Biomaterials Structure Dynamics and Properties	2006-2016	VINNOVA	70 (7.7)
7 sites	Swedish Brain Power159	2006-2011	6 financiers	100 (11.0)

Source: The Swedish Foundation for Strategic Research, The Swedish Research Council and VINNOVA.

Other R&D financing to TERM-related fields include R&D financing in small and medium-sized companies provided by VINNOVA. Also, the Innovation Bridge, a government-owned body, funds researchers, innovators and entrepreneurs wanting to develop a commercial product or service. The aim of the organisation is to increase commercialisation and utilisation of research funded through the state research financing system and this is done by supplying funding to individual companies and start-up activities and funding the holding companies linked to the universities. Almi gives support to individual firms for financing and business development that complements the market and does not have to be linked to research-intensive or high technology ventures.[160]

5.5.2 University and institute-based research in Sweden

The Swedish university and institute-based research in the TERM field is essentially located in the larger cities with universities and research hospitals; Stockholm-Uppsala, Gothenburg and Lund-Malmö. However, important activities can also be found in other parts of the country.

At Umeå Center for Molecular Medicine (Umeå University) Professor Helena Edlund's group is a leading resource for pancreas developmental biology focusing on the regulation of the insulin gene promoter. Her group has been able to link obesity to high levels of insulin and blood fats, thereby suggesting ways to prevent type-2 diabetes and liver degeneration. Research funded by the Swedish Research Council on molecular medicine focuses on such things as the conditions for hES cells (cell cultures, growth factors) to form insulin-producing beta cells.

The Stockholm-Uppsala hub is the largest in terms of number of researchers involved in TERM, with the Karolinska Institutet (KI) as a main actor. In Swedish terms, the Department of Cell and Molecular Biology (CMB) is a rather large constellation of research groups with a staff of 250 people, working on the themes of molecular cell biology, developmental and stem cell biology, gene regulation, genome structure and integrity, as well as infection and cancer. It is mainly financed by external grants.

A prominent example of the efforts at KI is Professor Urban Lendahl's group, working on the control of stem cell differentiation. The lab concentrates on embryonic stem cells, myogenic progenitors and vascular smooth muscle cells. Professor Frisén's lab also studies the regulation of cell production, paying particular attention to the adult central nervous system. Professor Thomas Perlmann works collaboratively with Professor Johan Ericson on engineering stem cells into various cell types.

The KI Department of Medical Biochemistry and Biophysics (MBB) has previously hosted three Nobel Prizewinners and developed the gas chromatograph-mass spectrometer as well as working on compounds such as heparin and prostaglandins. Today, Professor Arenas and his group of twelve researchers focus on stem cell neurobiology and conduct work on neurogenesis as well as carrying out stem cell assays for drug development and cell replacement therapies (with hES, adult and neural stem cells) in Parkinson's disease. They aim to engineer surfaces that lead differentiation into neurons by involving nanobiology and bioelectronics. Likewise, Professor Ernfors' group studies survival and differentiation of sensory neurons, focusing on how external signals are coordinated with cell competence. Also, neurological research conducted by Professors Brodin, Ibáñez, Hermanson and Shupliakov at the Department of Neuroscience deals with the synapse, signalling mechanisms and the functions of growth factors and their receptors in the nervous system as well as the development and function of neural cells.

Complementary research is conducted by Professor Muhr at the Ludwig Institute for Cancer Research centring on the molecular processes underlying neuron development. Similarly, work on embryonic stem cells

and the nervous system is conducted at the Center for Genomics and Bioinformatics (at KI) where Professor Björklund and 23 researchers deal with genomics and pathways in the nervous system relevant to drug discovery efforts.

The goal of Swedish Brain Power is to improve early diagnostics, treatment and care for patients with neurodegenerative diseases. The initiative is headed by Professor Bengt Winblad, Karolinska Institutet and is intended to take research from bench to bedside by forming a network between pre-clinical researchers and clinical practitioners and the initiative includes research projects in covering tools for early diagnostics, evaluation of different treatment and development of treatment and care. The knowledge of neurodegenerative diseases created in this initiative can be useful for TERM application but TERM-related applications are not generated in the Swedish Brain Power initiative.

Forming a critical mass of researchers in the field, there is the newly formed centre of excellence 'Developmental Biology for Regenerative Medicine' (DBRM), where researchers from the above four KI departments are active. This centre focuses on developmental biology, stem cell research and neurobiology and aims to become a Swedish knowledge hub. Whereas the European research into developmental biology is led by the UK and Germany, Sweden is truly prominent in the field. In fact, Professor Urban Lendahl (KI) was ranked globally as the fifth most-cited researcher in developmental biology and had co-authored the article with the most citations, where Jonas Frisén (KI) is ranked 16th and Christer Betsholtz (KI) is 23rd.[161] The above centre was established in 2006 with a 10-year grant from the Swedish Research Council (over EUR 1 million per year for 10 years). Importantly, there is a wish to improve the collaboration with clinical science and practice and work interactively to enforce a rapid knowledge exchange in the evolutionary process between basic and clinical research. The centre consists of thirteen research groups, connecting, say, CMB with other departments, each led by a prominent researcher. Some of these were mentioned above (Professors Lendahl, Frisén, Perlman, Ernfors, Arenas, Brodin, Ericsson, Hermansson, Ibanez, Shupliakov, Simon, Muhr and Uhlén).

An important connection between fundamental research and clinical practice has been formed through the Karolinska University Hospital in Huddinge and the Uppsala University Hospital. This was achieved with the Department of Clinical Sciences, Intervention and Technology (CLINTEC), acting as a platform. Professor Ringdén also works with tissue response to transplantations and heads the Department of Laboratory Medicine with 350 employees which acts as a hub for such things as biobanks of biological samples. Connected to this is Professor Nilsson's work at Uppsala

University near Stockholm on penetrating blood and tissue in regard to materials biocompatibility. Professor Betsholtz's efforts at the Division of Matrix Biology (at KI) centre on the relationship between genes and vessel formation. Vital work on mesenchymal stem cell therapy and allogeneic hematopoietic stem cell transplantation is performed by Professor Katarina Le Blanc and her group at the Division of Clinical Immunology at the Karolinska University Hospital.

On the engineering side of TERM, Professor Elmqvist (Department of Laboratory Medicine, Karolinska Institutet) has had a leading role the development of such things as the pacemaker. Also, Professor Albertsson at the Division of Polymer Technology at the Royal Institute of Technology, designs and syntheses resorbable functional polymers for use in such fields as tissue engineering. At nearby Uppsala University a number of professors are also working on related issues: Karin D. Caldwell, Jöns Hilborn, Håkan Engqvist, Leif Hermansson and Maria Strömme. Amongst other things, they are modifying polymeric materials to be able to attach proteins and biomolecules, developing hydrogel-based materials, intelligent biomaterials and injectable gels as matrixes for tissue engineering, and analysing the bone-material interface and mechanisms of friction and wear. Also in regard to biomaterials, the EXSELENT Berzelii Center in Stockholm has some 40 chemists with different scientific specialties and is collaborating with companies in the pharmaceutical, foodstuffs, cosmetic and chemical industries. At the Centre, zeolites are developed. These are specially-designed small crystals with cavities tailored to size. Corporate partners include AstraZeneca, Biovitrum, Perstorp and Nobel Biocare. Today, the research has little to do with TERM but materials and structures developed may be of interest to TERM applications in the future.

Moving south of Stockholm, at Linköping University Professor Gunnar Kratz heads the Materials in Medicine group and focuses on reconstructive surgery using tissue engineering. On the biomaterials side of TERM, Per Aspenberg's group does research on the interface between bone and implant. Pentti Tengvall and Bo Liedberg's groups focus on surface analysis. The Tengvall group develops biomaterial model surfaces and studies their characterisation (physically/chemically) and in vitro surface biology.

One centre not included in the above tables but to some extent related to the TERM field is the research initiative OBOE Bioelektronik, headed by Professor Magnus Berggren. This initiative is focused on a multidisciplinary research area combining the research on organic materials at Linköping University with principal investigators such as Professors Forchheimer, Ingänäs, Konradsson, Nilsson and Ynnerman. It also connects to the

industrial research institute Acreo and the research into cell and molecular biology, neurobiology and stem cells at Karolinska Institutet.

Clearly, in terms of research areas, there are several groups throughout the country active in each of the fields, even if there are traces of regional specialisation. Gothenburg has long been considered the centre of biomaterials research, largely due to the efforts started with Professor Per-Ingvar Brånemark's groundbreaking work on osseointegration. Today, the Brånemark Osseointegration Center (BOC) cares for patients and expands osseointegration research to teeth, limbs and ears. The biomaterials research is also thriving in several other constellations. In fact, it might be said that the development and commercialisation of biomaterials relating to dental, orthopaedic and oral maxillofacial applications is rather successful in Sweden. The Department of Orthopaedics, with its staff of 73, hosts Professors Rickard Brånemark and Johan Kärrholm focusing on osseointegration and implant surgery. Also, Professor Tomas Albrektsson heads the Department of Biomaterials at Gothenburg University, working on orthopaedic implants, oral and maxillofacial reconstruction and surface science. He collaborates with the dental company Astra Tech on the analysis of implants. Related to this is Professor Ann Wennerberg's work on oral prosthetics. In the cell biology group of the same department, Professor Peter Thomsen's group focuses on biomaterials interaction with cell and soft tissue. Finally, Professor Hans Elwing's work at Gothenburg University relates to the screening of biomaterials using surface-sensitive analytical methods.

Influential biomaterials research is also being conducted at Chalmers University of Technology, where Professor Bengt Kasemo at the Department of Physics is working with others including Associate Professors Julie Gold and Sarunas Petronis. The group conducts research related to surface science, biomaterials and nanotechnology and specifically addresses the biocompatibility of metallic and ceramic materials for medical implants, as well as cell surface interactions. Their work is also applicable to such fields as biosensors. Related research in Gothenburg includes that of Professors Bo Håkansson (Chalmers), Mats Brittberg (clinical research), Elis Carlström (the Swedish Ceram Institute). In regard to tissue engineering, Professor Paul Gatenholm at the Department of Chemical and Biological Engineering is looking into the relationship between structure and material properties of polysaccharides, as used in scaffolds for example. The work of this group also involves biomimetics.

The fact that Gothenburg is something of a biomaterials node for Sweden is also acknowledged by VINNOVA, since this is the home of three VINNOVA-funded centres relating to biomaterials, all co-financed by partners including companies, universities and local authorities. One is a

centre of excellence on supramolecular biomaterials structure dynamics and properties (called SUMO) and is led by Professor Ann-Marie Hermansson. Another node for biomaterials research is the centre of excellence, Biomatcell, which came about partly through the biomaterials division at Gothenburg University headed by Professor Peter Thomsen. Research is concerned with new active biomaterials for musculoskeletal implants (Professor Jukka Lausmaa). In vitro and in vivo studies of tissue regeneration using combinations of biomaterials and cell therapy are also being conducted under the leadership of Professor Anders Lindahl.

The third is a cluster development initiative called "Biomedical development in Western Sweden", aiming to build a strong regional innovation environment in terms of research as well as industry and complementary resources during its 10-year life span. Two R&D fields are in focus: biomaterial and cell therapy versus cardiovascular and metabolic science respectively. Activities include training future leaders in business development and attracting expertise and capital. Also, a more coherent infrastructure for the commercialisation of research is being set up, providing research projects and companies with a single point-of-contact. Calls have been launched for R&D projects and project assessment funding and coaching have been provided to explore their commercial potential. Until now, several early projects have involved cardiovascular or metabolic applications. The initiative builds on strong connections to existing research groups and firms. One such area is supporting existing as well as new biomaterials firms with the research tools and findings offered by academia. A focus is thus offering ways of studying the boundary zone between artificial materials and living tissue, to develop better dental implants for example, or improve wound care and skin-penetrating implants. Academic research throughout the region is tightly connected to the initiative in order to build such links and facilitate projects.

The biomaterials research in Gothenburg and elsewhere in Sweden is impressive and it is largely focused on osseointegration and metallic materials. Admittedly, there are important elements for TERM in the analysis of tissue-implant interaction and in relation to the modification of surfaces, as stated above. Also, some of the research has fruitful connections with clinical practice. However, although some important research is underway, relatively little attention is given specifically to bioresorbable materials or more generally to the development of new materials, or to soft tissue or cell interaction. In addition, there is no clear integration of the various elements of biomaterials research in Sweden.

As stated above, the Gothenburg region also hosts prominent stem cell research. At the Department of Clinical Chemistry and Transfusion Medicine at Sahlgrenska University Hospital/Sahlgrenska Academy, the

stem cell research is led by Professor Anders Lindahl. Since the early development of a transplantation method for cartilage injuries ((ACT), his group has devoted its attention to molecular and cellular aspects of heart cell and cartilage regeneration. The group isolates stem cells for clinical application as well as to understand their differentiation and search for new drug targets. Related to this, the group led by Professor Sven Enerbäck focuses on organogenesis and work is being conducted by Professors Håkan Nygren, Magnus Braide, Gunnar Bjursell, Lars Hamberger and Bo Risberg.

One large agglomeration of Swedish stem cell researchers is in the Lund-Malmö region with the Center for Stem Cell Biology and Cell Therapy, supported by the Swedish Foundation for Strategic Research, as stated above. A strength of the Centre is the close interconnection between fundamental, preclinical and clinical research. In fact, it houses a number of groups, with the Stem Cell Institute emphasising fundamental aspects of stem cell and developmental biology and the preclinical research groups focusing on development of cell replacement therapies. Finally, the clinical research groups have resources for transplantation, neural cell replacement and stem cell-based gene therapy.

In total, the Centre consists of 25 research groups and its leading scientists focus on such areas as neural cell replacement therapies for CNS disorders, hematopoietic stem cell (HSC) biology and gene therapy. The group conducts internationally recognised research on neural cell replacement therapies with Professor Anders Björklund (neurobiology) exploring neurobiology and Professor Olle Lindvall focusing on restorative neurology. Groundbreaking work has been done to develop cell replacement therapies for Parkinson's disease. The Centre also focuses on stem cell and developmental biology of the central nervous and blood systems and development of stem cell and cell replacement therapies. The research into hematopoietics involves two departments with Professor Sten Eirik Jacobsen (Department of Stem Cell Biology) and Professor Stefan Karlsson (Department of Molecular Medicine and Gene Therapy). In regard to diabetes, Professor Henrik Semb is an expert on the developmental biology of hES cells and the pancreas and works on cell-replacement therapies of diabetes. On neural applications, prominent research in the Lund/Malmö area includes the neural stem cell lab (led by Zaal Kokaia). Also, Professor Patrik Brundin analyses neuronal stem cells and aims to grasp the neurogenesis in the adult brain. The group's application focus is on brain repair for Parkinson's, Huntington's and Alzheimer's diseases. Another related research group is that of connective tissue biology at Lund University as led by Professor Dick Heinegård and with a staff of 20, focusing on bone, cartilage and joint diseases.

As regards biomaterials at Lund University, a number of researchers should be mentioned, including Professors Bengt Wesslén (Dept. of Polymer Science & Engineering) working on biodegradable polymers, Lars Lidgren (Dept. of Orthopaedics), developing biomaterials aimed at boosting implant survival and appreciating the biomaterial tissue interface and Fredrik Höök (Solid State Physics), combining knowledge on molecular biology with that of nanotechnology.

On the clinical side, Professor Göran Lundborg at the Department of Hand Surgery at Malmö University Hospital works on peripheral nerve repair and is pushing the development of an artificial hand. Also connected to this work is Associate Professor Nils Danielsen at the research group of Neural Interfaces, a group generally interested in biocompatibility at implantation in the brain or the spinal cord. Furthermore, Professor Lars Magnus Bjursten works with tissue response in vivo and collaborates with others such as Uppsala University on testing materials in animals.

5.6 Summary

There are a number of interesting conclusions to be drawn from the above review of some of the activities in the focus countries. It is obvious that public investments are largely located in the major city regions where the main universities are also located. As discussed in chapter 3, this is also where the firms are located and there seems a geographical clustering of TERM activities.

While the countries investigated all state that TERM is an important area, their investments and policies differ substantially. Such differences relate to the relative focus on basic versus applied research, the emphasis on inter-disciplinarity, the profile areas, the actors involved in strategy formulation and implementation etc. In the US, the UK and Japan, the policy goals are explicit and involve enhancing the critical mass of research and some efforts of industrial cluster-building whilst in Germany, the efforts are most clearly seen in terms of investment in creating critical mass.

The above analysis also reveals rather large variations in the countries regarding the *volume* of investments in TERM. As pointed out, these differences are difficult to assess due to the major variations in such things as the way data is collected and reported in the various countries. There are hefty deviations between the sizes of the countries analysed and therefore the volume of R&D spending differs.

Small countries such as Sweden cannot match larger countries' investments in absolute terms. However, in absolute terms a small country should be able to match funding for individual initiatives to develop research and

innovation environments for example. Also, even a small country like Sweden often has to build up general knowledge in many (if not all) the subfields in order to have 'receiver capacity' combined with being at the forefront of other parts of the field.

It is noteworthy that Sweden is only one of the five that has not formulated an explicit policy. Whilst the new Swedish research and innovation bill presented in October 2008 does not include provisions for a strategy formulation process, the significant funding directed towards the field still holds high potential for the future.

6 Scientific output

While the previous chapter presented the national initiatives as well as the major research groups in each of the five focus countries, this chapter analyses the scientific output of such research. This chapter will highlight the development of the scientific fields involved, as well as identifying the important countries and universities in each field and their interaction. A number of bibliometric studies of central knowledge fields within TERM were conducted in order to give this overview. The studies can be grouped into the following four sections: a) tissue engineering and regenerative medicine, b) stem cells and c) biomaterials. The areas were chosen since they constitute research areas which, as described in Chapter 2, can be called components of the multidisciplinary field of TERM.

After a note on the bibliometric methodology in section 6.1, section 6.2 reports the analysis of 'tissue engineering' and 'regenerative medicine' as search words, concluding that the field cannot easily be captured through a single search string. Therefore, section 6.3 focuses on stem cells and 6.4 on biomaterials.

6.1 Bibliometric methodology

In order to determine knowledge flows and knowledge production in a research-intensive field such as TERM, it was considered relevant to use scientific publications for the analysis. Admittedly, much knowledge production is never published, mainly that which results from research and development within business enterprises. In fact, the aim of these enterprises is to develop new products, processes or services and therefore the innovation process is publicised to the same extent as for public research organisations until a product is placed on the market or a patent application filed. Even so, bibliometry is useful when it comes to collaboration between public research organisations and industry, since there are strong incentives in academia for publishing scientific results. Accordingly, if companies collaborate with academic groups, it is likely that the results get published. Both academic positions and, to some extent, research grants are assigned on the basis of the volume and content of the scientists' output.

Bibliometrics is used to describe the tissue engineering and regenerative medicine fields at three levels: individual authors, organisations and countries. The global collaboration patterns within these three levels are also analysed using co-authorship statistics to identify interrelationships. The

selection of journals and journal categories chosen for the analyses is described and listed in the Appendix.

A description of the publication pattern of different organisations gives important information about which individual authors, organisations and countries that are most prominent in different scientific subject fields as well as relationships between those involved. The publication pattern of business enterprises is interesting since they largely develop new innovations in collaboration with public research organisations and many public efforts are directed towards increasing the knowledge exchange between the two types of organisation. The data gives insight into the dynamics of the collaboration and may indicate the success of the efforts made. Indications may be found regarding both national and international collaborations and strategies relating to outsourcing research and increasing in-house capabilities. The extent and dynamics of international collaboration between different research organisations within the area are of significance, since research investment in this field has increased in many countries. It is therefore interesting to learn whether this is manifested in the statistics of scientific publications, what the networks between prominent research environments look like and the position of Swedish researchers.

The position in absolute or relative terms for a whole country can only tell us about broad trends in different scientific fields. Looking at the performance of individual universities or groups of researchers may be more worthwhile if the aim of the study is to identify excellent research environments or whether an environment can be said to have a certain critical mass. It is likely that research environments with a critical mass and characterised by high quality research in a scientific field are attractive for both public and private investments. It is also likely that such environments have the capacity to generate breakthrough discoveries.

To study excellent research and innovation environments, it is therefore interesting to look at high-performing universities in a specific field, their industrial linkages and whether one also can identify startup companies relating to that environment. Thus, to identify top environments, a study has been made of publication volumes in absolute terms, in different datasets trying to address scientific excellence in fields relating to tissue engineering and regenerative medicine.

Since the main focus of the analyses is to identify strong research environments and the countries in which those are found, only the first section includes an analysis of the publication volume in relation to GDP and population as an example of the type of results such analyses will yield. In those analyses, the countries with smaller populations and strong

economies end up with a higher ranking than when absolute numbers are analysed.

As with any methodology, the results have to be interpreted with some caution. Since the amount of work needed for a publication, the difficulty of getting published and the impact factors of relevant journals varies between different scientific subject fields, a comparison of publication volumes between them needs to be analysed with some caution. Using quantitative citation data to compare impact is also hazardous for different fields of research, especially when comparing mature and new; broad and narrow or disciplinary with multidisciplinary areas of research.

In the present study, the detail of the analyses of organisations and networks differs between the sub-fields reported in this chapter. This depends to some extent on the size of the dataset. The largest datasets could not easily be imported into the Bibexcel software for co-authorship analyses and a detailed analysis of the very smallest datasets did not yield robust findings. Thirdly, a drawback with the methodology used is that it does not identify smaller top research units but focuses instead on identifying environments with large critical masses. Other methods need to be used to identify smaller research environments.

6.2 Tissue engineering and regenerative medicine

In the analysis, only 811 articles were found with the words “tissue eng*” or “regenerative medicin*” in 84 top life science and medical journals (according to impact factor), or with Science or Nature in title, keywords or abstract, for 2000 to October 2007. Most of the articles were published in journals in the fields of biochemistry, molecular biology, cell biology and haematology with the Journal of Biological Chemistry, FASEB Journal and Blood as the journals with the largest publication volume. The US has over six times as many publications as the next countries on the list: the UK, Japan and Germany.

The top 15 organisations are listed in the table below and of these only one, Osaka University, is non-US.

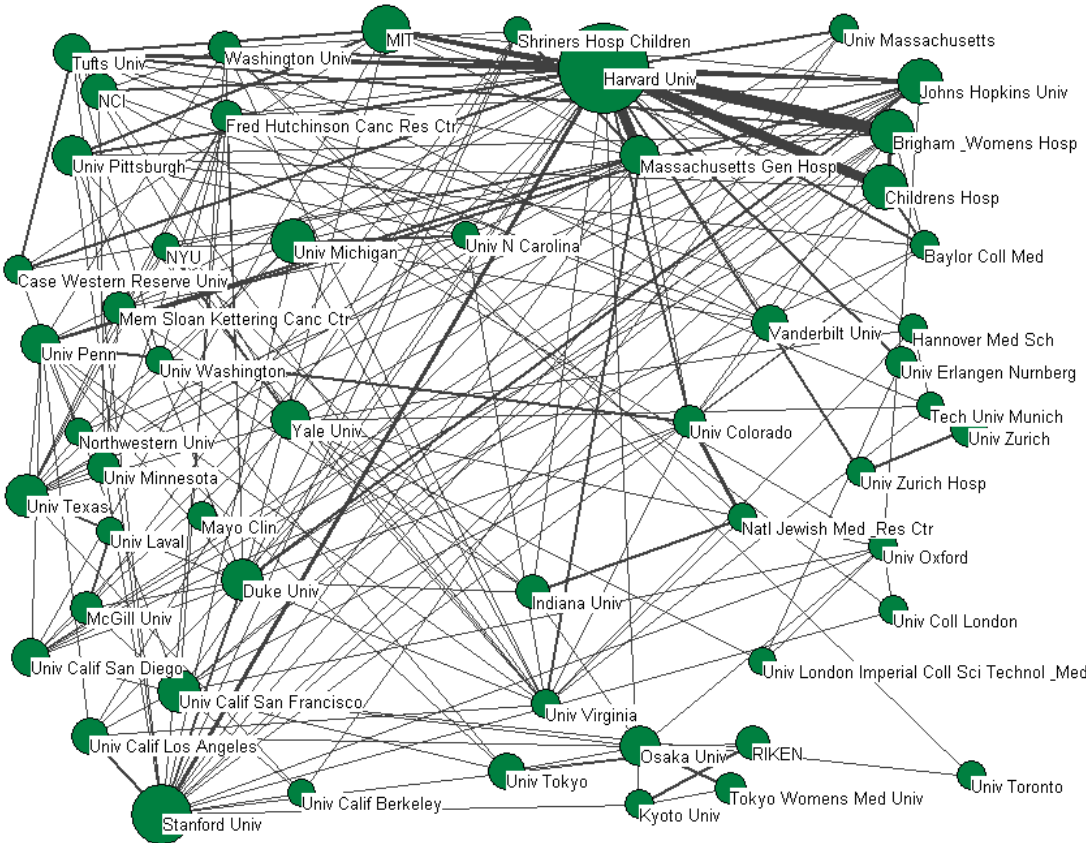
Table 6.1. The 15 organisations with the largest publication volumes using the words "tissue eng*" or "regenerative medicin*" in 84 top life science and medical journals according to impact factor or Science or Nature in title, keywords or abstract, 2000 - October 2007

No. of articles	Organisation
71	Harvard Univ
32	Stanford Univ
21	MIT
19	Children's Hosp
19	Johns Hopkins Univ
18	Brigham & Womens Hosp
18	Univ Michigan
17	Univ Calif San Francisco
17	Univ Texas
16	Duke Univ
15	Osaka Univ
15	Univ Pittsburgh
14	Yale Univ
14	Massachusetts Gen Hosp
14	Univ Penn

Source: Web of Science (Thomson Scientific), analysis by VINNOVA.

The collaboration patterns between the top organisations appear below. Besides the US, countries with organisations among the top performers include Canada, the UK, Switzerland and Germany. The thickness of the lines is proportional to the number of co-authorships. In this dataset, the lines between top-performing organisations reveals few links between countries. Most links are between organisations in the same country. None of the top organisations are Swedish.

Figure 6.1. Co-publication pattern between authors from the organisations with the largest publication volumes in 84 top life science and medical journals (according to impact factor) or Science or Nature with the words "tissue eng*" or "regenerative medicin*" in title, keywords or abstract, 2000 - October 2007



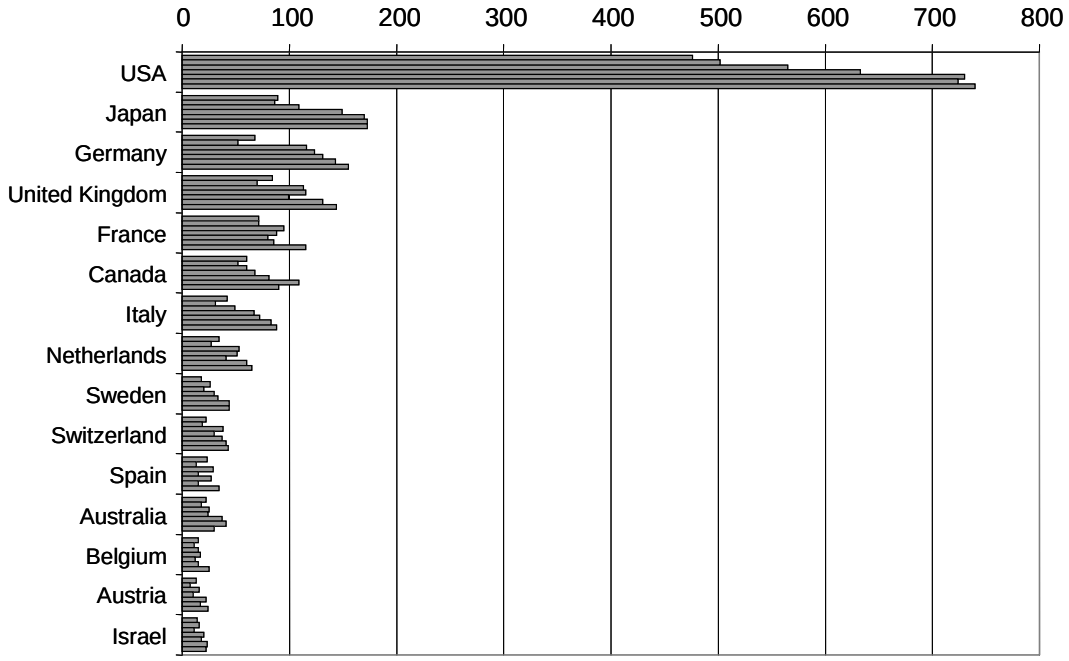
In summary, trying to capture the tissue engineering and regenerative medicine research field in one search in the database proved not to be that easy. The search string used resulted in only 811 articles in top medical life science or multidisciplinary journals. Again, Harvard University topped the statistics with over twice as many articles as from Stanford University, which was the number two organisation. The problems of capturing the TERM field with one search string led us to focus on three subareas: stem cells, biomaterials and biomimetics respectively.

6.3 Stem cells

The word "stem cell*" was identified in the title, keywords or abstract of 8,091 articles in top *life science* and *medical* journals from 2000 until June 2007 with almost the same number of articles in the two types of journals.[162] The analysis shows that for the stem cell area, the US dominates the field in terms of publication volumes in this dataset. The most frequent research organisation in the statistics is Harvard University followed by the University of Texas and University of Washington. This search found the research to be dominated by research into the field of Haematology with the

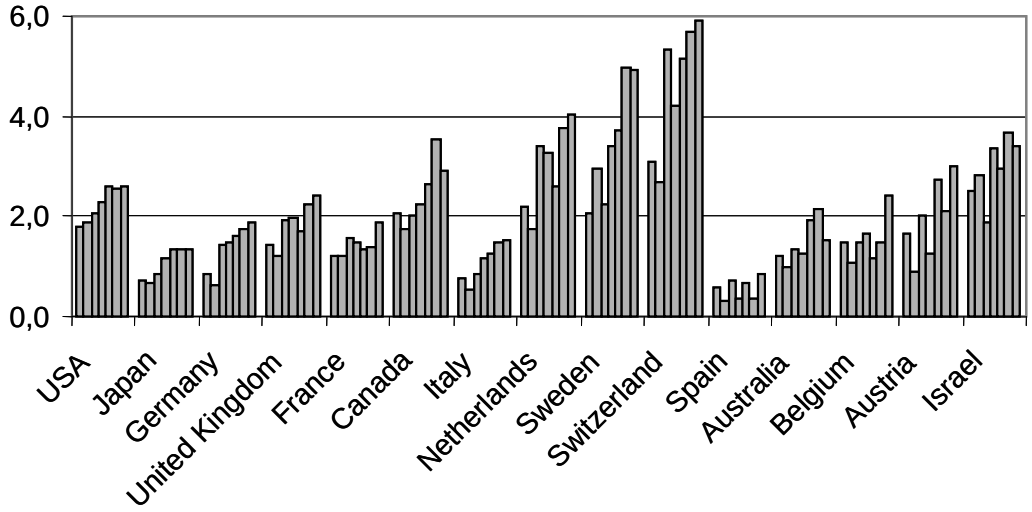
journal “Blood” contributing to as many as 1,062 of the 8,091 articles. If this journal is excluded, the University of Tokyo has the third largest publication volume after Harvard University and the University of Texas. The number of articles by researchers from different countries, including the journal “Blood”, is shown in Figure 6.2.[163]

Figure 6.2. Publication volumes in 84 top life science and medical journals according to impact factor with the words “stem cell*” in title, keywords or abstract, 2000-2006



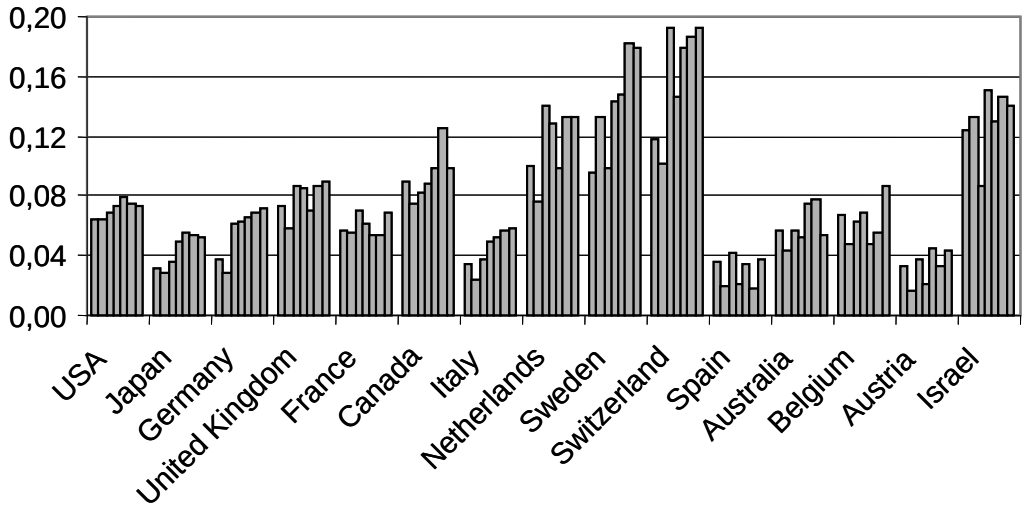
Now, if the number of publications from the countries above in relation to population is studied instead, the relatively small countries Switzerland, Sweden and Netherlands are the top performers, in that order (Figure 6.3).

Figure 6.3. Publication volumes in relation to population for the top 15 countries according to publication volume in 84 top life science and medical journals according to impact factor with the words "stem cell*" in title, keywords or abstract, 2000-2006



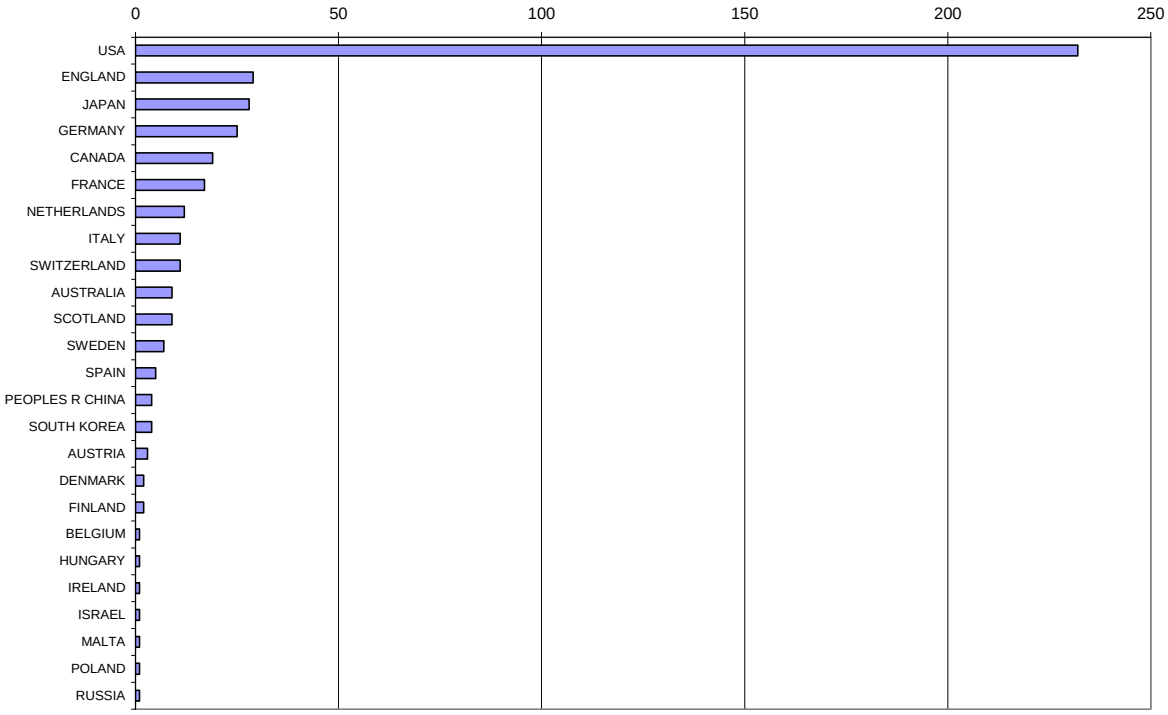
The result is similar when measuring the publication volume in relation to the Gross National Product of a specific country, as shown in the diagram below (Figure 6.3) although it is also clear from this graph that Israel ranks highly.

Figure 6.4. Publication volumes in relation to GDP (thousand current PPP$) for the top 15 countries according to publication volume in 84 top life science and medical journals according to impact factor with the words "stem cell*" in title, keywords or abstract, 2000-2006



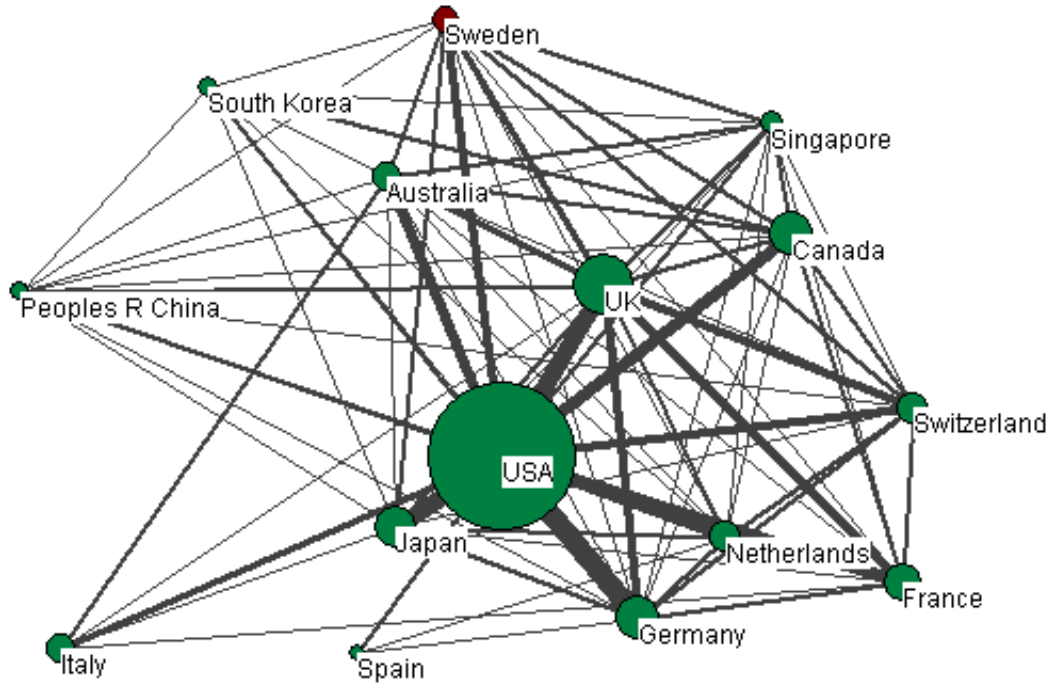
In order to study co-authorship patterns in influential journals and, thus, have an indication of the scientific networks in this field, the high impact journals Science and Nature were chosen for the selection of the dataset. In these two journals, the US is even more dominant(Figure 6.4).

Figure 6.5. Countries with the largest no. of publications in Nature and Science with "stem cell*" in Title, Keywords or Abstract, 2000 - June 2007



Analysing the number of co-authorships between countries reveals the US has the strongest research links in the two journals with Germany, Japan, the United Kingdom, France and Canada, in that order. Sweden has the strongest links with the US, the United Kingdom and Canada in the group of top-performing countries.

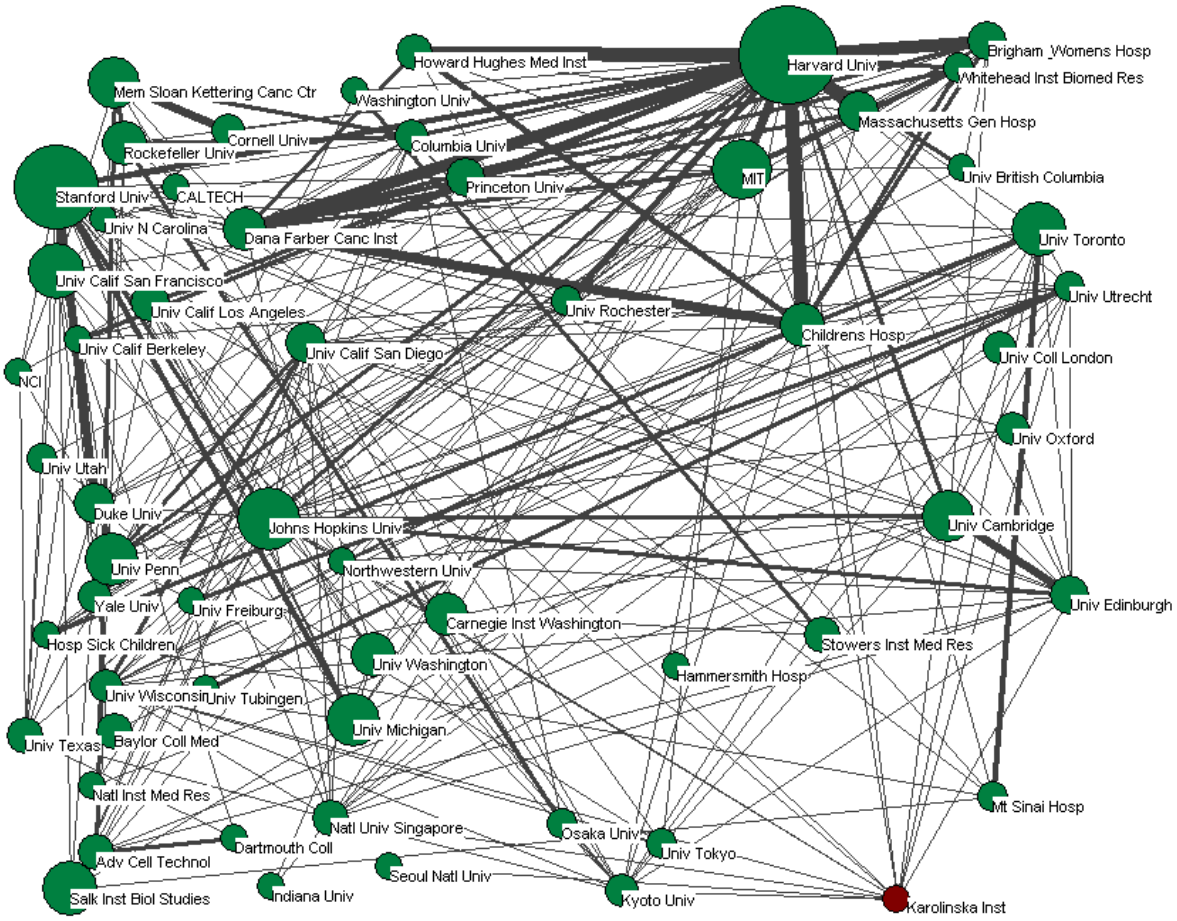
Figure 6.6. Co-publication pattern between authors from the countries with the largest publication volumes in Nature and Science with "stem cell*" in title, keywords or abstract, 2000 - June 2007[164]



When trying to identify the top research environments in the world in a scientific field, the total publication volume is a better measure than relative measures. This gives an indication of the absolute strength and critical mass of the environment. In the dataset with all SCI covered journals, 80% of the 40 top-performing organisations in terms of publication volume are US and about 10% each are Asian and European. The figure below illustrates the co-authorship pattern between the organisations with the largest publication volume in Science and Nature with the word "stem cell*" in Keyword, Title or Abstract.

The US organisations dominate the picture but also a number of Asian Universities like the Japanese universities in Osaka, Tokyo and Kyoto as well as South Korean Seoul University and Singaporean National University of Singapore are among the top organisations. The European organisations in this picture include the British Universities of Cambridge and Oxford as well as the University College of London and the Swedish Karolinska Institutet. In Canada, the largest player is University of Toronto. The US players predominately collaborate with other US players, according to this dataset.

Figure 6.7. Co-publication pattern between authors from the organisations with the largest publication volumes in Nature and Science with "stem cell*" in title, keywords or abstract, 2000 - June 2007



6.3.1 Stem cell research in neuroscience

In order to investigate research activities related to stem cell research in the neuroscience field, a search was made using the words "stem cell* and neur*" in two different set of journals: all journals covered by SCI and the top journals in life science and medical fields (impact factor larger that 6). The first search generated a dataset of 8,557 articles and the second dataset 1,475 articles. Both datasets covered the years 2000 until June 2007. Figures 6.7-6.9 show the number of articles, number of articles in relation to population and number of articles in relation to GDP respectively, for researchers from the top countries in terms of publication volume for the first dataset of 8,557 articles.

Figure 6.8. The 27 countries with the largest number of scientific publications in SCI with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000-2006

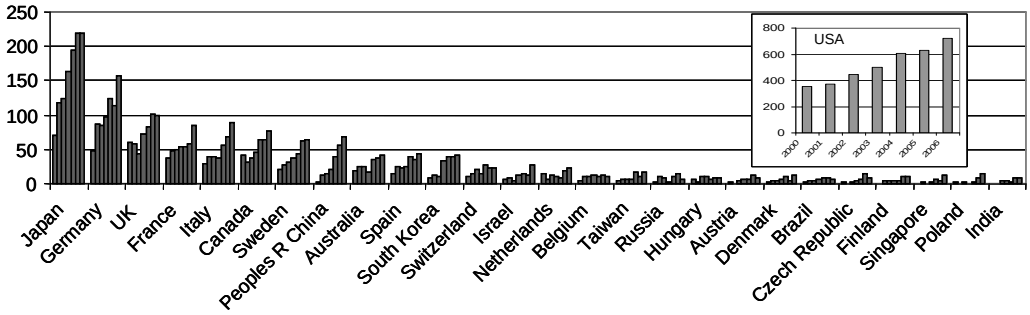


Figure 6.9. The 21 countries with the largest scientific publications in SCI with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000-2006, publication volume in relation to population

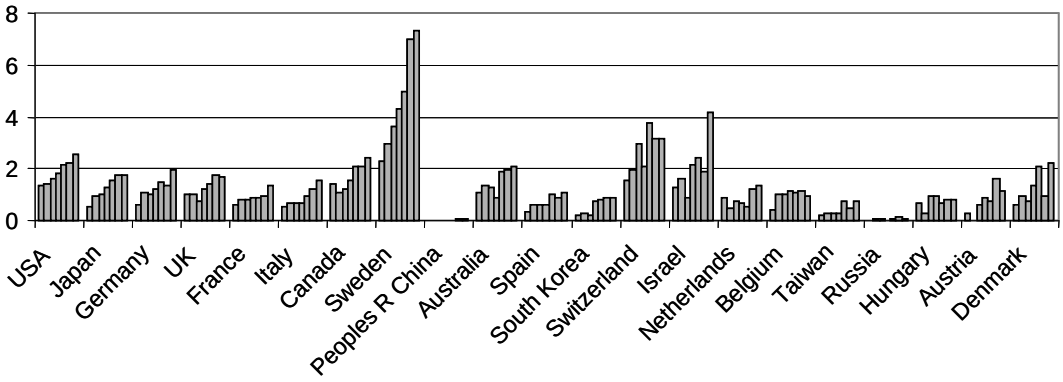
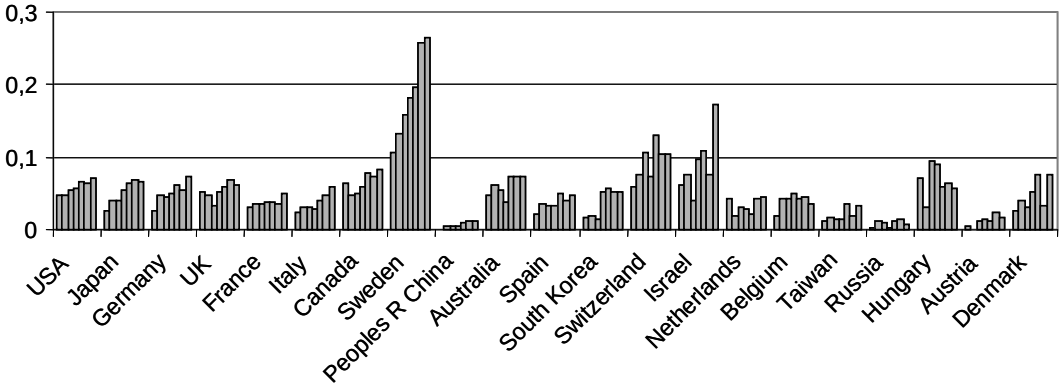


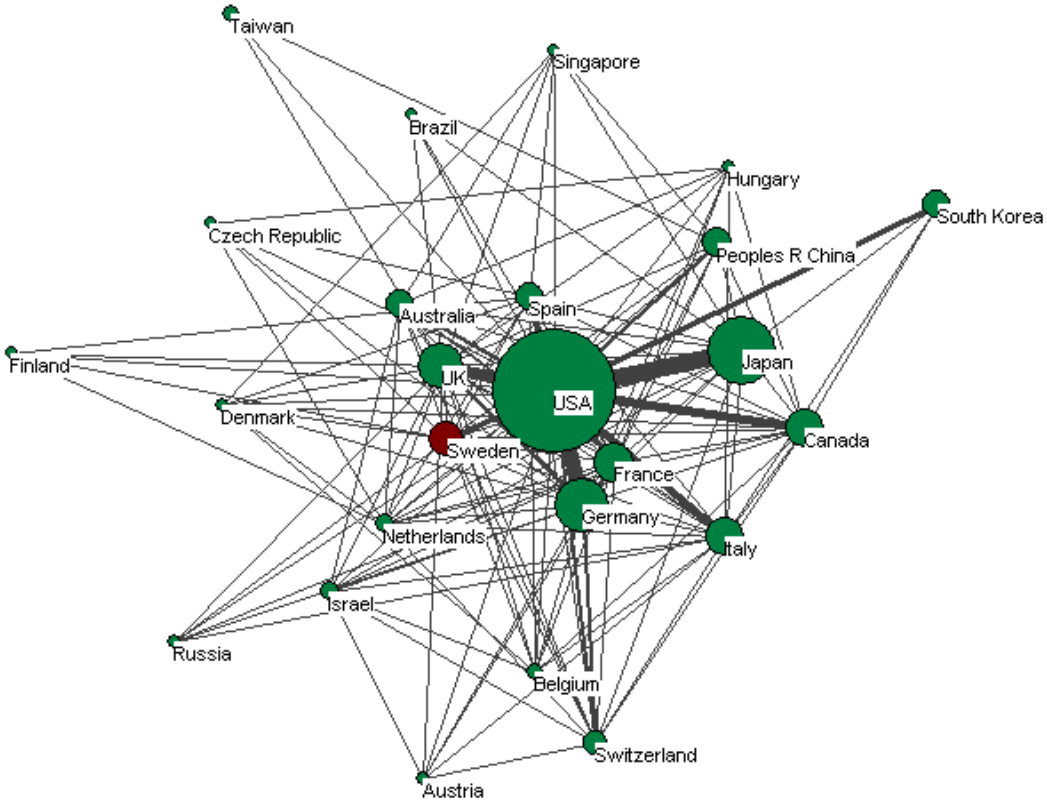
Figure 6.10. Publication volumes in relation to GDP (thousand current PPP$) for the 21 top countries according to publication volume with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000-2006



It is clear that, in relation to GDP and population, Sweden has a very large and steeply increasing publication volume. However, the dominant country in absolute numbers is the US.

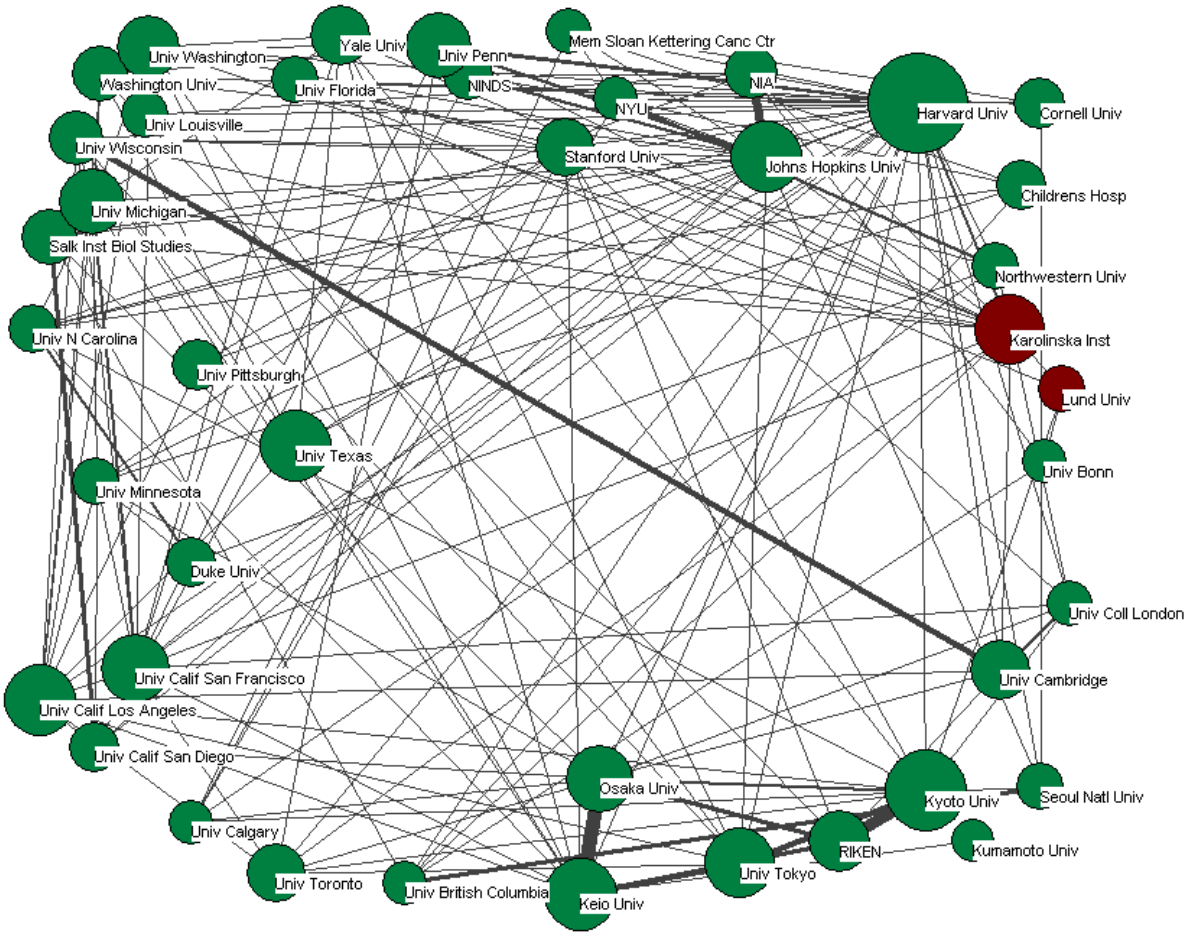
The co-authorship pattern of the top countries in terms of publication volume can be seen below. Looking at the figures for collaboration, it appears that the largest collaborative partner of the US is Japan, but even this collaboration only amounts to 3% of the total US publication volume in this dataset. For the smaller countries like Sweden and Switzerland, collaboration with the US amounts to 13% and 14% respectively and the corresponding figure for South Korea and Japan is 20% and 10% respectively. For all these countries, the largest collaboration is with the US.

Figure 6.11. Co-publication pattern between authors from the countries with the largest number of articles with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000 - June 2007



The figure below shows, the co-authorship pattern of the organisations with a publication volume larger than 50 in SCI journals with the words stem cell* and neur* in Title Keyword or Abstract. This dataset shows that the publication volume of Karolinska Institutet and the top US or Japanese Universities is more comparable than for the more general dataset encompassed by the words "stem cell*" only. Lund University also has a significant publication volume.

Figure 6.12. Co-publication pattern between authors from the organisations with the largest publication volumes for articles with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000 - June 2007



The dataset for "stem cell* and neur*" in top medical and life science journals shows a somewhat different picture than for the broader selection of journals. Countries with large publication volumes in the stem cell neuroscience field with research gaining publication acceptance in the top quality journals (by impact factor) are shown below. Compared to the statistics for all journals in SCI, Canada surpasses France and Italy and the People's Republic of China drops many positions. Switzerland gains many positions and South Korea has almost the same position as in the total set of journals. Other countries making gains include Singapore and Finland.

In relation to population and GDP, Sweden tops the statistics for the latter years but Switzerland has a larger average publication volume for the whole period. Another country with top performance in these respects is Israel.

Figure 6.13. The 27 countries with the largest publication volumes in 84 top life science and medical journals according to impact factor with the words "stem cell*" and "neur*" in Title, Keywords or Abstract 2000-2006

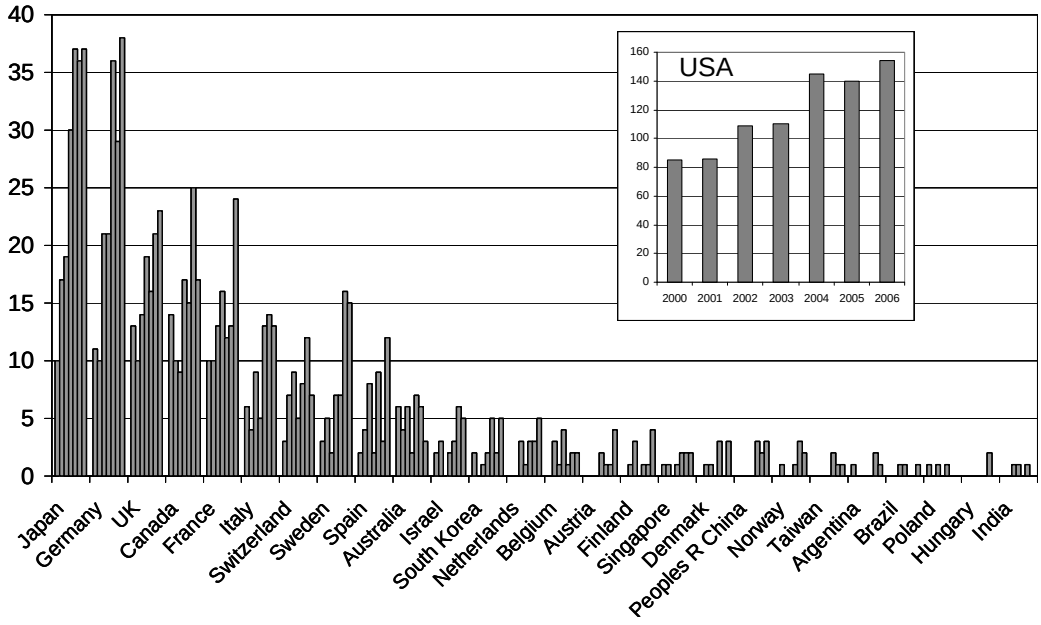


Figure 6.14. Publication volumes in relation to population for the top 23 countries according to publication volume in 84 top life science and medical journals in terms of impact factor with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000-2006

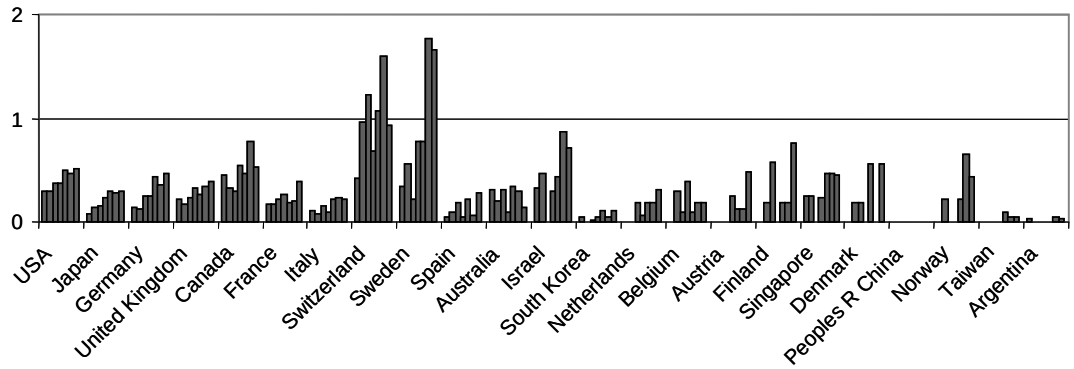
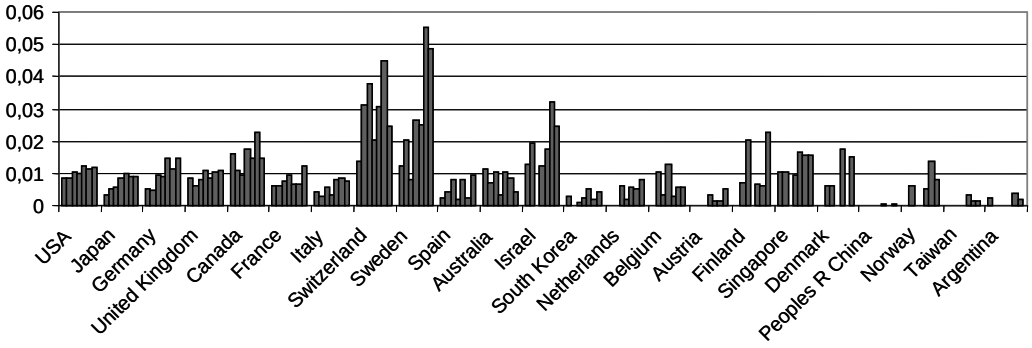


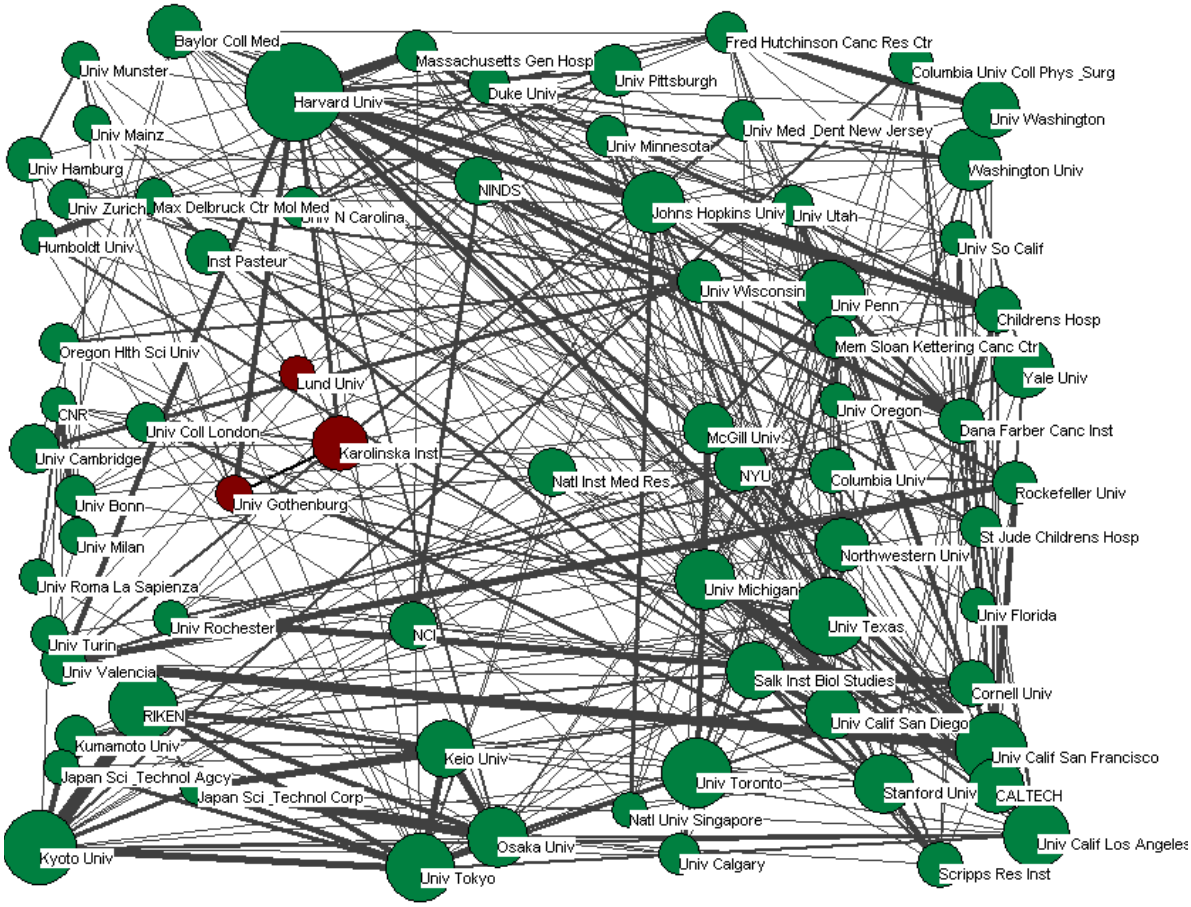
Figure 6.15. Publication volumes in relation to GDP (thousand current PPP$) for the top 23 countries according to publication volume in 84 top life science and medical journals in terms of impact factor with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000-2006



Looking at the collaboration pattern between the 20 countries with the largest publication volumes in terms of co-authorships in this dataset, the US has the same volume of co-authorships with Japan as with Germany and then come the UK and Canada. The top collaborative partner of Switzerland is Germany and for Sweden, the corresponding partner is the US.

Again, when trying to identify the top research environments, the total publication volume is a better measure than relative measures since this gives an indication of the absolute strength and critical mass of the environment. The collaboration pattern of organisations with over 10 publications in the top life science or medical fields with the words "stem cell*" and "neur*" in title, keywords or abstract appear below[165]. Again, it can be seen that contrary to the picture for countries, individual American organisations (with the exception of Harvard University) are not as dominant. Concerning European performance, three Swedish universities are among these top organisations plus a few British, German, Swiss, French and Italian organisations.

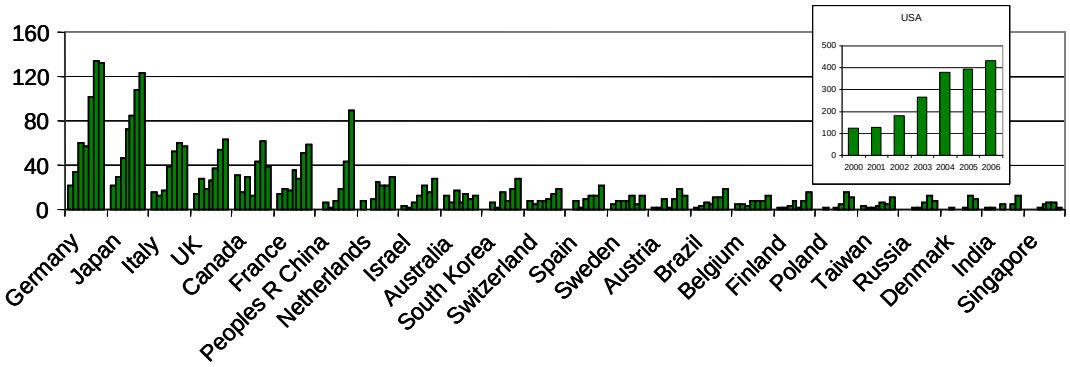
Figure 6.16. Co-publication pattern between authors from the organisations with the largest publication volumes in 84 top life science and medical journals (according to impact factor) with the words "stem cell*" and "neur*" in title, keywords or abstract, 2000 - June 2007



6.3.2 Stem cell research in the cardiovascular field

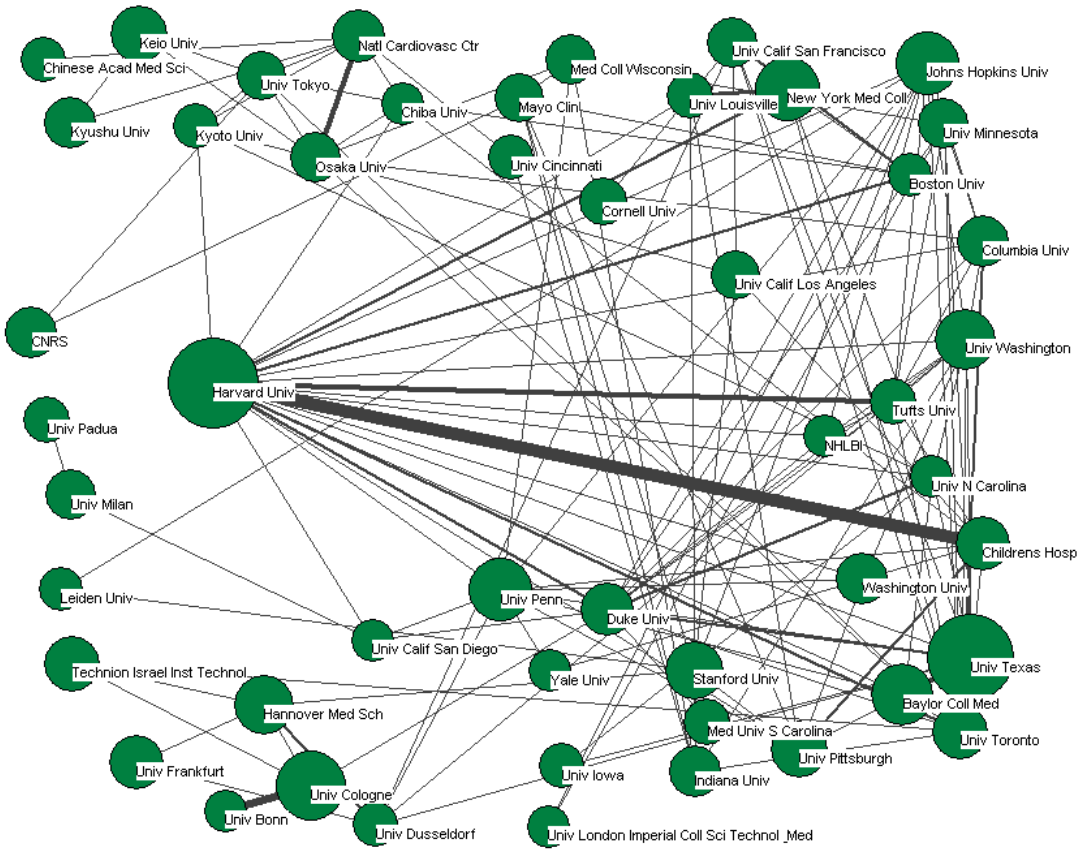
To investigate the cardiovascular field, a search using the words ((stem cell*) AND (card* OR heart)) was made, including 2503 articles 2000 until June 2007. Below the publication volumes for the top countries in this dataset are shown. As is seen there has been a tremendous development for People's Republic of China.

Figure 6.17. Publication volume for the 27 countries with the largest number of scientific publications in SCI with the words "stem cell*" and "card* or heart*" in title, keywords or abstract, 2000-2006



The co-authorship pattern between the top 50 organisations in the stem cell and cardiovascular field in all SCI-covered journals is illustrated below. Not one Swedish organisation is among them. Several organisations are from Japan and China as well as a few European organisations, mainly from Germany, Italy and the Netherlands. Harvard and Texas University are the two dominant organisations. The picture illustrates the relatively few links between countries in this dataset, the thickest line corresponds to 16 co-authored articles between two organisations.

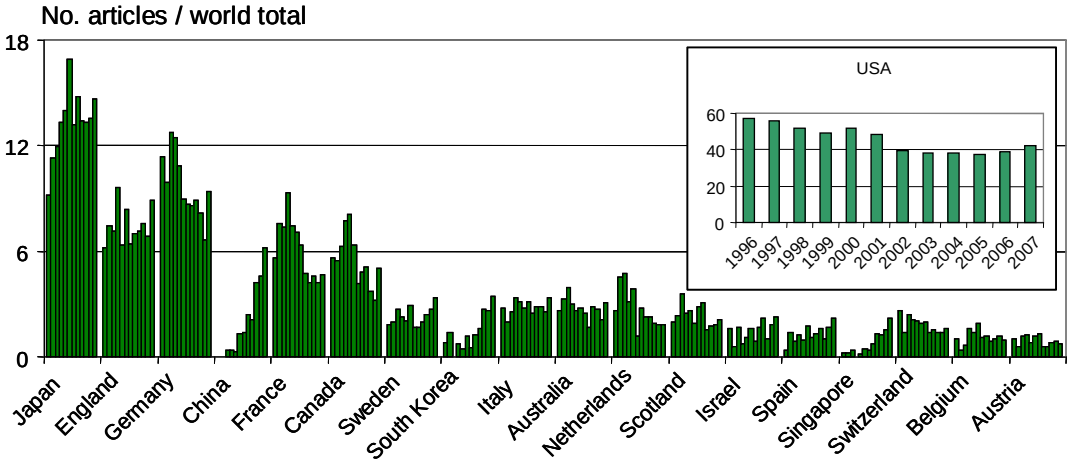
Figure 6.18. Co-authorship pattern between the 50 organisations with the largest number of scientific publications in SCI with the words "stem cell*" and "card* or heart*" in title, keywords or abstract, 2000-2006



6.3.3 Embryonic stem cell research

To investigate embryonic stem cell research, a search using the words ((stem cell*) AND (embryo*)) was made. Thus 11,621 articles for 1990-2006 were identified. The publication volumes for the top countries in this dataset are shown below.

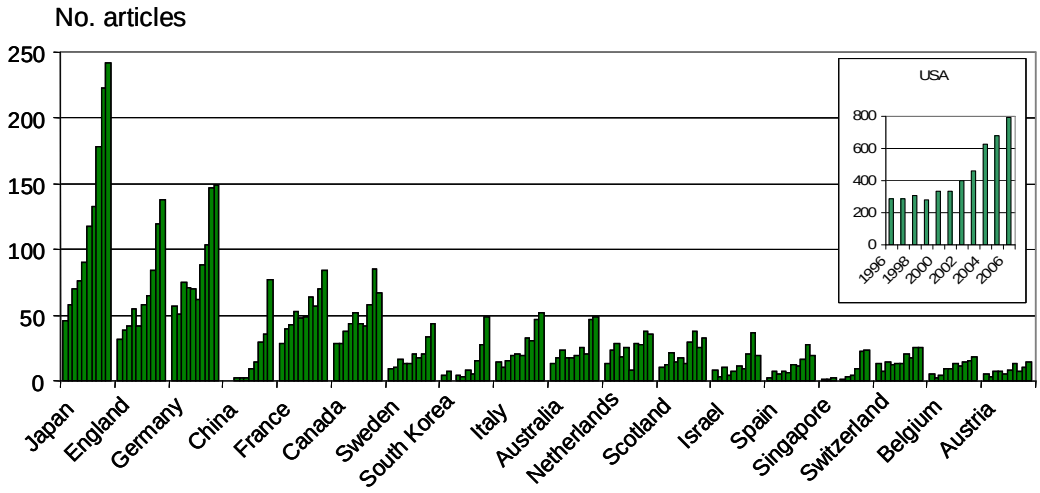
Figure 6.19. The 18 countries with the largest number of scientific publications in SCI with the words "stem cell*" and "embryo*" in title, keywords or abstract, 1990-2006



All top countries show a steep increase in publication volume with the words "stem cell*" and "embryo*" in title, keywords or abstract, 1990-2006. The US has almost three times the publication volume compared to the second country, England.

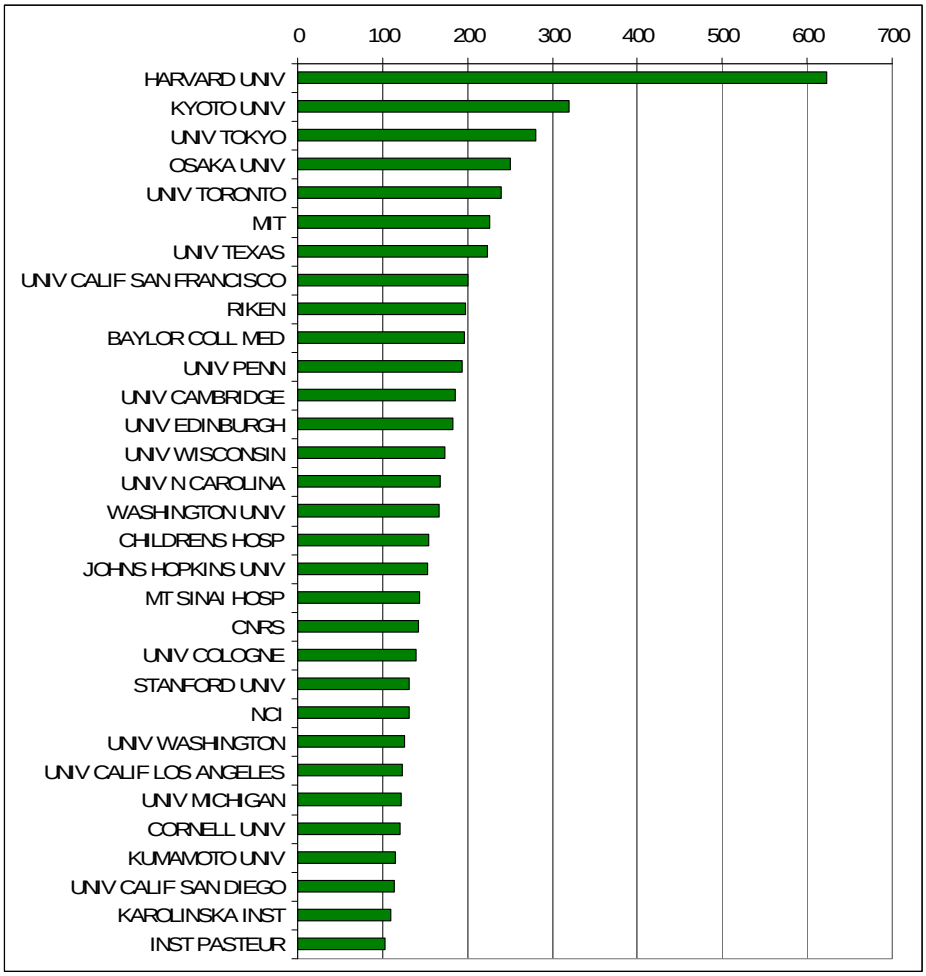
The figure below shows the development of the share of the world total for the top 19 countries, 1996-2007.

Figure 6.20. Share of the world total publication volume for the 18 countries with the largest number of scientific publications in SCI with the words "stem cell*" and "embryo*" in title, keywords or abstract, 1990-2007



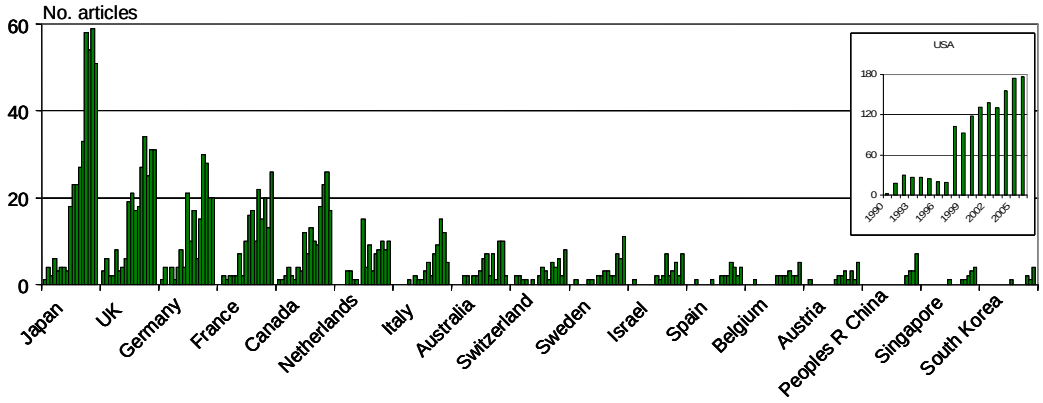
The top organisations in this dataset are listed below. As can be seen, Harvard University has the largest publication volume followed by three Japanese universities. The first European university is the University of Cambridge in the UK, followed by the University of Edinburgh in Scotland. Karolinska Institutet is in 30th position and the only Swedish organisation among the top 50.

Figure 6.21. Organisations with the largest no. of publications with "stem cell*" and "embryo*" in title, keywords or abstract, 2000 - June 2007



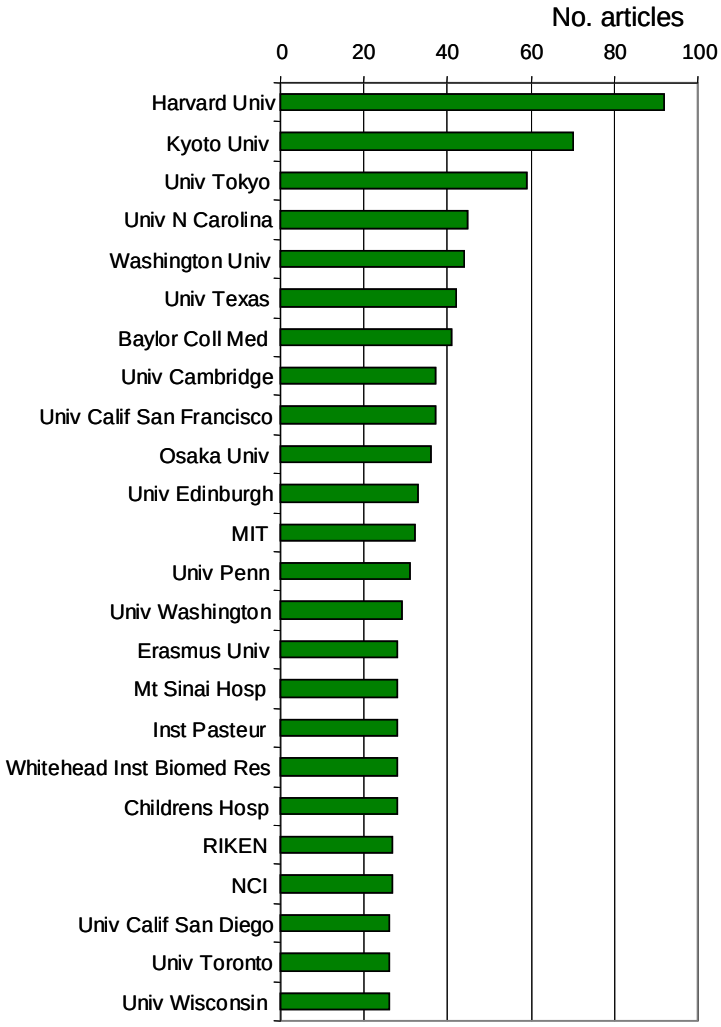
The second dataset on embryonic stem cell research included only articles published in the top life science and medical journals. For this dataset, the next figure shows top countries ordered according to the number of articles during the total time period.

Figure 6.22. The 18 countries with the largest number of scientific publications in top medical or life science journals with the words "stem cell*" and "embryo*" title, keywords or abstract, 1990-2006



The top organisations in this dataset are listed below. Again Harvard University has the largest number of publications followed by Kyoto University and University of Tokyo. The list is dominated by US organisations and the first European organisation is again the University of Cambridge. The top Swedish organisation is Karolinska Institutet with a publication volume in top journals among the top 40 organisations.

Figure 6.23. Organisations with the largest no. of publications with "stem cell*" and "embryo*" in title, keywords or abstract, 1990 - October 2007



6.3.4 Leading US research groups in the stem cell area

As described above, the US universities have an outstanding lead when it comes to publishing in the stem cell area. This section provides a flavour of the composition of the top US research groups in the stem cell area.

Table 6.2 The top 10 US universities

University	No. of publications during the period 2000-2006
Harvard University	477
University of Texas	243
University of Washington	238
University of Pennsylvania	193
The National Cancer Institute NCI	156
Stanford University	145
Fred Hutchinson Cancer Research Center	143
University of California, San Francisco	142
University of Michigan	135
Duke University	133

Source: Web of Science (Thomson Scientific), analysed by the authors.

It is clear that *Harvard University* is the leading University in stem cell research, with a total of 477 publications during the period 2000-2006. Several affiliates and departments at Harvard are involved in stem cell research. One key player is the *Harvard Stem Cell Institute* which, based on private donations, supports over 750 scientists in 11 research hospitals in the Boston area. With a budget of USD 5.3 million in 2006 and USD 17 million in 2007 the institute supports research into both embryonic and adult stem cells and focus on developing new therapies for diseases such as diabetes, neurological disease, cardiovascular disease, blood disease and cancer. The *Center for Regenerative Medicine Laboratories* at Harvard Medical School including Professors Scadden and Hock focuses on understanding how tissue is formed and may be repaired. Research includes analysis of the regulation of the cell cycle and the transcriptional regulation of normal blood cell development and leukaemia with the use of hematopoietic stem cells. At the *Department of Cell Biology at Harvard Medical School* three labs are involved in stem cell research, with Dr Chien leading the university-wide *Cardiovascular Stem Cell Biology Program*, Dr Green focuses on differentiation of human embryonic stem cells into somatic cell types as well as keratinocytes for epidermis regeneration in severe burn patients. Dr McKeon studies mechanisms for controlling chromosome segregation, T cell activation and epithelial stem cell maintenance. At the Dana-Farber Cancer Institute, Professor Antin targets cancer and related diseases through research into such areas as cellular engineering and

Professor Orkin focuses on the molecular genetics of blood cell development and stem cells.

The second largest publisher within stem cells in the US is the University of Texas (243 publications) where the Stem Cell Transplantation & Cellular Therapy Programme is chaired by Dr Champlin and has a staff of 29 researchers. Another key researcher at this centre is the Professor of Stem Cell Transplantation, Sergio A. Giralt. He focuses on the optimisation of blood and marrow transplantation in treatment of a variety of hematologic malignancies. Other notable Professors are Marcos de Lima with his research into transplants and Michael Andreeff studying hematologic malignancies, apoptosis, drug resistance, stem cells and gene therapy.

Third in the list of US publishers is the University of Washington where the Fred Hutchinson Cancer Research Center is a main player (independently ranked 7th). Stem cell research at the centre takes place in the Transplantation Biology Programme headed by Drs Rainer Storb and Beverly Torok-Storb. The Transplantation Biology Programme focus on understanding and eliminating major barriers to successful allogeneic hematopoietic stem cell transplantation and includes host-versus-graft reactions, graft failure, acute and chronic graft-versus-host disease (GVHD), regimen-related toxicities and induction of graft-versus-tumour reactions. The goal is to use stem cell transplantation to treat patients with malignant and non-malignant hematologic diseases. Stem cell research at the centre uses adult stem-cell transplantation to treat blood cancers such as leukaemia, but is currently investigating the possibility of using embryonic stem cells in treating other diseases. However, embryonic stem-cell research might possibly be used for the development of new treatments for Parkinson's disease, Alzheimer's disease and spinal cord injuries. Also at the University and in relation to the Institute for Stem Cell and Regenerative Medicine, the National Institute of General Medical has funded a new research programme on human embryonic stem cells led by Professor Blau with funding of USD 10 million over five years. They will study the pathways human embryonic stem cells use to self-renew and how they differentiate into heart muscle cells and retinal nerve cells. The Institute has also received USD 17 million from private donors in response to the goal of the University to raise a minimum of USD 50 million for human embryonic stem cell research.

Stem cell research at the *University of Pennsylvania* (ranked 4th) is taking place in the School of Engineering and Applied Science, the School of Medicine, the Abramson Family Cancer Research Institute and the Wistar Institute.[166] One example of research is Professor Dennis Discher focusing attention on adult stem cells and how these can turn into bone, muscle, neurons or other types of tissue.

The stem cell research at *Stanford University* (ranked 6th) is gathered at the Institute for Stem Cell Biology and Regenerative Medicine, headed by Dr Irving Weissman and focusing on the origins of cancer, diabetes and other genetically inherited diseases as well as the future of stem cell-based therapies. The group was early in isolating stem cells leading to the first clinical trials in which patients received cancer-free stem cells after their blood-forming system had been obliterated by chemotherapy. Researchers at Stanford have also been leading in many aspects of stem cell applications. For instance, Stanford scientists were the first to discover and isolate many cancer stem cells such as those for human leukaemia and human breast cancer stem cells. Also, researchers at Stanford were first to discover and isolate tissue-forming stem cells and to replace blood formation in women with breast cancer. This was achieved by a group led by Karl Blume in the Stanford Bone Marrow Transplant programme. Stanford researchers were also first to develop technologies crucial to stem cell research. For example, Professor Patrick Brown developed Microarray technology in the early 1990s that enabled stem cell researchers to assess differences in genetic expression between different stages of development and between normal and cancerous tissues.

Also in California is UCSF (the University of California in San Fransisco) where the Institute for Regeneration Medicine (IRM) and the Human Embryonic Stem Cell Research Center are co-directed by Renee Reijo-Pera and Susan L. Fisher. Other key researchers are Dr Andrew Leavitt (adult hematopoietic stem cells), the Ramalho-Santos Lab (embryonic stem cells, pluripotency), Dr Caroline Damsky (cell-extracellular matrix interactions, tissue remodelling, cell signalling). The research at the Centre includes a broad range of embryonic and adult stem cell studies involving animal and human cells. The goal is to develop fundamental information about human development and in particular birth defects, as well as the potential of stem cells to treat disorders, including diabetes, cardiovascular disease and neurological diseases, such as multiple sclerosis and Parkinson's disease. UCSF is collaborating with Karolinska Institutet in a possible exchange of "each other's human embryonic stem cell lines, with the goal of carrying out complementary studies to characterise physical distinctions between what are considered some of the best stem cell lines in the field".[167] Susan Fisher, PhD, UCSF Professor of cell and tissue biology has been appointed to lead the UCSF effort "examining which proteins are expressed by individual cell lines, while scientists at the Karolinska Institutet would examine the genes that are turned on, or "expressed," in these lines.

Many types of stem cell research are being done at the *University of Michigan* (ranked 9th). It seems as if the University has made a consistent move in the stem cell field. The *Michigan Center for hES Cell Research* as

led by Professor K. Sue O'Shea was established in 2002 with university funding, but later received NIH funding. Importantly, it supports researchers from various labs with human embryonic stem cell lines. Also, the Center for Stem Cell Biology is headed by Dr Sean Morrison and was initially funded by the university for USD 10.5 million in 2005. It focuses on the mechanisms that regulate stem cell function in the nervous and blood-forming systems. Other important labs are the ones headed by Drs Engel (developmental biology) and Krebsbach (bone growth and bone marrow).

Finally, research at *Duke University* is organised through two programmes, the *Adult Bone Marrow and Stem Cell Transplant Programme* and the *Stem Cell Biology Research Program*. The former is headed by Dr Nelson Chao and has over 70 professional researchers from various disciplines and the latter comprises 30 laboratories from 12 different departments and covers basic, translational and clinical research on stem cells.

6.3.5 Conclusions on the scientific hubs in stem cells

Concerning stem cell research, the results indicate that Sweden has a top position in relation to GDP and population for stem cells linked to neuroscience and 6th position in absolute terms. The People's Republic of China and South Korea also show a steep increase in stem cell research.

From the analyses of prominent organisations, it is clear that Harvard University is outstanding in all datasets of articles selected for analyses of stem cell research environments. In some datasets however, the gap to the organisation with the second largest publication volume is not so wide. For instance, the top universities in stem cell datasets, apart from the ones from the US, come from Japan, Sweden, England, Switzerland, Germany, Singapore, Italy and Canada. In top journals in terms of impact factor and in stem cell research related to neuroscience, Sweden's Karolinska Institutet is the top European organisation. The top non-US organisation in the same dataset is Japanese Kyoto University at 3rd position. Other prominent Swedish research organisations in the stem cell datasets are Lund University and Gothenburg University. Looking in detail at the leading research environments at the US-based universities it is evident that there are at least 10 groups that have achieved a critical mass of resources to perform outstanding scientific results.

In summary, in the specific area of stem cells, influential research is conducted in many countries including the US, the UK, Germany, Italy, Sweden and Australia, but several other countries, such as Singapore and China, are moving into the arena with impressive resources.

While Sweden has a good position in terms of publications per GDP or as related to the size of the population, the situation is less impressive in terms

of a critical mass of research. To move out of this situation, extensive efforts have been made, such as the formation of a stem cell centre at Lund University. It is likely that more efforts are needed to not only defend the current research strengths but also to move aggressively into new areas. Catching up and creating critical mass also seems possible if resources and coherent policies are in place. As an example, in the case of Japan interviews indicate that in 2005, the country was generally in a catch-up situation regarding stem cell research and cellular markers. This seems due in part to cultural barriers to transplantations and organ donation and thereby a lack of adult stem cells and to some legal obstacles to the use of foetal stem cells. A centralised approach was taken with the 2002 Biotechnology Strategy Guidelines, stating a focus on culturing stem cells and establishing a stem cell bank.[168] Thus, Japan has moved from a catch up status to being listed among the top universities in the stem cell area.

6.4 Biomaterials

In an often-cited report from 2002, specifically relating to biomaterials in the TERM area, the most advanced R&D area globally is found to be that of adapting biomaterials and bioactive materials and the knowledge is globally well diffused (see Table 6.3).[169] As regards design of new materials – often with a biomimetic approach – extensive efforts have been made but the knowledge base is as yet insufficient. The report claims that at that time the US was the most advanced in linking biomaterial design to cell biology but in general, worldwide research efforts regarding this had not been prioritised when the report was issued and clinical applications were scarce.

Table 6.3. Assessment of global R&D efforts in biomaterials

R&D Topic	Global R&D Knowledge	Global R&D effort	Leading Region in R&D
Adapted biomaterials & bioactive materials	Advanced	Extensive	US/EU/Japan equal
Biomaterial design	Incomplete	Extensive	1) US, 2) Europe, 3) Japan
Linkage of biomaterial Design to cell biology/ development	Incomplete	Modest	US
Clinical application of novel concepts	Incomplete	Little	US/EU/Japan equal

Source: McIntire et al (2002).

Our analysis of biomaterials relates to the subareas of scaffolds/matrices, ceramic materials, osseointegration and biomimetics. In the process of choosing these sub-areas many different search strings were developed and tried in an attempt to capture the research of a number of known prominent scientists in the field of biomaterials and biomaterials research linked to

TERM applications. The selection thus tries to capture two types of stable biomaterials, the use of scaffolds and matrices in TERM applications and also the field of biomimetics. Instead of creating a keyword search listing the manifold of polymers used as biomaterials for TERM purposes, a keyword set was chosen based on scaffolds and matrices trying to capture such research. The words scaffolds or matrix/matrices in combination with words relating to the aim of combining biomaterials with biological tissue were used. The same approach was used for ceramic materials combining the word ceramic with words relating to biological tissue. The research of tissue interaction with titanium alloys was studied with datasets created from the word osseointegration. The results of the analyses of these datasets are described in the following sections. The biomimetics area may include biomimetic applications other than TERM-related ones. However, other applications seem not to constitute a large share of the captured articles in that dataset.

6.4.1 Research into scaffolds or matrices

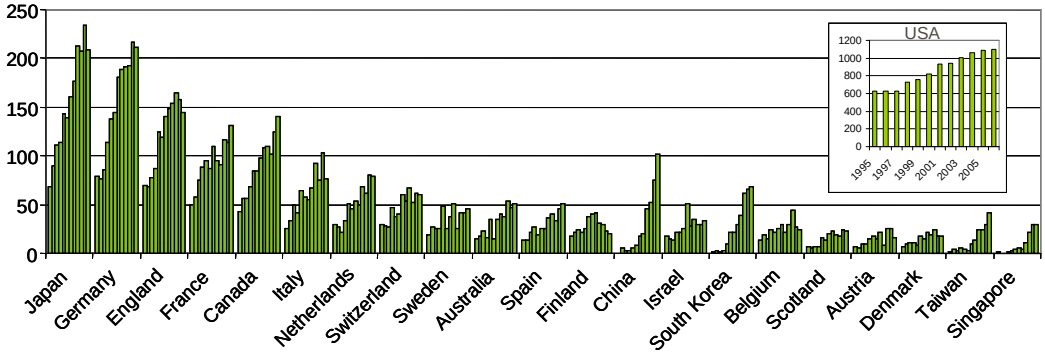
According to impact factor, a total of 19,559 articles were identified in top medical, life science and material science journals with the words (scaffold* and (cell* or tissue)) or (matrix and (cell* or tissue)) or (matrices and (cell* or tissue)) in title, keywords or abstract for 1995-2007. The number of articles per year has doubled over the period. The journals with over 500 articles in this dataset are shown below.

Table 6.4. Number of articles in the largest top medical, life science and material science journals according to impact factor with the words (scaffold* and (cell* or tissue)) or (matrix and (cell* or tissue)) or (matrices and (cell* or tissue)) in title, keywords or abstract, 1995-2006

Journal	Number of articles 1995-2006
Journal of Biological Chemistry	3,583
Biomaterials	1,365
Cancer Research	905
Proceedings of the National Academy of Sciences of the United States of America	822
Journal of Cell Science	734
American Journal of Pathology	676
Journal of Cell Biology	670
Journal of Immunology	588
Journal of Biomedical Materials Research Part A	582
Oncogene	509

The development of the number of articles for the top countries is shown below and an impressive development can be seen for Asian countries, especially the People's Republic of China but also South Korea, Taiwan and Singapore. All those countries start with a very limited number of articles yearly in the first part of the period studied and show a steep increase.

Figure 6.24. Articles in top medical, life science and material science journals according to impact factor with the words (scaffold* and (cell* or tissue)) or (matrix and (cell* or tissue)) or (matrices and (cell* or tissue)) in title, keywords or abstract 1995-2006

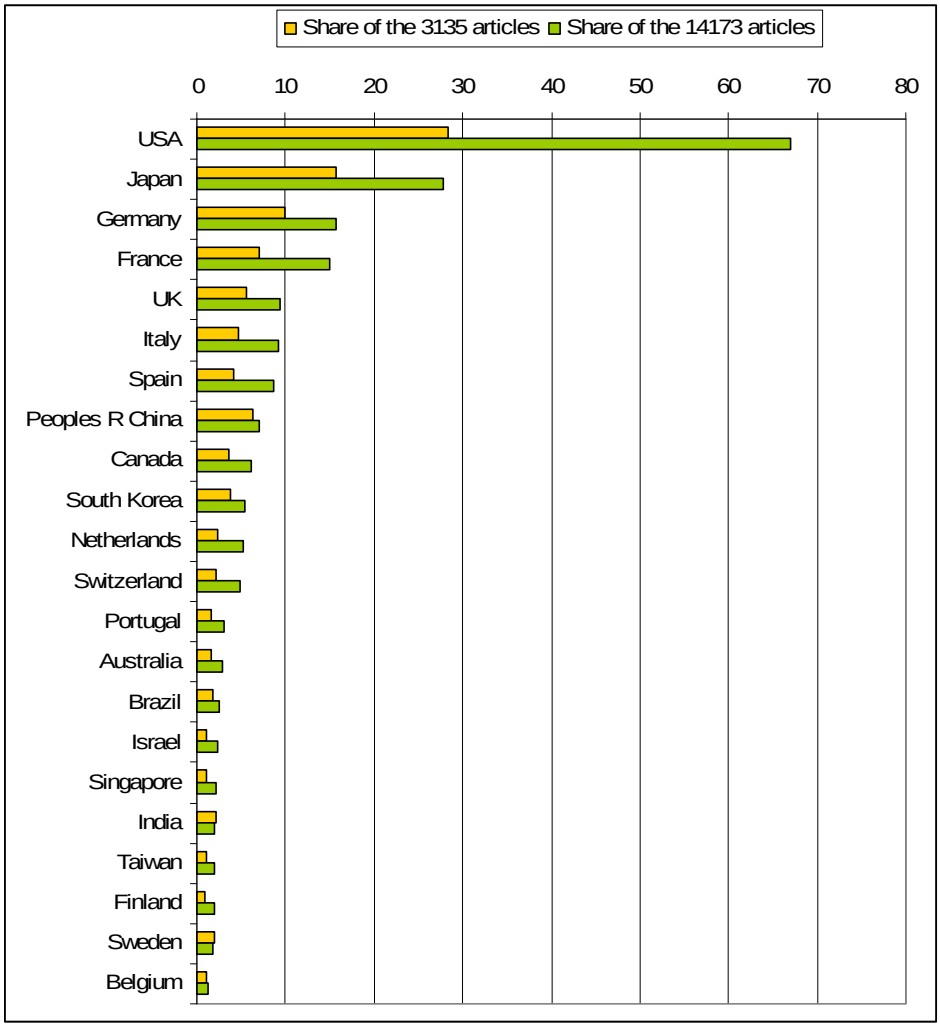


The six top organisations in terms of publication volume in this dataset are from the US with the Universities of Harvard, Texas and California San Francisco as leading organisations. Toronto University is 7th and the University of Tokyo has 10th position. US organisations are found in all other top ten positions.

6.4.2 Ceramic materials

Two datasets for the research field involving ceramic materials in combination with biological tissue were analysed. In the search covering all SCI Journals, the ones with the largest publication volumes are: Journal of Biological Chemistry; Biomaterials; Journal of Biomedical Materials Research; Journal of Materials Science- Materials in Medicine; Journal of the European Ceramic Society; Journal of the American Ceramic Society; FEBS Letters and Journal of Materials Research. A total of 14,173 articles were included in the dataset. The journals with the largest publication volume in the second dataset of 3,135 articles in top medical, life science, materials and multidisciplinary journals are: Journal of Biological Chemistry; Biomaterials; Journal of Biomedical Materials Research; Journal of the American Ceramic Society; Cancer Research and Journal of Immunology. The top countries in the two datasets are shown in the figure below.

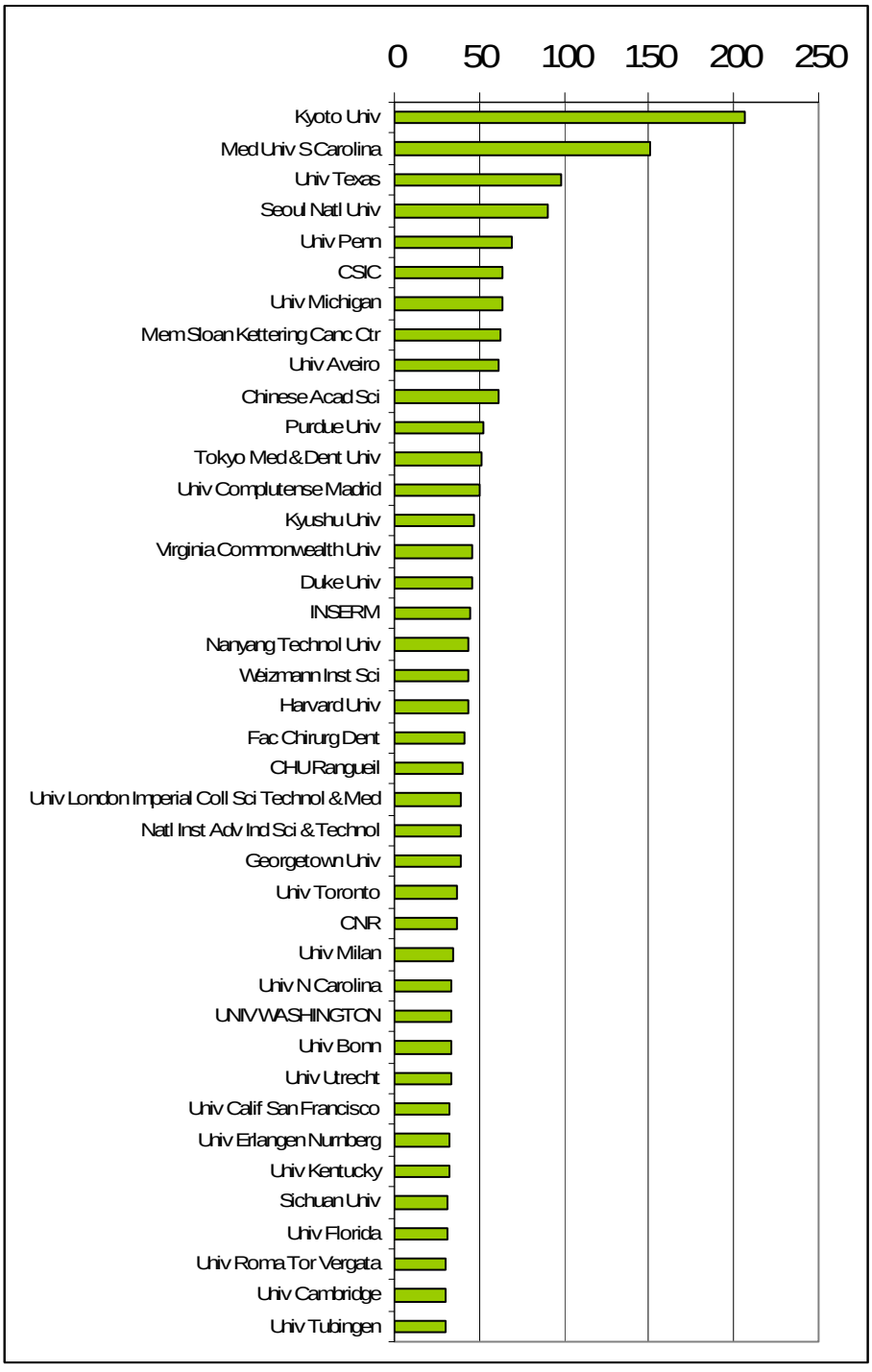
Figure 6.25. Share of the total publication volume for authors from the 22 countries with the largest publication volumes with the words "Ceram*" and ("cell*" or "tissue*" or "bio*" or "protein*") in title, keywords or abstract, 1996 - October 2007, in all SCI journals and in top medical, life science, materials and multidisciplinary journals, respectively[170]



The US is not as dominant according to this selection of articles as in the stem cell-related datasets. Also Canada, which has had a strong position in the other biomaterials categories, has a less prominent position.

The pattern concerning dominating research organisations also differs from the results in the stem cell related fields. Of the 40 top organisations shown below, 40% are North American, almost 40% are European and 20% are Asian.

Figure 6.26. Number of articles by authors from the organisations with the largest publication volumes in top life science, medical or material science journals (according to impact factor) or Proceedings of National Academy of Sciences, Science or Nature with the words "Ceram*" and ("cell*" or "tissue*" or "bio*" or "protein*") in title, keywords or abstract, 1996 - October 2007

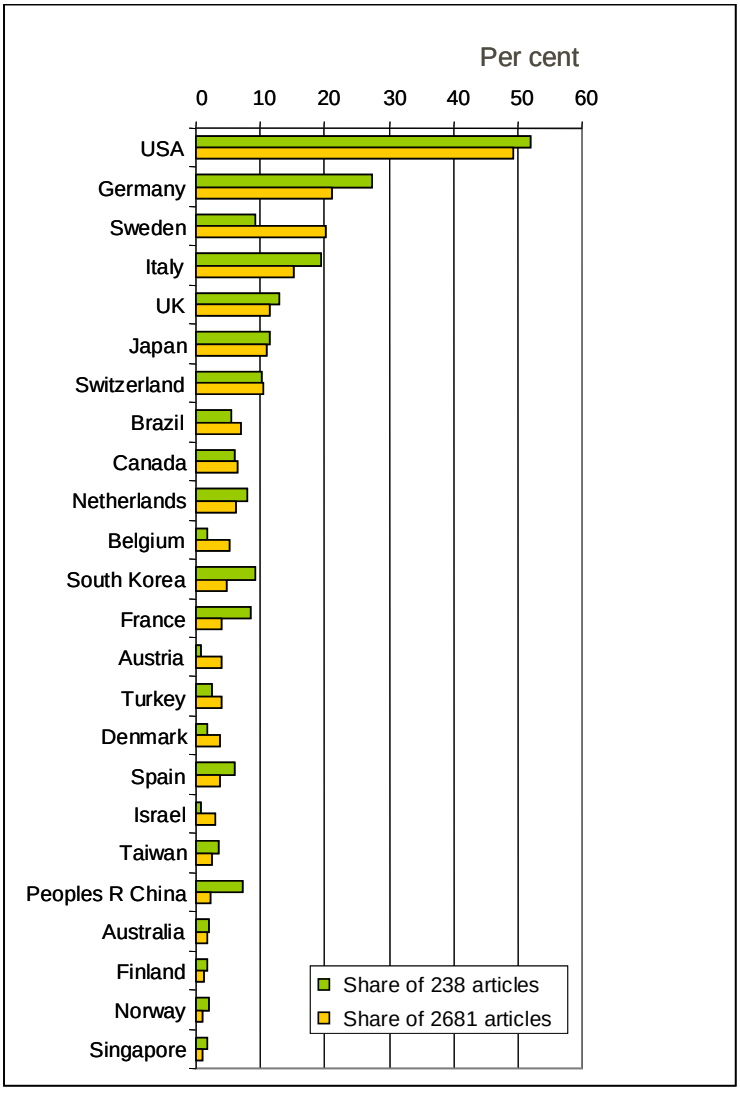


6.4.3 Osseointegration

Again, two datasets were created, one with all SCI journals and one with life science and medical journals with an impact factor larger than 6, materials journals with an impact factor larger than 1.5 as well as Nature or Science. The first dataset included 2,681 articles and the second a total of 238 articles. The majority of the 238 articles are found in the journals Biomaterials and Journal of Biomedical Materials Research. The journals with the largest number of articles in the 2,681 dataset were: International Journal of Oral & Maxillofacial Implants Research, Journal of Prosthetic Dentistry, Journal of Peridontology, International Journal of Perodontics & Restorative Dentistry, Biomaterials, International Journal of Prosthodontics, Journal of Oral and Maxillofacial Surgery and Journal of Biomedical Materials Research.

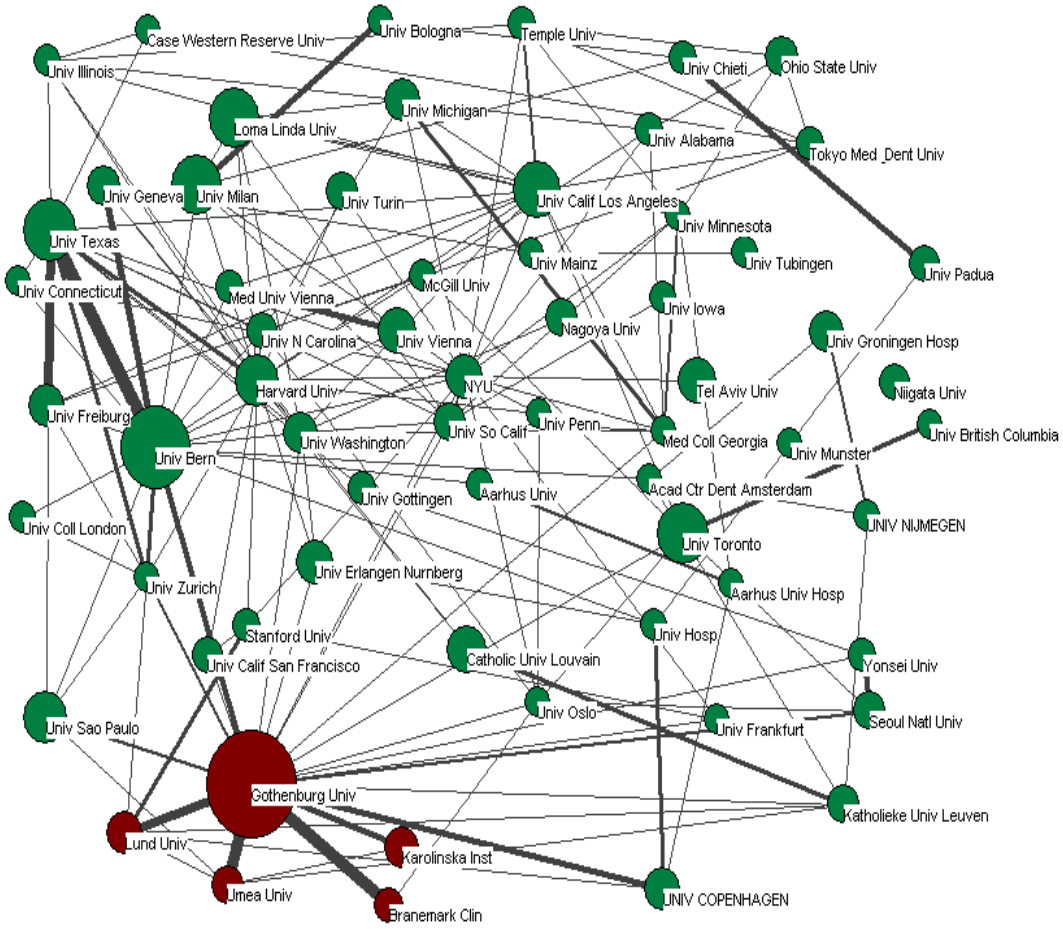
Germany, South Korea, France and China are among the countries with a significantly larger share in top journals than in all SCI covered journals as seen in the figure below. Sweden, on the other hand, has a significantly larger share in the dataset with articles from all SCI covered journals.

Figure 6.27. Share of the total number of articles for countries with the largest publication volume in two datasets: 238 articles in top life science, medical journals or material science (according to impact factor) or Science or Nature and 2,681 articles in all SCI covered journals with the word "osseoint*" in title, keywords or abstract, 1996-2006



The co-authorship pattern of organisations the 2,681 articles in all SCI covered journals is shown below and the next figure lists the top organisations in the top journal dataset of 238 identified articles. Gothenburg University is the top organisation in both these datasets. The dynamics for the 2681 articles indicates that is a growing research area. However the pattern differ between countries, were some of the top countries have a steep increase and others show a moderate increase.

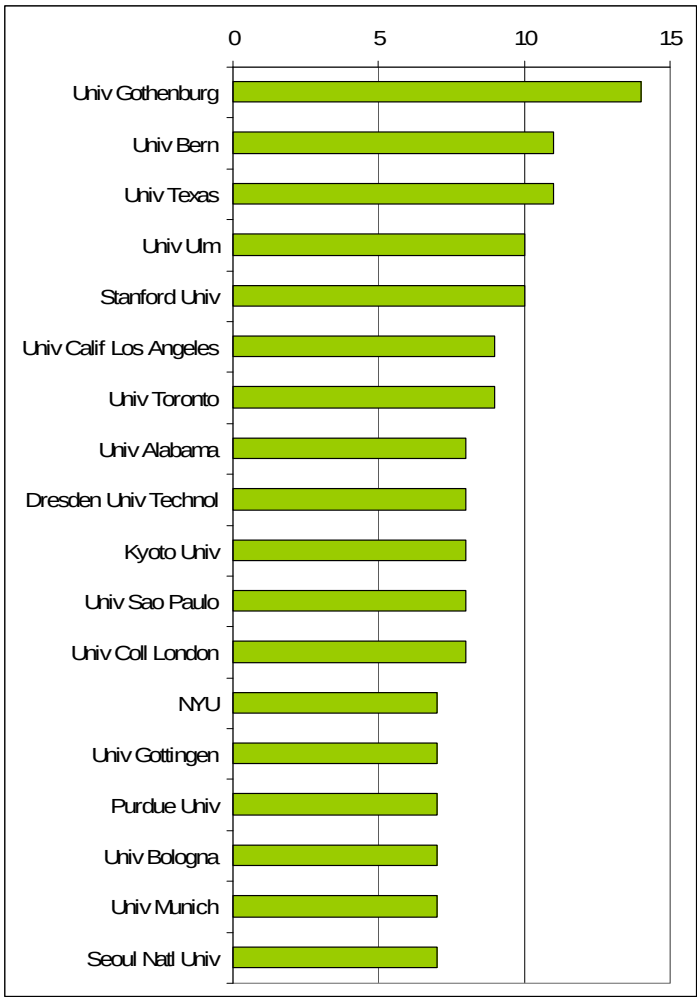
Figure 6.28. Collaboration pattern between the researchers from the countries with the largest publication volumes with the word "osseoint*" in title, keywords or abstract, 1996 - October 2007, 2,681 articles in total [171]



In the figure above, it is apparent that the number of US organisations among the top-performing and their relative publication volume is lower in the research field covered by this dataset than in the other fields studied in this chapter.

The figure below shows that of the 18 organisations with the largest publication volume in top journals, eight are European, six are from the US and two are Asian.

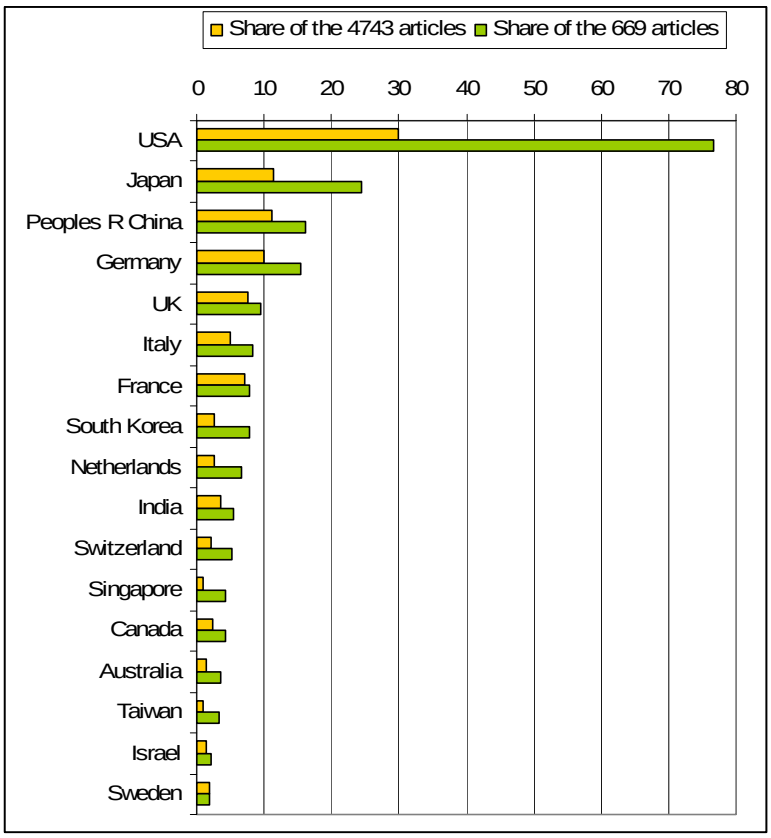
Figure 6.29. Number of articles by authors from the organisations with the largest publication volumes in top life science, medical or material science journals (according to impact factor) or Science or Nature with the word "osseoint*" in title, keywords or abstract, 1996 - October 2007



6.4.4 Biomimetics

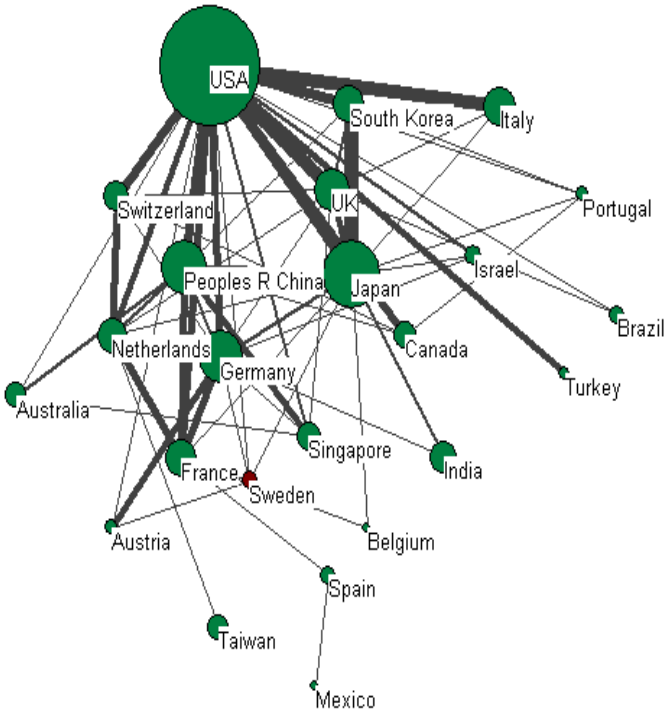
Two datasets were created to study biomimetics research, one including all SCI covered journals (4,743 articles identified) and one covering top medical, life science, materials and multidisciplinary journals (669 articles identified). The top journals in terms of publication volume in the first dataset were: Journal of the American Chemical Society, Biomaterials and Tetrahedron Letters and for the second dataset: Biomaterials, Journal of Biomedical Materials Research and PNAS. In the first dataset, the countries listed below had the largest share of the articles in 1996-2006. The figure also shows their share of the publications in all SCI-covered journals.

Figure 6.30. Country shares of the total number of articles in two datasets: 669 articles in top life science, medical journals or material science (according to impact factor) or Science or Nature and 4743 articles in all SCI covered journals, all with the word "biomim*" in title, keywords or abstract, 1996 - October 2007



The US has over twice the share of the articles in top journals than in the dataset covering all SCI included journals. A similar trend is seen for all top countries, that they are having a larger share of the articles in the top dataset. This is due in part to the larger dataset being spread across almost twice the number of countries and a more intense national co-authorship pattern in the smaller dataset. In other words, countries collaborate more on articles published in top journals.

Figure 6.31. Co-authorship pattern between researchers from the countries with the largest publication volumes in top life science, medical or material science journals (according to impact factor) or Proceedings of National Academy of Sciences, Science or Nature with the word "biomim*" in title, keywords or abstract, 1996 - October 2007[172]



The country co-authorship pattern in the top journal dataset of 669 articles is illustrated above. In this field, the collaboration pattern is truly global with strong links between European, Asian and North American countries.

6.4.5 Conclusions on the scientific position in the biomaterials area

Biomaterials research in the US has been coordinated in rather large R&D programmes such as those at Cal Tech, Case Western Reserve, Georgia Tech's ERC for Engineered Tissues, MIT's Biotechnology Process Engineering Center, Rice, University of Michigan, Rutgers, U.C. Santa Barbara and University of Washington Engineered Biomaterials Engineering Research Center (ERC). As stated above, US players are good at the increasingly important integration of various disciplines. Funding comes from such sources asNIH and NSF but also from industry. Industrial advisory boards and the involvement of bodies like the National Heart, Lung and Blood Institute have also ensured industrial involvement.[173] As is obvious from the bibliometric analysis, the US standing within biomaterials is prominent, with nine out of the ten top organisations in regard to scaffolds and matrices being American.

In Europe there is also a long tradition of outstanding research in biomaterials with work on such things as degradable materials, production design, understanding of molecular characteristics and design, enhancing polymer functions, etc. However, in the bibliometric study, the first European organisations appearing in the statistics concerning scaffolds and matrices are only at about 30th position in terms of publication volume in top journals. In Japan, earlier studies indicate that research has not been as strong and also more focused on modifying existing materials instead of creating new ones.

From early on, the Japanese focus has been on applications for bone repair and liver assist devices. The analysis of scientific publications shows that especially Kyoto and Tokyo Universities are prominent in many of the biomaterials sub-fields. For Kyoto University, this is especially true in ceramics and biomimetics and for Tokyo University, the field of scaffolds and matrices is the most prominent field.

Importantly, both Europe and Japan have been in somewhat of a catch-up situation as compared to the US in the tissue engineering part of the biomaterials field. This is also clear from the bibliometric results where it is seen that the publication volumes of Japan and a few countries in Europe, such as Germany, England and France, have increased more rapidly than those in the US. However, these also rose during the studied time period. Nevertheless, increasing government funding has now allowed the building of academic competence centres.

In summary, the Ceramics field is topped by Kyoto University in both datasets. Equal shares of the top 40 organisations, amounting to a total of 80%, come from European countries and North America. In the field of osseointegration, Gothenburg University tops the statistics both in the dataset of all SCI-covered journals and that of top materials, medicine, life science and multidisciplinary sciences journals and is followed by the Universities of Bern and Texas. Among the top organisations in the biomimetics research field is Kyoto University again and in the top journals, other organisations include the Universities of Michigan, Bologna, Seoul and California Los Angeles. Outside the area of osseointegration, Swedish research organisations are not found among the top 30 organisations in the biomaterials field, apart from Lund University in biomimetics. Of course, there may be top researchers in smaller groups in Sweden in other biomaterials fields as well as research groups not identified with this methodology due to not having sufficient critical mass to compete with other top organisations by publication volume.

7 Summary of empirical results

This report discusses the current state and activities of an emerging and fast-moving knowledge field: that of tissue engineering and regenerative medicine, or TERM for short. In the present study, regenerative medicine is defined as medical treatments, be they biological or synthetic, which enhance, repair or replace cells, tissues and organs using bioengineered materials, cellular technologies as well as some forms of implants. Many nations are focusing on TERM research and it seems as though most countries with prominent biotech-related research have some activities within the field. Major players on the international arena include the US, Canada, Germany, the UK, France, Switzerland, Sweden, China, Japan, South Korea, India and Singapore.

In terms of clinical use and industrial development, TERM is still at a very early stage. As an emerging field, it is subject to all the general uncertainties of evolving competence areas and industries. Exactly how the field and its associated industries will evolve is highly undecided and this goes for the timeframe of clinical applications as well as viable business models. There are indications that Sweden and Swedish players can take an active role in contributing to the field as well as reaping its returns. Within the adjoining field of biomaterials there is historically strong Swedish research as well as an industrial base, partly paving way for potential successes within TERM. As regards TERM related research there is today a track record of successful Swedish players in academia and a number of companies have emerged.

Given the in some respects impressive Swedish achievements to date as well as the challenges at hand for Sweden to draw on international advances within TERM and provide its citizens with the best health services possible, the aim of this study is to understand the Swedish position in an international comparison. Also, it aims to identify what initiatives could stimulate knowledge creation and innovation processes leading to new therapies and products beneficial to patients and which might also ultimately contribute to economic growth in Sweden. Thus, in the present study the Swedish situation has been compared with that of some of the leading nations globally: two European countries, Germany and the UK; one Asian player, Japan; and the US, with particular attention to one region there, California. All the chosen countries are very much larger than Sweden concerning the size of the population and GDP and they are among the most prominent countries in life science R&D. As a consequence of this they also contribute much larger investments in TERM R&D and have a larger

TERM industry than Sweden. The countries have been chosen since they stand for a major part of the scientific and industrial development of the field. This is for instance evident from the bibliometric analysis. Players in these countries to a large extent form the TERM development and it is also with individual players in these countries, Swedish research environments and companies are likely to compete and collaborate. To have knowledge of the development in these countries is thus of importance to Swedish players.

The analysis in the report is based on a number of complementary sources. To form a general definition and understanding of the dynamics at hand, the authors own and interviewed experts' knowledge of the scientific and industrial field has been built on. A large number of books, reports, articles and journal papers have been scrutinised, some of which are especially noted in the list of references. Using a country case study approach, detailed interviews with various types of players have been conducted: researchers, representatives of technology transfer offices, small firms, large companies and venture capital companies as well as policymakers and experts in the five focus countries. A total of 58 interviews were conducted. A systematic approach to identify and characterise firms has been developed, including all companies identified globally, but with special attention to the five focus countries to get the fullest coverage possible. These firms are classified according to such things as type of cells used, type of application and phase of development. National initiatives have been identified and a mapping of research environments and individual researchers working in the TERM area conducted. The mapping of initiatives and research environments does not aim to give full coverage to the whole dynamic area, but merely illustrates the volume of investments and activities. Finally, through a bibliometric analysis the report gives an estimation of the scientific output from and networks between countries and research environments.

7.1 Knowledge areas, applications and firms

The type of products and services that will prove commercially viable is not easy to foresee and it also difficult to know what type of companies will bring them to the market and how the industry will mature. It is likely that the products and services TERM will result in will play a decisive role in a range of industries; the pharmaceutical, orthopaedic, dental industry, etc. TERM may also give rise to new industries, that do not fit easily into current industry definitions. TERM-related products may also be influential in various parts of the value chain, through the development of materials, therapeutics, diagnostics, tools, or specialised services for example. In the five countries selected for an in-depth analysis, 303 companies were identified, out of which 73 firms are developing organ specific tissue-engineered products. The remaining companies are found in fields relevant

to tissue engineering such as drug discovery and development and biomaterial implants. They develop products which can be used for TERM purposes, for instance growth factors, cell handling solutions or scaffolds. Tissue engineering includes the development of therapeutic solutions based on a combination of a) scaffolds based on biomaterials, b) cells and tissue and c) biomolecules. TERM is commercially still an area in early phase of development and the firm population in Sweden as in other countries thus constitutes a relatively small part of the life science industry. Concerning organ specific tissue engineering applications three Swedish companies were found. Two of these companies are very small and the third and only large company no longer pursues tissue engineering activities.

TERM related applications which to a large extent have matured before the tissue engineered solutions include applications in drug discovery and development and tools for cell and tissue handling. These include the use of growth factors to stimulate regeneration, new stem cell-based platforms for drug discovery and development and drug delivery with the aid of biomaterials. Sweden has three companies in the following categories related to pharmaceuticals: drug discovery using stem cells, drug discovery to stimulate regeneration and tools using stem cells for drug discovery and development, for example to use cells to do toxicological and metabolic studies of drug candidates under development. These are all academic spin-off companies that are still quite small and have yet to show commercial success. Even so, there are indications that they have a significant commercial potential and one is now moving ahead with clinical trials and another has agreements with large pharmaceutical companies. Concerning companies developing tools for cell handling, Sweden has two established firms coming from the in vitro fertilisation field and one academic spin off company that develops tools for drug discovery and development using stem cells.

The area of biocompatible materials is an important field in and of itself, since they are integral to various forms of implants, for instance for orthopaedic or dental purposes. This type of companies may in the future find that TERM products and services will compete with their established products and they may also enter the TERM field themselves. Few examples of biocompatible material implant companies moving in this direction have however been identified in the present analysis. While such products are not included in the definition of TERM, there has been a mapping of the relevant Swedish firms (but not in other countries) in order to relate the current Swedish strengths in this field to the potentials of TERM. In Sweden, about 15 companies are developing stable biomaterial products, SMEs as well as large firms. There are also about five established firms and two recent start-up companies using biodegradable biomaterials.

This includes companies using biomaterials as dermal filler, degradable implants that help regenerate body functions, bone-anchored titanium alloy dental implants and hearing aids, bone cement products etc. Thus, the commercial knowledge base in relevant areas is substantial. Sweden thus has a definite strength concerning biomaterial products.

In summary, there in Sweden are two small start-up companies developing tissue-engineered products. As regards tools for cell handling there are three Swedish firms, of which two originate from the in vitro fertilisation field. Concerning pharmaceutical applications, three small start-up companies are found and some of these are showing a promising development, although not yet a commercial success. Thus, the Swedish firm population, besides the commercial strength in biomaterials, includes in total eight companies and these are commonly small, often academic spin-offs, with a wide variety of TERM-related applications.

7.2 The path to market

While the overall market for future TERM products is judged by most analysts to be quite large, for many companies this is still more vision than reality. Besides the financial uncertainties concerning financing of R&D and future reimbursement policies the report discusses some other specific hurdles firms may meet on the path to market. Firstly, in the specific case of stem cells the market path will be designed on the basis of scientific realities as well as public and political acceptance of these technologies. Such concerns have led to the issue of type of cell source being high on the agendas in many countries, leading to differing circumstances for firms located in these countries or regions. As the type of cell source to some extent guides the market possibilities and specific path to market the firm may take, understanding national differences and their implications is of strategic importance.

Secondly, legitimacy and political receptivity is a key issue. While the reasons for lacking legitimacy may differ between different cultural settings, it leads to similar types of constraints, for example in terms of uncertainties concerning future reimbursement systems and issues regarding approval processes. It seems to be generally understood that one aspect that will change the situation is when technological uncertainties are removed. For example, it may be that when a proven life-saving therapy is brought out, legitimacy will be forthcoming from both the general public and policymakers concerning that particular application. Until that day, firms bear a heavy load of proving the worth of the new technologies and products to the market and must seek out strategies to overcome problems of absent

legitimacy. However, it is not necessarily the case that such a breakthrough for one application leads to increased acceptance for other applications.

Thirdly, in this early phase of the field, much experimentation with different types of business models is taking place, balancing high potential products with more easily attainable goals. The choice of business model also involves determining the company's role in a value chain and what competencies are needed in-house and how to solve the need for externally provided development tools, production technologies, service provision and equipment. In addition, specific demands for production and distribution will come into the equation and there is also a notion in the field that service provision is likely to become an important part of the commercial development.

Fourthly, the path to market is partly guided by the firm's location. This is due to matters of legitimacy, reimbursement, legislation, approval processes etc., as stated above, but also to the resource network. Recruitment of speciality skills, access to custom designed development tools, knowledge of new scientific discoveries, financial potential and possibilities for innovative collaboration may all depend on where in the world firms are established and grow. The analysis of the geographic location of the 73 firms developing organ-specific TERM products in the five focus countries indicates that they are largely found in established life science clusters where there are public and private research organisations, clinics, firms, service providers, consultancies, etc.

7.3 Market approval regulations in the EU

In an analysis of regulatory issues related to clinical trials and market approval in the EU, the present report argues that Europe has long lacked a synchronised agenda regulating market approval of tissue-engineered products. Today, a common regulation has been shaped and will be in force from December 30, 2008. This new regulation is likely to be a crucial step for Europe to continue its prominence in this field. Aimed at advanced-therapy medicinal products, it includes products based on genes, cells and tissues and a centralised marketing authorisation procedure giving successful applicants direct access to the entire European market. With the pooling of experts in the European Medicines Agency (EMEA) it also builds a common understanding of the emerging field as a whole. Importantly, the analysis illustrates that TERM products are not easily classified into the traditional categories for regulation of pharmaceuticals or medical devices and that the products also link to the category of biologics used in the US system. The EU regulation stresses recognition of new types of products, combining biological material and chemical structures.

Importantly, both scaffolds and stable biomaterials are pointed out to be of crucial importance, further linking the biomaterials field to tissue engineering, which is of particular importance to Sweden.

Also, the regulations place specific emphasis on making sure small and medium-sized enterprises have equal opportunities as large ones. One concern raised by various stakeholders involved in the review process is the balance between regulatory flexibility on the one hand, and product standards on the other. It is a field where scientific development is ongoing and therefore flexibility needs to be retained, simultaneously as reducing uncertainty is crucial from the researchers' as well as firms' perspectives.

It is not far-fetched to think that the situation with unclear or lacking regulation has weakened the development of the field in Europe and possibly led to fewer products being placed on the market. In fact, various countries have put their custom designed approaches into practice, which is likely to have led to excessive costs for companies adapting their applications to different markets with dissimilar requirements. In addition, opportunities for cooperation and marketing across nations have been inhibited.

7.4 Policy initiatives and research in academia

For the TERM area to mature, it is important to have strong research and innovation environments and for those to be connected to international counterparts. In a detailed account of the types and volumes of national or regional initiatives relating to TERM in the countries chosen for an in-depth analysis in this study (Germany, the UK, Japan, US and Sweden), it was clear that TERM is a prioritised area. TERM policies and investments however differ in regard to the relative focus on basic versus applied research, attention to inter-disciplinarity and translational research, profile areas, actors involved in strategy formulation and implementation and absolute volume of investments. Within TERM, public investments, main universities and firms are geographically clustered to the major city regions. Even a small country like Sweden often has to build general knowledge in many (if not all) the included subfields in order to have 'absorption capacity' combined with being at the forefront of other parts of the field. Sweden is notable as the only one of the five countries that has not formulated an explicit strategy. The increased funding presented in the Swedish research and innovation bill in October 2008 directed towards research and innovation activities in the field does not include provisions on a strategy formulation process.

The German government has recently initiated centres of excellence in Dresden, Hannover, Leipzig and at the Berlin-Brandenburg Centre for

Regenerative Therapies, all centres involving leading universities. The idea is to co-locate a range of competencies to form *centres* as opposed to the more loose collection of TERM activities within a region. These may just be the seeds needed to build major research constellations.

The research councils in the United Kingdom prioritise the TERM area and, with other players, have launched a set of initiatives. These include the UK Stem Cell Initiative (UKSCI), the UK Stem Cell Bank, the Scottish Centre for Regenerative Medicine (SCRM) and the Wellcome Trust Centre for Stem Cell Research (CSCR). Also, a number of non-governmental foundations and trusts are active, including the UK Stem Cell Foundation (UKSCF) which relies on financial backing from individuals, trusts and companies.

As regards university research in the UK, over 20 universities are involved in TERM-related research, including University College London, Imperial College London and the universities in Leeds, Sheffield, Nottingham, Strathclyde, Cambridge, Southampton and Sussex. For stem cells and tissue engineering, the Institute for Stem Cell Research at Edinburgh University, the Centre for Stem Cell Biology at the University of Sheffield and the stem cell group at King's College London are standouts. The work at Queen Mary (London) can be mentioned in regard to biomaterials and medical devices.

As stated in the Japanese Biotechnology Strategy Guidelines, Japan has high hopes of taking a leading position in TERM research. Beginning with the Millennium Project 2000-2004 and continuing with the 10-year national "Project to Realize Regenerative Medicine" (2003-2012) and the establishment of various centres of excellence as well as attention given to the national medical centres, funds are provided through the MEXT, METI and MHLW ministries. These are complemented by an array of industrial and regional support programmes. Some important centres and research groups include the RIKEN Centre for Developmental Biology, the Institute for Integrated Cell-Material Sciences (iCeMS) at Kyoto University, the Center for Experimental Medicine at the University of Tokyo, The Department of Physiology at Keio University, Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University, the Department of Oral and Maxillofacial Surgery at Nagoya University and the Research Institute for Cell Engineering within AIST.

The US investments into TERM research are most impressive in absolute numbers. Government funding for TERM comes from the National Institute of Health (NIH), the National Science Foundation (NSF), the National Institute of Standards and Technology (NIST), as well as from NASA, the Department of Defense and the Department of Energy. Importantly, for the

field of tissue engineering (more narrowly defined than the entire TERM area) the NIH funding has been dominating and crucial to develop the scientific results, supporting own laboratories, universities, medical schools, hospitals and research institutes, nationally as well as abroad. Particularly interesting is that the large funding of stem cell related research has during the period 2004-2008 focused largely on non-embryonic stem cells, something that may very well shift with the new governmental regime now in place. As regards NSF funding, a large number of grants for TERM research has been awarded, where e.g. the centres at Georgia Tech, University of Washington and MIT stand out. Moreover, NIST has financed work to improve various measurements methods for tissues and cells, as well as techniques for medical imaging. In addition to federal financing, several foundations and philanthropists are also key sources of funding for TERM research; embryonic stem cell research in particular. In order to link various scientific disciplines working with biomedicine and deal with the high levels of complexity involved, the National Institute of Health (NIH) took the initiative to develop a 'roadmap' to identify the major opportunities and gaps in biomedical research. As one result relating specifically to TERM, various stakeholders were engaged in the Multi-Agency Tissue Engineering Science (MATES) working group, aimed to discuss and negotiate priorities and common agendas for scientific funding, thereby avoiding duplication of efforts. A related strategic initiative for the area as such is the National Tissue Engineering Center (NTEC), both developing technologies and assisting in the development of a national tissue engineering strategy.

Swedish governmental agencies have not formulated overall strategies and programmes for the TERM area. However, TERM projects and centres are financed by both public and private organisations through the research and innovation funding system of Sweden. Thus, funding is currently in place for a few centres of excellence and one cluster development initiative in the field. Also, quite a few TERM projects are given funding through grants to individual researchers. There are three main funding organisations in Sweden involved in the TERM area: the Swedish Foundation for Strategic Research (SSF), the Swedish Governmental Agency for Innovation Systems (VINNOVA) and the Swedish Research Council. In Chapter 8, the implications of the recent research and innovation bill are discussed. The bill suggests a new SEK 65 million investment in stem cells and regenerative medicine 2010-2012.

7.5 The scientific output

The scientific knowledge base for tissue engineering and regenerative medicine applications can be described as a multidisciplinary combination

of materials science, fundamental biological sciences and pre-clinical and clinical medicine. A number of bibliometric studies were conducted in order to study the development of the scientific fields involved and identify important players and their interaction. These studies can be grouped into the following three sections: Stem cells; Biomaterials and Tissue engineering & Regenerative medicine. The fields studied have differing size thus the analyses is made based on relative differences between countries and organisations within a particular field.

In absolute terms, the US has the top publication volume in all studied scientific fields, the second country often being Japan, Germany or the United Kingdom. However, this is not true in relative terms, in other words the publication volume in relation to population or GDP. Using those measures, the smaller countries like Sweden, Switzerland or the Netherlands often top the ranking depending on the scientific field.

Concerning the performance of countries, it is clear that some Asian countries such as the People's Republic of China, South Korea, Taiwan and Singapore, with little previous history of excellent research in the scientific fields of this study are showing increasing activity in both top journals and the broader selection of journals. Above all, this development is evident in some of the categories relating to material science such as scaffolds and matrices and ceramics. The Asian countries which show this trend and are also among the top-performing countries are first of all the People's Republic of China but also South Korea, Taiwan and Singapore. They usually appear in this order in the statistics with respect to publication volume. This is an impressive development, especially for the relatively smaller countries: South Korea, Taiwan and Singapore, with populations of 48.3, 22.8 and 4.5 million inhabitants respectively. Concerning stem cell research, the results indicate that Sweden has a top position in relation to GDP and population for stem cells linked to neuroscience and 6th position in absolute terms. Also, in stem cell research the People's Republic of China and South Korea show a steep increase.

The position in absolute or relative terms for a whole country can be used to analyse broad trends in different scientific fields. For a more in-depth analysis and to identify excellent research environments or whether an environment can be said to have a certain critical mass, analysing the performance of individual universities or groups of researchers is more relevant. It is likely that research environments with a critical mass and characterised by high quality research in a scientific field are attractive for both public and private investments. It is also likely that such environments have the capacity to generate breakthrough discoveries.

In studying excellent research and innovation environments, it is therefore interesting to look at high-performing universities in a specific field, their industrial linkages and whether start-up companies relating to that environment can also be identified.

In the analyses of research top performing stem cell research environments it is clear that Harvard University is outstanding. Top universities in, apart from those in the US, come from countries such as Japan, Sweden, England, Switzerland, Germany, Singapore, Italy and Canada. In top journals in terms of impact factor and in stem cell research related to neuroscience, Sweden's Karolinska Institutet is the top European organisation and the top non-US organisation is Japan's Kyoto University in 3rd position. Other prominent Swedish research organisations in stem cell research are Lund University and Gothenburg University. Looking in detail at the leading research environments, it is evident that about 80 per cent of the top 40 university environments are US.

In summary, in the specific area of stem cells, influential research is conducted in many countries including the US, the UK, Germany, Japan, Italy, Sweden and Australia, but several other countries such as Singapore and China are moving into the arena with impressive resources.

While Sweden has a good position in terms of publications per GDP or as related to the size of the population, the situation is less impressive in terms of a critical mass of individual research environments. Even though a few of them are clearly visible on the international arena, none of them is among the top ten universities in the analysis. Extensive efforts have been made to move out of this situation, such as the formation of the stem cell centre at Lund University. For stem cell research related to neuroscience, bibliometric data does not show a clear trend of increasing shares of the scientific output for the three top Swedish organisations. A corresponding analysis has not been made for other areas. It appears that that more efforts are needed to not only defend current research strengths but also to move into new areas. A catch-up and creation of critical mass seems possible if significant resources and coherent policies are in place. For example, the Japanese interviews indicate that in 2005, the country was generally in a catch-up situation as regards stem cell research as well as on cellular markers. This seems to due in part to cultural barriers to transplantations and organ donation and thereby a lack of adult stem cells, as well as legal obstacles to the use of foetal stem cells. A centralised approach was taken with the 2002 Biotechnology Strategy Guidelines, stating a focus on the culturing of stem cells and establishment of a stem cell bank with significant resources. Thus, Japan has moved from a catch-up status to being listed with the top universities in the stem cell area. Recent breakthroughs in iPS cell

research are possibly to some extent changing the dependence on embryonic stem cells.

Different biomaterial fields were included in the analysis. The Ceramics field is topped by Kyoto University in both top journals and journals chosen without excluding those with lower impact factor. Equal shares of the top 40 organisations, amounting to a total of 80%, come from European countries and North America. In the narrow field of osseointegration, Gothenburg University tops the statistics both in the dataset of all SCI-covered journals and that of top materials, medicine, life science and multidisciplinary sciences journals and is followed by Universities of Bern and Texas. Among the top organisations in the biomimetics research field is Kyoto University again and in the top journals, other organisations include the Universities of Michigan, Bologna, Seoul and California Los Angeles. No Swedish research organisation was identified among the top 30 organisations in the biomaterial fields outside the area of osseointegration with the exception of Lund University in biomimetics. Swedish research environments at one research organisation which has a critical mass large enough to compete with other top organisations in terms of publication volume have otherwise not been identified. There may however, be top researchers in Sweden in smaller research environments in biomaterials fields.

Co-authorship links between countries and organisations indicates that researchers from smaller countries are more prone to international collaboration, especially if compared to researchers from the US. It also seems as if international collaboration is more common in top ranking journals than in analyses of all SCI covered journals. This is in agreement with a study by the Swedish Research Council where the citation level of articles co-authored by researchers from more than one country had higher average citation levels than non-international papers in the medical field.

8 Discussion

Sweden takes a distinctive position and has definite strengths in the international development of the field. The present analysis shows clear strengths as regards to scientific profile and achievements, regulatory position, and a firm population with some promising activities. This chapter conducts a discussion on a number of issues which must be tackled if Sweden is to maintain – or in some respects build – a strong international position within TERM.

8.1 TERM – a strategic area

The potential outcome for medical uses from the competence fields of TERM globally are vast, and include generally improved quality of life, treatments of previously untreatable conditions as well as reduced cost of treatment for some medical conditions. As a result, the area is prioritised by policymakers in many countries and many research and innovation promotion efforts have been set up to develop the field. This is the case even though TERM is an emerging field with many uncertainties as to what products and services will be developed and how they will be reimbursed and reach clinical practice. Thus far it is unclear how the TERM related industries will mature.

All countries chosen for more detailed analysis are very much larger than Sweden concerning the size of the population and GDP and they are among the most prominent countries in life science R&D in the world. The countries have been chosen since they stand for a major part of the scientific and industrial development of the field. Players in these countries to a large extent form the TERM development and it is also with individual players in these countries Swedish research environments and companies are likely to compete and collaborate. As a consequence of this they also contribute much larger investments in TERM R&D and have a larger TERM industry than Sweden. Some countries do make impressive investments and achieves striking results in terms of scientific output but also in terms of (the early phases of) product development. In fact, it is clear from the overview of national initiatives that there are a number of countries which consider TERM highly prioritised. The US makes by far the largest investments as regards *input* in TERM-related R&D, which is to be expected considering it is the country with the largest public R&D budget. While other countries may have difficulties in matching the US figures in absolute terms, significant and increasing investments are being made. Apart from Japan and a number of countries in Europe seriously contributing to the global

research efforts, countries such as China, South Korea, Singapore, Australia and Israel are also very much involved in research and innovation activities within this field. In 2002, Japan set out to become a global leader within TERM, aspiring to compete with the US and Europe and be quicker to move than they were for some other biotech-related areas. This is also emphasised by major financial investments in TERM-related research and innovation initiatives. The up-scaling in Japan also includes initiatives to promote the recent breakthrough in iPS cell research and those initiatives are examples of quick policy response to research discoveries.

The larger countries invest much more in the field (in absolute figures) than Sweden ever could (see examples in chapter 3). A small country like Sweden is not likely to become a research leader, nor an industrial leader in the overall area of TERM, but individual players or groups of organisations can still be leaders in a few subfields. These areas may be those where Sweden already has a strong position and where a critical mass of both research and industrial activities may be obtained. The Swedish focus may also include strategic areas deemed important for the future development of TERM where Swedish research today is not as prominent.

Bibliometric studies indicate some definite Swedish R&D strengths in fields relevant to TERM. According to bibliometric data, Sweden has scientific excellence in stem cells, especially in the neurological field. In regard to biomaterials, the strengths relate primarily to osseointegration.

Stem cell research is a growing and prioritised research field globally and the fact that Sweden has some strength in the field is a good foundation for future knowledge creation. The narrow field of osseointegration is also growing according to the analysis but the patterns differ between countries, with some of the top countries having a steep increase and others showing a moderate one. However, according to the present bibliometric analysis Swedish players show weak performance in fields like matrices and scaffolds, ceramics and biomimetics. Whilst individual eminent professors and groups do constitute important exceptions, research into new materials, bioresorbable materials, soft-tissue responses, biomimetics or scaffolds is generally not internationally leading. Note that the way the analysis has been performed means that small groupings of excellent research players might have been missed since the measure is publication volume in selected journals. It may be that Sweden has small research groups performing well in an international comparison but lacking critical mass enough to be identified using the present methodology. Thus, the bibliometric analysis has its shortcomings and should be expanded if it is intended for use in a strategy development process.

One may speculate that if such 'gaps' in the general Swedish research profile exist, they may constitute a stumbling block in the overall promotion and commercialisation of TERM. On the whole, the literature indicates that, in order for a nation to have 'absorption capabilities' good enough to access, link to and explore new scientific and technological advances, it is important for there to be a 'basic' competence level within the country.[174] In the case of Sweden, this may imply that although it is a small country unable to lead in all sub-fields, a good knowledge base for each subfield must be ensured.

Research into new materials, bioresorbable materials, soft-tissue responses, biomimetics and scaffolds are areas of importance to the development of TERM. The trend is an increase in scientific output in these fields, especially in some Asian countries such as China, South Korea, Japan and Taiwan. Initiatives for the development of TERM in focus countries include such R&D efforts.

TERM includes several growing scientific areas and Sweden appears to have strengths in only some of these. This pattern should be taken into consideration in a strategy development process. One way to strengthen scientific areas is for researchers to link to international nodes of scientific excellence. The environment however needs to be viewed as an attractive partner in order to accomplish this. By combining scientific world-class excellence in some subareas, with a more 'basic' level of national scientific competence in others, Sweden can ground its position within TERM.

Moreover, the analysis of the specific research groups showed that the research was located in the main city regions and that there are some geographical profiles to the research. Whilst the study has not investigated links between specific researchers or groups of locations, interconnections between regional research efforts may - especially in a small country like Sweden – be a way to build critical mass and implement an overall national research strategy.

So far, there has been no explicit or coherent policy agenda for the TERM area in Sweden, and no national consensus around specific initiatives. However, many research groups, larger research environments and individual projects in the field have attracted financing from the Swedish research and innovation funding system. Even so, one argument in this report is that a more coordinated and strategic effort would likely have a more pronounced effect on research and innovation in this field than the way the field has been developing thus far. In the research and innovation bill[175] presented in October 2008, stem cells and regenerative medicine was identified as one of 24 strategic areas. It was proposed the field should receive an earmarked budget of SEK 65 million (EUR 6.5 million)

corresponding to 4 per cent of the total budget allocated to the 24 strategic areas for R&D investments for the period 2010-2012. In the research and innovation bill, the Swedish Research Council has been given responsibility for handling the initiatives for this strategic area. Thus, the Swedish Research Council will be responsible for suggesting the distribution of the budget earmarked for research and innovation activities in this strategic area to the universities to the Government. This will be done after a call for proposal and evaluation procedure.

Concerning developing a common strategy, Swedish policymakers may get inspiration from how this has been done in the US where a working group has been set up to coordinate discussions and bring negotiations and various views to the fore. A multiparty process including relevant public authorities in the research and innovation funding system has thus been developed. At NIH, a common roadmap was first developed to coordinate the efforts of various parts of NIH, (the various NIH institutes for example), which may be isolated from one another and working on different aspects of TERM. Then the working group was formed involving several of the federal agencies (14 organisations in total) to enable information flows between these agencies, as well as coordination of and negotiation about strategic funding decisions. Such a joining of forces is also taking place in the UK, where the Department of Health and the Department of Business, Enterprise and Regulatory Reform (BERR) are working together to stimulate a positive development of TERM. A ten-year strategy has thus been developed, including decisions on such areas as secure stem cell bank resources, centres of excellence, cell production facilities, clinical research and translational efforts. In this process, the Ministries have consulted with industry as well as academia. In Japan, a biotechnology strategy identifying coordinated measures aimed for the regenerative medicine area was formed in 2002. The strategy was developed by a committee comprising representatives from ministries, industry and academia. Since then, a number of different initiatives have been launched and the funds are being provided through MEXT, METI and MHLW, with these ministries taking responsibilities for different activities. The largest investment is made through a 10-year national “Project to Realize Regenerative Medicine” (2003-2012). As a result of the breakthrough in iPS cell research, efforts are currently made to further strengthen the coordination among ministries, including the speeding up of regulatory processes. Coordination between governmental agencies on research and innovation investments and the formation of a working group with a variety of relevant players to formulate and follow up a strategy for this field are processes in other countries from which Swedish policymakers thus might learn.

To have national research environments involved in the field gives companies more easy access to such environments for collaboration concerning identifying clinical needs and requirements as well as the development of products and services. The presence of research also increases the chances of new treatments beneficial to patients, being early adopted in clinical practice.

Despite the investments in R&D made by many countries, there are stumbling blocks on the way to successful new TERM treatments. Not only have research efforts in many countries been intensified in recent years, but issues of critical mass, multidisciplinarity and translational efforts have also been addressed, as discussed below.

8.2 Multidisciplinarity and translational research

The scientific knowledge base for tissue engineering and regenerative medicine applications can be described as a multidisciplinary combination of materials science, fundamental biological sciences and pre-clinical and clinical medicine. Such subareas are increasingly intertwined within TERM. Indeed, the present study highlights the need to move in a more inter-disciplinary direction. This implies that not only is there a matter of handling multiple disciplines (multidisciplinarity), but also the interaction and potential integration between them (inter-disciplinarity). This has proven to be demanding task. In Japan, this is currently considered a prime issue within TERM. Whilst new centres do have this concept of integrating biology, medicine and engineering there is no tradition of multidisciplinary or pre-clinical and clinical research collaboration in Japan, and it may take some time before such routines are established. Another difficulty is that researchers from the various fields may underestimate the time required to adapt to advances in other fields. Therefore, inter-disciplinarity must be visible in education, research and commercialisation. Such multi-skilled groups with clinicians, biologists, bioengineers and material scientists and interconnections between specialist groups have long been functioning in the US, and are now also underway in Japan (through such things as the Japanese National Project to Realize Regenerative Medicine) and Europe (the UK Manchester/Liverpool Tissue Engineering Centre, bioengineering at the University of Liverpool and matrix biology at the University of Manchester for example).

The US approach with coordination of government agencies is one way to stimulate increased awareness of activities across disciplines. In the UK, integration has to some extent been accomplished through the nationwide ‘UK Stem Cell Initiative’ and through the ‘UK National Stem Cell

Network'. These arenas facilitate knowledge spill-over and meetings between professions, organisational groups and disciplines.

In order for products to be developed, there must be a bridge between the biology and engineering of TERM and the pre-clinical and clinical medical aspects of the field. Likewise, there must be a bridge between research and the practical issues clinical practitioners and firms face when developing therapies in regenerative medicine. Thus, there is a need for a flow and exchange of knowledge between pre-clinical and clinical scientists on the one hand and between the academic scientists and companies on the other. In the US, when players active in forming TERM policy examine the efforts to date, they consider that efforts in basic research may need enhancement if they are not to lose ground in relation to Europe and Asia. This is however not seen from the bibliometric analysis in the present study. In Europe and Japan, the view among national policymakers is that multidisciplinarity, translational research and commercialisation need to come more into focus. Such concerns illustrate that it is difficult to obtain an optimum balance between basic and applied research on a national level, or between efforts to enhance scientific excellence and to commercialise existing research.

8.3 Critical mass and clustering

In the development of TERM products, there is thus a need for integration of knowledge areas and cooperation between scientists in different research disciplines as discussed above, but also between clinicians and industrial players. Even though much scientific knowledge exchange can take place over geographical distances, interviews in the present study indicate that the tacit and frequent exchange of co-located players is of importance. Life Science is an industrial sector which often is described as benefitting from clustering of activities within a geographical area. California is a good example of where such clustering has successfully taken place within the life science area in general, a situation from which TERM is likely to benefit. TERM is commercially still an area in early phase of development and the firm population in Sweden as in other countries, thus constitutes a relatively small part of the life science industry and the firm activities are primarily dispersed in prominent life science regions. In general terms, the literature suggests that clustering is fruitful for industrial development. One reason is that knowledge-sharing and mobility between players spurs innovation and speeds up the path to market and that this more easily occurs with short distances between players. Another reason is that clustering may attract international players to collaborate, invest or locate activities to such environments. Examples of this are the recent decisions of US Pfizer to establish a regenerative medicine R&D unit in Cambridge and of Danish Novo Nordisk to invest in a regenerative medicine research collaboration

project between the company, the Lund Stem Cell Research Centre and the Swedish company Cellartis.

The agglomeration also generates a critical mass of job opportunities for life science specialists, which may reduce risk-adverse behaviour among individuals and make it easier for start-ups to recruit. A pool of competence for recruitment by life science ventures is thus created.

The study shows that the analysed countries agree on the importance of creating a critical mass of both research and industrial activities, and the importance of geographic research centres and cluster development initiatives. In the UK, TERM is seen as a highly prioritised research area and the resources devoted to the field are considerable. In particular, the focus on stem cell research in the UK is evident from the doubling of resources between 2006-2008, and an emphasis on the stem cell bank giving a variety of players access to stem cell lines. The strategy is largely to create a critical mass through research centre building. In Germany too, critical mass is built through creating centres of excellence as well as cluster initiatives. Financial resources are channelled to the field by federal as well as regional organisations. Concerning centres of excellence, three geographic centres have recently been initiated and their results are yet to take full effect. However, respondents point out that the volume of financing for these centres is still rather limited, and their link to industry not so clear. In Japan, initiatives to strengthen regional innovations systems specifically in the field of regenerative medicine have been launched in the Kansai region. The aim is to create new industries and develop existing ones from biotechnology research by encouraging partnerships among private companies, public bodies and academia. In Japan, a policy measure has been launched, including speeding up and streamlining of regulatory processes, to stimulate relevant ministries and agencies to combine their various instruments and support joint development projects in Japan between leading research groups and companies in a particular field. Of 24 selected projects, seven are in the regenerative medicine area. One of the projects involves Japanese industry in the development of iPS cell technology, including three companies and four research centres in a five-year cooperative project.

On the research side, Swedish policymakers have taken steps towards creating critical mass through the establishment of centres of excellence in fields related to TERM. Some of the well-financed Swedish centres will receive SEK 10 million per year for ten years (EUR 1 million), but there are also centres with shorter-term fixed funding. Some centres or networks receive more funding and a number receive less. Usually, the known duration of funding is 4-10 years and totals SEK 5-15 million per year, per centre. There are examples of centres or networks of research group in other

countries which seem to be built on a larger scale. For example, the Scottish Centre for Regenerative Medicine at Edinburgh University received EUR 80 million in 2007 as start-up financing to create a physical environment where 20 research groups with a total of 150 staff will collaborate using their funding from several public and private financiers. Also, the Centre for Regenerative Therapies at the University of Dresden has a staff of over 100 and has received EUR 67.5 million for the period 2006-2017. The Berlin-Brandenburg Centre for Regenerative Therapies received EUR 50 million for the period 2007-2010.

It should be of interest to Swedish policymakers investing in TERM R&D how centres of excellence in other countries are organised and structured in regard to multidisciplinarity, translational research, commercialisation, industry involvement, etc. The Canadian programme "Networks of Centres of Excellence" is an example of how to generate critical mass and accomplish synergies through linking nodes of complementary but related excellent research centres. One of the networks is in the stem cell research field and includes many companies and almost 80 researchers, excluding PhD students and technicians. It is spread all over the country and has a ten-year budget of almost SEK 420 million (EUR 41 million). In the networks, partners from academia and the industrial, public and non-profit sectors conduct research together. In Japan, one approach to nationally linking excellent research nodes is the recent creation by MEXT of a network in iPS cell research. The motives include better handling of knowledge diffusion as well as managing IPR in a more comprehensive and integrated way across a growing number of Japanese research organisations in the field. The basic principle is that intellectual property created by members of the network is made available inside the network free of charge for research purposes. These examples are of interest considering such things as the geographic distribution of Swedish centres of excellence in the stem cell field.

In addition, achieving research excellence and critical mass also requires a sufficient human resource base. It is important to take into consideration how an area can grow through expansion of domestic human resources or foreign recruitment. Here, Sweden has a challenge from the relatively low salaries and non-competitive conditions offered in relation to the most prominent environments in countries such as the US[176].

The firm population developing tissue-engineered products or in TERM-related fields analysed in the present report indicates that Sweden has a versatile pool of commercial competence with relevance to TERM development. This is primarily found in the three major city regions. The area with a definite commercial strength at present is biomaterial products. This is not explicitly included within the TERM area but highly related. The biomaterial product companies may find that TERM products and services

will compete with their products and they may themselves enter the field. There is also an 'embryo' of a company cluster within the core area of TERM, with eight companies throughout Sweden and if TERM-related companies are included, e.g. biomaterials companies, the population is about 30 companies. To spur the development, Swedish players need to provide good conditions for the existing companies to grow and for the establishment of new ones, and ensure it is attractive for foreign firms to locate in the country.

The literature points to intra-firm interaction and collaboration as useful for cluster development, as well as international links and knowledge flows. Whilst it is clear that some of the firms collaborate with academic research groups (often the same environment that they stem from) the present study has not analysed the extent to which Swedish companies communicate, collaborate or have staff mobility between them. The firms have diverse applications (many being very small start-up companies focusing on developing their first products/services) and are geographically dispersed. This could indicate a limitation on their possibilities for interaction. An arena for dialogue between industrial players could improve the interaction between the companies and leave room to elaborate on synergies and possible collaboration.

International experience shows that it takes a long time to build strong research and innovation environments and networks. Long-term stability is important to reduce uncertainty and increase the attractiveness of such environments. There are examples from Sweden and other countries of research and innovation environments failing to continue their efforts after the public funding which supports the constellation has ceased. Such need for continued support must be taken into consideration when balancing the renewal of R&D with the needs of established environments and networks. In some cases, continued support may be seen as part of an attraction and retention policy in the field for academia as well as industry. Maintaining research and innovation environments may lead to further attractiveness of, say, investments and human capital. This in turn may spur growth of established ventures as well as stimulating indigenous innovation. At the same time a field in early phase of development needs a certain degree of flexibility to allow for adjustments in priorities according to research breakthroughs and other changes in conditions for the field difficult to foresee.

8.4 Public acceptance, reimbursement and regulation

Another challenge is that of easing regulatory hurdles. The introduction of therapeutic technologies and treatment based on regenerative medicine has

so far been slow in most countries. The challenges for governments and regulatory authorities entail finding socially acceptable and medically relevant legislation and guidelines to ensure the safe and ethical use of the new therapeutic methods based on TERM. Countries differ in their approaches and, as discussed earlier in the report, particular issues are to the fore in the case of stem cells. The Swedish system has benefitted from the existing stem cell regulation. However, it is worth noting that the competitive advantages of the more liberal regulation previously enjoyed by Swedish science and business may not be so apparent in light of recent changes in various countries. Swedish stem cell research, and the availability of ES cell lines, has been marketed to attract direct investments by foreign companies, but this strategy may have to be revised in the light of the policy revisions by various governments. The ongoing work in Japan to liberalise the use of hES-cells as well as the breakthrough in iPS cell research are interesting from a Swedish point of view. The Japanese move towards a less restrictive attitude to the use of ES-cells, embryos and therapeutic cloning gives Japanese academic labs and companies similar opportunities to those in Sweden. Also, bearing in mind the recent presidential election, there may be a shift in US federal policy. In 2005, President Elect Obama voted in favour of allowing federal funding to be used for research on stem cell lines obtained from discarded human embryos originally created for fertility treatments. Thus, the Swedish advantage in liberal stem cell regulation may not be as significant any more. A recent development is the FDA clearance that US Geron Corporation recently received to begin the world's first human clinical trial of an embryonic stem cell-based therapy in patients with acute spinal cord injury.

Regarding reimbursement, even when the stumbling blocks of market approval regulation have been passed the road to success is not guaranteed for the TERM companies. In fact concerning reimbursement, in most countries with regulated health markets the insurance companies have not yet recognised and accepted regenerative medicine therapies. There are simply not enough long-term studies showing efficacy and safety, or economic benefits to the healthcare system in comparison with traditional therapies for the specific medical conditions. Reimbursement for many of the upcoming products is therefore not yet guaranteed. Naturally, in the absence of any compensation for buyers of these products, the industry faces a stiff challenge in commercialising its innovative technologies. The situation concerning future reimbursement schemes for TERM products is thus still very unclear in many countries and hampers the development of commercial products. These uncertainties lead to a higher risk for investors and entrepreneurs and possibly increasing reluctance to enter TERM ventures. Making the reimbursement issue more forecastable would thus benefit risk assessment.

8.5 Suggestions to policymakers

If policymakers wish to prioritise TERM and make a focused effort to stimulate a positive development of the field the analysis in this report leads to the following suggestions:

1 Multiplayer strategy development

In a number of countries, TERM strategies have been developed by multiplayer working groups which in some cases have also been involved in monitoring implementation of the strategy. It is likely that such a strategy development process would complement the present funding of projects, centres and cluster development and be beneficial for the development of TERM knowledge and innovations in Sweden. Such a working group could include government agencies, as well as relevant organisations in the R&D financing system, academia and industry.

Importantly, such broad engagement of players is also a way to remove uncertainty and create stability in the field. Interviews indicate that clarity and predictability concerning, for example, regulation and reimbursement issues are crucial to research and innovation processes in firms and academia. Regulation is mainly decided on the European level and it is important that the national strategy includes a thorough agenda based on Swedish players' viewpoints and a strong Swedish engagement.

2 Emphasis on the multidisciplinary and translational challenge

Seamless interaction between scientific disciplines, between science and clinical practice and between academia, the healthcare system and industry has been a problem in most countries engaging in the field. In other countries, one way of handling some of these concerns has been the initiation of centres to stimulate multidisciplinary TERM research, and connect pre-clinical and clinical efforts. Such aspects should be included in the proposed strategy development process and Swedish policymakers may thus learn from experiences in other countries. Issues such as an internationally competitive scale of R&D funding of specific initiatives and the balance between continuity and flexibility in funding for such ventures in a field in early phase of development, also need to be addressed in the strategy development process,.

3 Industry involvement and stimulation of innovation

While much research is performed by academic organisations and clinical practitioners, companies also perform both basic and applied research and take a dominant role in advancing research results into innovations. Their knowledge and experience should thus be involved in the strategy development process. They might also have an operational presence in the

centre projects, facilitating commercialisation and promoting mutual learning between academy and industry. When building a successful research and innovation environment, it is also important to consider other issues concerning safeguarding IPR, thoughts on business models, reimbursement issues etc.

4 National networks of research and innovation environments

As part of an attraction and retention policy for the field, building strong research and innovation environments for attraction of investments, human capital, etc. should be included. This may spur growth of established ventures and stimulate indigenous innovations. Thus, public policy must ensure long-term stability of such environments and networks at the same time as a field in early phase of development needs a certain degree of flexibility. Such centres should have a balance between basic and applied research, between disciplinary and multidisciplinary research efforts as well as between pre-clinical and clinical projects. Commercialisation aspects, the involvement of industry and industrial needs should also be components in these centres of excellence; in some cases, perhaps emphasised in the longer-term perspective.

The strategy should formulate ways to build critical mass of activities at a selected number of geographical locations within Sweden functioning as nodes in a national network. There are interesting examples in other countries, such as Japan and Canada, of how such national networks are promoted. Ways to handle initiatives in a cross national region such as Medicon Valley must also be taken into consideration.

A number of different sources and initiatives may thus come together to support such efforts, including peer reviews based individual research grants, centres-of-excellence and network funding, initiatives for cluster development, promotion of international collaboration and public private partnerships, and initiatives to stimulate commercialisation.

5 Strengthening international links and knowledge flows

A small country like Sweden needs international collaboration in order to link into and gain access to the most recent knowledge developments. The national TERM strategy should address such internationalisation, and consideration should be given to the issue of how to provide a basis (such as updated international mapping and benchmarking) for individual strategy implementation of various environments. The industrial and academic leadership (in, say, each field or region) may build such strategies on current collaborations and networks, new needs emerging, and an understanding of the relevant international nodes.

The present analysis indicates that Swedish players show a relatively weak performance in some field relevant to TERM. The Swedish focus may include such strategic areas deemed important for the future development of TERM. An additional way to strengthen scientific areas is for researchers to link to international nodes of scientific excellence. The environment however needs to be viewed as an attractive partner in order to accomplish this.

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Appendix

Research design, sources and sample

Method for the bibliometrics analysis

Dataset selection

The analysis is made based on publication volumes in datasets of articles identified according to a combination of two types of criteria: keywords to identify the scientific fields to study and a selection of relevant journals to which the keyword searches are applied[177]. A number of datasets where generated for in-depth studies using different combinations of these two criteria for different time periods.

Keywords:

- stem cell*
- stem cell* AND neur*
- stem cell* AND (cardio* OR heart*)
- tissue eng* OR regenerative medicin*
- bioresorb* OR biodegr*
- (scaffold* AND (cell* OR tissue)) OR (matrix and (cell* OR tissue)) OR (matrices AND (cell* OR tissue))
- (ceram* AND (cell* OR tissue* OR bio* OR protein*))
- osseoint*
- biomim*

Journals:

- All journals covered by Web of Science®
- 47 non review Life Science journals with an impact factor > 6
- 46 non review Materials Science journals with an impact factor > 1.5
- 40 non review Medical Science journals with an impact factor > 6
- Nature, Science and Proceedings of the National Academy of Sciences
- The datasets extracted from the Web of Science[178] platform are analysed using the freeware Bibexcel.[179]

Only journals listed in *Web of Science*, were included. The journal coverage of *Web of Science* can be said to encircle basic research quite well. *Web of Science* covers over 9,000 international and regional journals and book series in every area of the natural sciences, social sciences and arts and humanities. Journals to be included are evaluated according to citation

levels. This includes citations to the journal itself, as expressed by *Impact Factor*[180] and/or total citations received and the citation record of the contributing authors, a useful study in evaluating new journals where a citation history at the journal level does not yet exist.

However, its set of journals includes some journals with a rather low impact factor, i.e. they are infrequently cited in relation to the relevant discipline. In order to reduce the number of marginal journals in terms of impact, the analysis in different datasets was limited to life science and medical journals that had reached an impact factor of at least six and/or materials science journals that had reached an impact factor of at least 1.5 according to Thomson Scientific Journal Citation Report.[181] The rationale for applying these criteria is that the *Web of Science's* coverage is quite good when it comes to influential core journals, whereas the coverage of less significant journals is more arbitrary. The method, however, has the drawback that journals focusing on narrow fields run the risk of not being included in those more selective datasets, even though they may be of good quality. Therefore both datasets were analysed. A dataset was also made based on publications in the high impact influential journals Nature and Science and in some instances also including Proceedings of the National Academy of Sciences.

Thomson journal subject categories

Medical subject categories

ALLERGY; ANATOMY & MORPHOLOGY; ANDROLOGY; ANESTHESIOLOGY; CARDIAC & CARDIOVASCULAR SYSTEMS; CLINICAL NEUROLOGY; CRITICAL CARE MEDICINE; DENTISTRY, ORAL SURGERY & MEDICINE; DERMATOLOGY; EMERGENCY MEDICINE; ENDOCRINOLOGY & METABOLISM; GASTROENTEROLOGY & HEPATOLOGY; GERIATRICS & GERONTOLOGY; HEALTH CARE SCIENCES & SERVICES; HEMATOLOGY; INFECTIOUS DISEASES; INTEGRATIVE & COMPLEMENTARY MEDICINE; MEDICAL ETHICS; MEDICAL INFORMATICS; MEDICAL LABORATORY TECHNOLOGY; MEDICINE, GENERAL & INTERNAL; MEDICINE, LEGAL; MEDICINE, RESEARCH & EXPERIMENTAL; NURSING; NUTRITION & DIETETICS; OBSTETRICS & GYNECOLOGY; ONCOLOGY; OPHTHALMOLOGY; ORTHOPEDICS; OTORHINOLARYNGOLOGY; PARASITOLOGY; PATHOLOGY; PEDIATRICS; PERIPHERAL VASCULAR DISEASE; PHARMACOLOGY & PHARMACY; PHYSIOLOGY; PSYCHIATRY; PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH; RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING; REHABILITATION; REPRODUCTIVE BIOLOGY; RESPIRATORY SYSTEM; RHEUMATOLOGY;

SUBSTANCE ABUSE; SURGERY; TOXICOLOGY; TROPICAL MEDICINE; UROLOGY & NEPHROLOGY

Life Science subject categories

BIOCHEMISTRY & MOLECULAR BIOLOGY, CELL BIOLOGY, NEUROSCIENCES, IMMUNOLOGY, GENETICS & HEREDITY, BIOTECHNOLOGY & APPLIED MICROBIOLOGY, BIOCHEMICAL RESEARCH METHODS, DEVELOPMENTAL BIOLOGY, BIOLOGY, EVOLUTIONARY BIOLOGY and BIOPHYSICS

Material science subject categories

MATERIALS SCIENCE, BIOMATERIALS; MATERIALS SCIENCE, CERAMICS; MATERIALS SCIENCE, CHARACTERIZATION & TESTING; MATERIALS SCIENCE, COATINGS & FILMS; MATERIALS SCIENCE, COMPOSITES; MATERIALS SCIENCE, MULTIDISCIPLINARY; MATERIALS SCIENCE, PAPER & WOOD; MATERIALS SCIENCE, TEXTILES

Applications and firms included

For the analysis in this study a database of 970 companies world-wide was constructed, based on a wide range of sources. Firstly, companies from the various studies of tissue engineering and regenerative medicine that have been conducted in different countries were included.[182] Secondly, there are also a number of conferences, networks and societies listing companies in this field which were thus entered into the database.

A more detailed analysis and categorisation of the firms were made for the companies in the five countries (Sweden, Germany, United Kingdom, the US and Japan) that this study focuses. Firstly, the listing of companies was further verified and expanded by asking people interviewed to complement the list for their country and to verify the profile of the firms. Secondly, for the focus countries, the individual firms were analysed as regards field of application and classified into categories. The categorisation was made based on interviews and information on the companies' home pages. In this way, about 290 companies where considered to fall within the definition of the field. Several companies are placed in more than one category since they have more than one application. The categorisation primarily included addressing the field of application for the tissue-engineered and regenerative medicine products that these companies develop and the following categories were used:

- Skin, cartilage, bone or neurological
- Cardiovascular
- Neurological
- Pancreas, liver or kidney
- Dental

- Ophthalmic
- Drug discovery for tissue engineering and regenerative medicine applications, e.g. growth factors
- Stem cells used for drug discovery and development
- Tools specifically for tissue engineering and regenerative medicine applications

In addition to the categories above, in Appendix some biomaterials companies, both companies using stable materials and biodegradable and companies developing tools for tissue engineering and regenerative medicine applications are found. These companies where analysed and categorised and information about them entered into the database. However, it is not likely that an even nearly complete coverage of those companies is present in the database as they were not selected for detailed analyses in the study. As regards biomaterials companies, only those for which explicit information regarding applications that combined biomaterials with stem cells were included in the detailed analysis of the report.

Two additional aspects of the firms' profiles were identified:

- The phase of development of the first product a company has in the different fields of application (pre-clinical, clinical or product on the market).
- For the companies with applications related to different types of human tissue it was when possible, also identified what cell source was used: adult or embryonic and in the case of adult whether it was autologous or allogenic. The type of cells used was identified, e.g. bone marrow, umbilical cord or adipose cells and also if it was a xeno-application.

Biomaterials and the relation to TERM

In general, biomaterials are used to enhance, repair or replace human body functions and include naturally derived, semi-synthetic or synthetic materials, as well as biocompatible surfaces. Definitions may also include materials that are originally/mainly used for other purposes but also used in the human body.

In layman terms, biocompatible materials are materials that are compatible with the human body and where rejection, inflammation or scarring is minimised. When a foreign object is implanted into a human, the body often reacts with inflammation and subsequent scar formation at the area where material and body tissue meet and in many instances the body rejects the implant. Biomaterials are designed to avoid or at least minimise such reactions and depending on the application there are a number of different properties that may be desired from a biomaterial, such as non-toxicity, non-immunogenicity, resorption or mechanical ability to bear a load. The properties needed are largely dependent on the type of tissue adjacent to the implant, where implant design and surface properties are important.

Some biomaterials are biodegradable and gradually dissolve inside the body. This degradation causes the implant's mechanical properties to change over time which may cause problems and this is thus a focus for research. This illustrates one of the main challenges with biomaterials. The outcome of the dynamic interaction between the material and the body in-vivo is difficult to predict and therefore usually needs to be studied in animal models and clinical trials over time. Extensive research has been conducted on materials surface and cell interaction in order to develop predictive tools for "biocompatibility". Disappointingly, there is a poor correlation between in vitro studies and the in-vivo outcome. Thus, there is as yet a need to develop predictive tools for the understanding of biological outcome of implanted materials involving studies of how mechanical, chemical, morphological cues and biological signals affect the in-vivo outcome. In this, one moves from traditional cell biology to more quantitative tools for analysis.

Biomaterials may be naturally derived (e.g. collagen that exists naturally in the body or material derived from e.g. clams), semi-synthetic or synthetic. Many biomaterials are rather common materials adapted for specific implant needs. For example, the first artificial hearts in essence used a material similar to that in nylon stockings and adapted it accordingly. This was an approach initiated by US firms and copied globally, perhaps particularly in Japan. Today, many biomaterials are designed on the drawing board for very specific product and patient needs and biomimetic materials –

materials in essence mimicking natural materials – are of growing importance. However, from the point of view of obtaining fast regulatory approval biomimetic materials potentially involve hurdles. In fact, it may instead be advantageous to modify a material that has been proven safe and non-toxic in previous studies and that already has been approved for clinical use.

Identified companies in the five focus countries

Below the identified companies in the five focus countries are listed.[183]

GERMANY

Alcedo Biotech GmbH

Amaxa GmbH

Ars Arthro AG

ARTISS GmbH

Axiogenesis AG

B.Braun Melsungen

Biomet Deutschland GmbH

Biomet Merck Biomaterials GmbH

BIOPHARM GmbH

BioTissue Technologies AG /GmbH

Cell Concepts GmbH

CellGenix

CellMed AG

CellSystems Biotechnologie Vertrieb GmbH

CellTec GmbH

Celonic GmbH

CO.DON Tissue Engineering AG

Curasan

CureVac GmbH

Cytonet AG

DeveloGen

Dr SuwelacSkin & Health Care AG

EDI GmbH

Envision Tec.

Epiontis

Eufets AG

Euroderm GmbH

Hemoteq

Hybrid Organ GmbH

In Vitro Systems and Services GmbH

Innocoll GmbH

Kourion Therapeutics AG (ViaCell)

Matricel GmbH

MeGa Tec GmbH

Miltenyi Biotec GmbH

Minucells and Minutissue Vertriebs GmbH
mnemoScience
Novo Nordisk Pharma GmbH
Oligene GmbH
Ormed GmBH
Orthogen AG
Osartis GmbH & Co KG
Ossacur
Osteogenetics GmbH
ProBioGen AG
SanguiBioTech GmbH
Scil Technology
SOURCON-PADENA GmbH & Co. KG
TETEC Tissue Engineering Technologies GmbH/Tetec AG
The Kompetenzzentrum Tissue Engineering (KTE)
Trans Tissue Technologies GmbH
Tutogen Medical
VasoTissue Technologies GmbH
Verigen Transplantation Service International AG
VITA 34 Gesellschaft für Zelltransplantate mbH/ Vita 34 AG
VITA 34 INTERNATIONAL AG
Nephrogen LLC

JAPAN

Amniotec Inc
ArBlast Co Ltd. (earlier OsteoGenesis Inc.)
BCS Inc.
Beacle Inc.
BioBank Co., Ltd.
Cardio Inc.
Cell Seed Inc.
DNAVEC Corp
Effector Cell Institute, Inc.(ECI)
Gunze
J-TEC, Japan Tissue Engineering Co.
Kaken Pharmaceutical Co., Ltd.
Kirin Brewery Co.
Koken
Kyocera

Lymphotec Inc.
Lynphocyte-bank Ltd.
MeBiol Inc
Medinet Co.
Meneki Bunseki Kenkyu Center Corporation
Nippi Collagen
Nipro
Olympus Biomaterial
OneCell Inc.
PhoenixBio.Co., Ltd.
ReproCELL Inc
Stem Cell Institute
Stem Cell Sciences K.K., SCS KK
StemCell Sciences Ltd
Takara Bio Inc.
Tanabe Seiyaku Co Ltd
Terumo Corporation
The Institute of Gene and Brain Science
Ube Kosan

UNITED KINGDOM

Advanced Medical Solutions
Axordia
BioActa Ltd.
Biocomposites Inc.
CellTran
Clinical Cell Culture
Critical Pharmaceuticals Ltd
Euroheal Ltd.
Giltech Ltd
GlaxoSmithKline
Intercytex Limited
Invinity Bioscience Ltd
Isolagen Inc
Johnson&Johnson Advanced Wound Care
NovaThera Ltd
Odontis
Plasticell Ltd
Protherics, PLC

Proxima Concepts Ltd
Regentec
Remes
ReNeuron Holdings Plc
ReNeuron Ltd
Renovo Limited
Smith&Nephew Ltd
StemCell Sciences Ltd
Tissuemed Ltd
TissueScience Laboratories
TriStem Corporation
VetCell Ltd.
Controlled Therapeutics
Hannah Cell Science
ProStrakan

USA

3D Matrix Inc./3DM Inc.
3i
Aastrom Biosciences, Inc.
Acorda Therapeutics Inc
Acusphere, Inc.
Advanced Cell & Gene Therapy, LLC
Advanced Cell Technology (ACT)
Affinergy
Agennix
Albany International Research Co.
Aldagen
Alkermes
AllCells, LLC.
Alpha Cord
Amcyte (earlier Vivorx)
Anika Therapeutics Inc.
Applied Tissue Technologies
Arbios Systems Inc.
Artecel Sciences, Inc.
Arteriocyte, Inc.
Articular Engineering
Athersys

Bacterin
Battelle Healthcare Products
Baxter Healthcare Corporation
BD Biosciences (earlier Tissue Transformation Technologies)
Biocoat Inc.
Biocoral
BioE
Bioheart, Inc.
Biolife Solutions
Biomet Biologics (Cell Factor Technologies)
BioMimetic Therapeutics, Inc. (Biomimetic Products, BioMimetic Pharmaceuticals)
Bioptechs
BioSphere Medical, Inc.
BioSurface Engineering Technologies, Inc
BioVest International, Inc.
Birmingham Polymers, Inc. (BPI)
Boston Life Sciences (NASDAQ:BLSI)
Boston Scientific Corporation
Brainstorm Cell Therapeutics Inc.
C. R. Bard, Inc
California Cryobank
Cambrex Corporation /Cambrex Bioproducts
Cambridge Polymer Group
CardioTech International Inc.
CBR Systems, Inc./Cord Blood Registry
CellECT Bio, Inc
Cellerant Therapeutics
Celprogen Inc
Cerco Medical (earlier Islet Sheet Medical)
Chondros, Inc
Chrysalis BioTechnology, Inc. (OrthoLogic)
Cognate BioServices, Inc.
Confluent Surgical
Convatec
Cook Biotech Incorporated
CorCell
Cord Blood America
Cryobanks International

Cryo-Cell International + Cryo-Cell Europe N.V.
CryoLife
CyBios Inc.
Cytograft Tissue Engineering, Inc.
Cytomatrix, Inc/CordLife, Inc
Cytomatrix, LLC
Cytori Therapeutics
DePuy Mitek, Inc., (earlier Mitek)
DePuy Spine, Inc.(former Acromed Inc.)
Derma Sciences
Encelle
ENDOVASC Inc.
EnduraTEC Systems Group
ETEX Corporation
ETHICON
Fibrogen
FMC BioPolymer
Fziomed, Inc.
Genentech
GenVec (Diacrin, Inc.)
Genzyme Biosurgery (former Genzyme Tissue Repair, former Biosurface Technologies)
Genzyme Corporation
Geron Corp.
Gore Medical
Haemonetics Corporation
Harland Medical Systems
Hemogenix, Inc.
HepaLife Technologies, Inc
Human Genome Sciences
Hydra Biosciences, Inc.
Hydromer
Immunicon
INAMED Corporation
Infigen
Integra Life Sciences
Integrated Surgical Sciences
Interpore Cross International, Inc.
Isto Technologies

Ivoclar Vivadent (former Dentigenix, Inc.)
Ixion Biotechnology, Inc.
Kensey Nash
Life Cell Corporation
MacroMed
MacroPore Biosurgery (earlier StemSource, Inc.)
MatTek
MaxCyte,Inc.
Medtronic ENT (including Medtronic Ophthalmic products)
Medtronic Sofamore Danek
MG Biotherapeutics, LLC
MicroIslet,Inc.
Morphogenesis, Inc.
MultiCell Technologies, Inc.
Nanomatrix
Nanotherapeutics
Nephros Therapeutics Inc
NeuralStem Inc.
Neuronyx Corp.
New England Cord Blood Bank
Newborn Blood Banking Inc
NovaBone Products
NovaStem
Novocell (acquired by Neocrin and CyThera, Inc.)
Nucryst Pharmaceuticals Corp.
Opexa Therapeutics (former PharmaFrontiers)
Organogenesis Inc.
Ortec International, Inc.
Orthovita Inc.
Osiris Therapeutics, Inc.
OsteoBiologics
Osteotech
Poly-Med, Inc
PrimeCell Therapeutics (owned by PrimeGen BioTech Corp.)
Progenitor Cell Therapy Inc
Proneuron Biotechnolgies
Protein Polymer Technologies, Inc.
Quark Biotech, Inc.

Raven Biotechnologies, Inc
ReGen Biologics
Regeneration Technologies, Inc
Rena Med Biologics (earlier Nephros)
ReNeuron Inc
Revivicor, Inc
RheoGene, Inc.
Saneron CCEL Therapeutics, Inc.
Securacell Inc
Sertoli Technologies Inc
SoloHill Engineering, Inc.
StemCell Sciences Ltd
StemCells, Inc
StemCyte
Stryker Biotech Corp.
SurModics
Synovis Life Technologies, Inc
Synthecon
Tengion
Tepha Inc.
Tissue Growth Technologies
Titan Pharmaceuticals (Theracell)
USBiomaterials
Vesta Therapeutics
ViaCell, Inc.
ViaCord
VistaGen Therapeutics, Inc.
Vital Therapies, Inc
Vitro Diagnostics Inc
Wright Medical Technology, Inc
Xenogenics Corp.
Ximerex
Zen-Bio

SWEDEN (both TERM companies and those related to the field) [184]

CellMatrix AB
Karocell Tissue Engineering AB
Gambro AB
Gambro Healthcare Sweden AB

Gambro Lundia AB
Cellartis AB
NeuroNova AB
AngioGenetics Sweden AB
NidaCon International AB
Vitrolife Sweden AB

Ademrac AB
Artimplant AB
Avaris AB
Biora AB
Bohus BioTech AB
Camurus
Carmeda AB
Celltrix
Mölnlycke Health Care AB
Q-Med AB
Bone Support AB
Brånemark Integration AB
Craniofacial Reconstruction TA AB
Doxa AB
Elos Medical AB
Abigo Medical AB
Ardent, AB
Astra Tech AB
Atos Medical AB
Biomet Cementing Technologies AB
Brånemark Center Göteborg AB
Cresco Ti Systems AB
Dentatus AB
Cochlear Bone Anchored Solutions AB (earlier: Entific Medical Systems AB)
ErySave AB
Eutech Medical AB
Glycorex AB
Glycorex Transplantation AB (publ)
Hemapure AB
Integration Diagnostics AB
Integrum AB

Medtentia AB
Micromuscle AB

Nobel Biocare AB
Nordiska Dental AB
Octapharma AB
Octapharma Nordic AB
Olerup SSP AB
P & B Research AB
Perimed AB
Q-Sense AB
St. Jude Medical AB

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Brånemark, Rickard (2004): Integrum AB.

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Caram-Lelham, Ninus (2004): Q-Med AB.

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Edgar, Boo (2004): Cellartis AB, Sweden.

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Frank, Curtis (2006): Professor, Department of Chemical Engineering, Stanford University, California, USA, July 2006.

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Hedman, Lars (2004): Cell Matrix AB.

Hedrick, Marc H. (2006): President, Cytori Therapeutics, California, USA, July 2006.

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Inami, Masaharu (2005): President & CEO, BCS, Inc. Japan, Nov 2005.

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Lampeter, Eberhard (2006): VITA34, Germany, 17/8/06.

Lindahl, Anders (2004): Professor, Gothenburg University.

Mathisen, Torbjörn (2004): Radi Medical Systems AB.

Mizuno, Hitoshi (2005): CEO, Olympus Biomaterial Corp., Japan, 16/11/05.

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1 The focus in this report is on medical applications only.
2 Hüsing et al, 2003:1.
3 Lloyd-Evans, 2004.
4 DG Enterprise, 2004: 3.
5 Nelson and Winter, 1982; Nelson, 1987.
6 Utterback, 1994.
7 EC, 2001:7.
8 For a list of interviews see the Appendix. For our own previous work on the topic, see Rickne (2003; 2004) for example.
9 Annika Rickne and Anna Sandström have developed the overall content and analysis in the report. The section on Japan has been written by Henrik Fridén, except for section 5.3.4, which has been written by Lennart Stenberg, both at VINNOVAImportant contributions have been made by Astrid Szogs (Lund University) in the sections on German research initiatives and the EU regulation, as well as by Stian Nygaard (Lund University) in the chapter on research initiatives in the UK, the US and Japan. Grateful thanks also to Emelie Stenborg (Lund University) for assistance in the data collection.
10 Lysaght and Reyes, 2001; Lysaght and Hazlehurst, 2004. Note that this definition was not the same as the broader defined TERM area used in this report and did not include biomaterials firms.
11 Lysaght and Hazlehurst, 2004.
12 Hüsing et al., 2003.
13 Fridén, 2005.
14 These companies are listed in Appendix.
15 The Appendix also has a listing of 29 Swedish companies not primarily involved in the TERM activities listed above, but in fields related to them. However, these firms appear under a separate heading in the Appendix list.
16 Therefore the coverage of firms listed in Table 2.1 is likely to be less complete than in Table 2.2.
17 Skalak and Fox, 1988.
18 EC, 2001: 2. See also Langer and Vacanti (1993) and Galletti, Hellman and Nerem (1995) for similar definitions.
19 Langer and Vacanti, 1993.
20 EC, 2001: 1.
21 McIntire et al., 2002, p. 33. The authors provide a detailed analysis of research activities, players and how the different regions fare within the sub-fields of degradable synthetic bulk polymers, synthetic gels, natural polymers, synthetic materials with tailored biological ligands and scaffold technologies for implantable devices and tissues.
22 MATES IWG, 2007.
23 Yang et al., 2006; Yamato and Okano, 2004.
24 Drury and Mooney, 2003; Khademhosseini and Langer, 2007.
25 MATES IWG, 2007.
26 A complementary way to classify cells is as primary cells (directly from an individual) or secondary cells (from a cell bank).
27 Note that there is a debate as to whether such cells should be called stem cells, or if the term ought only to be used for totipotent and pluripotent cells.
28 Another type of application is drug discovery for nerve regeneration. Five companies with this type of activities have been identified which are not included in this category. They are found under drug discovery.
29 Out of these 27 analysed firms, 16 were located in the US, three in the UK and Germany respectively, three in Japan and two in Sweden.
30 Out of these 27 firms 13 were US companies, while five were located in the UK, four in Germany, three in Japan and two in Sweden.
31 Note that the total pharmaceutical industry has not been analysed in order to identify companies. This most probably leads to an underestimation of the number of regenerative

medicine drug discovery companies.
32 Hou et al., 2004; Kretlow et al., 2007.
33 No data was available for the use of other alloys, bone cement or ceramics for dental applications which are also mature parts of the industry involved in dental applications.
34 Stem cells may be differentiated but they do not produce tissue. Tissues are defined by shape, organisation, function, ECM and cell types. When implanted, these cells may favour repair and regeneration.
35 American Chemical Society, 2006.
36 US interviewees point out that while much interesting stem cell research takes place at, say, Lund University or Karolinska Institutet, the magnitude seems to be small due to lack of funding.
37 Lundvall and Borras (1997, p. 39), Asheim and Isaksen (2002).
38 Bathelt, Malmberg and Maskell (2004), Maskell, Bathelt and Malmberg (2006).
39 The term modern biotechnology often means knowledge and techniques that have emerged during the last few decades, based on cell and molecular biology, molecular genetics, immunology and other disciplines within the bio-sciences.
40 Tokyo University Hospital, 2007.
41 This section is based on Szogs and Rickne (2006). Thanks to Astrid Szogs for assistance in the data collection.
42 EC, 2005: 5.
43 EC, 1965, Article 1 of Directive 65/65/EC.
44 Hüsing, 2005.
45 Elmalem, 2002, in Kleijwegt, 2003: 29.
46 The Medical Device Directive belongs to the so-called 'new approaches' in legislation, considered to be somewhat more innovative in that only the goal is defined - i.e. what the final product should look like - but leaving more room for the producer to decide how he/she wants to reach this goal. This implies, however, that the manufacturer needs to prove in detail how he/she actually produced the product.
47 EC, 1995: 3-4.
48 Kleijwegt, 2003: 27.
49 EC, 1993.
50 For instance, the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) stated that "although some aspects of complex tissue engineering may well be suitable for regulation under an existing European Directive, for example in relation to medicinal products, or medical devices, or clinical trials, it is unlikely that all aspects of tissue engineering can be encompassed by current legislation (EC, 2001: 8). Also, Directive 2004/23/EC of the European Parliament and of the Council clearly expresses the need for standards in the field by saying that: "as tissue and cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standards" (EC, 2004).
51 Rossignol, 2007.
52 The main players on the regulatory side can be divided into international regulatory agents and national authorities for regulation. The key international body working towards the harmonisation of the pharmaceutical market and thus including responsibility for TE products is the European Commission. Directorate C of "enterprise and industry" focuses on regulatory policy for TE in particular.
53 EC, 2000: 9. For more details of the decision-making process, which parties are involved, how many days they have etc. in the procedure see EC, 2000: 9-12.
54 In cases where this is not possible, the EMEA is involved for the preparation of a binding arbitration. It is still possible to receive purely national authorisation for medicinal products to be marketed in one member state.
55 The procedure is laid down in Council Directives 93/39/EEC and 75/319/EEC. Note that in order to be eligible for this procedure, a product needs to have already been authorised for marketing in one member state and sufficient data needs to be accessible.
56 DG Enterprise, 2004.

57 In this respect, it is important to know that "small business operators, hospitals and tissue banks often produce autologous products for local or "in- house" use. This does not mean that autologous products are produced exclusively for the local market or for internal use: tissues may be processed outside the donor's country and should therefore be able to circulate within the Community.
58 EGLS, 2004: 11.
59 However, in Italy artificial reproductive techniques are practiced.
60 In the UK, however, only creation of embryos for research purposes is allowed when it relates to treatment of infertility or to avoid genetic disease
61 EC, 2002: 14.
62 EC, 2005: 14.
63 Rossignol, 2007.
64 Putting medical drugs on the market is currently regulated in Germany by the Medical Drug Act, which defines production, market approval and follow-up. (At present in its 14. AMG Novelle version).
65 In Germany, research on human embryonic stem cells has been forbidden under the Stem Cell Act since 18th July 2002.
66 Stem Cell Network NRW, 2007.
67 Hoffmueller, 2006.
68 The important players involved in regulation of TERM in the UK are the Human Tissue Authority, Human Fertilisation and Embryology Authority and Medicines and Healthcare products Regulatory Agency. In terms of responsibility, the HTA is the authority responsible for the Tissues and Cells Directive in England, Wales and Northern Ireland, whilst the Human Fertilisation and Embryology Authority (HFEA) has the regulatory lead concerning the Directive's requirements for reproductive cells. The government intends to merge the HTA and HFEA in the near future to form the Regulatory Authority for Tissue and Embryos (RATE).
69 MHRA, 2006.
70 UK Stem Cell Bank, 2006.
71 The section on Japan is based on Fridén (2005) and parts of the section on Germany are based on Szogs and Rickne (2007). Thanks to Astrid Szogs for assistance in the data collection on Germany and to Stian Nygaard for assistance in the data collection on the UK, the US and Japan.
72 In order to assure comparability, all figures have been expressed in the same currency.
73 There are also several other BioRegio initiatives partly relating to the field.
74 BMBF, 2007.
75 Other involved partners are the University of Potsdam, Technical University Berlin, Max Planck Institute for Molecular Genetics, Fraunhofer Institute Teltow, Deutsches Rheuma-Forschungszentrum, Deutsches Herzzentrum Berlin and Max Delbrück Center.
76 One quarter of the space there is taken from research groups. The remaining space goes to biotech and other related companies and laboratories.
77 The big research organisations in Germany have recognised the potential and importance of TERM and reacted accordingly. They are supporting the development of the field through various projects and programmes.
78 It invests around GBP 336 million (EUR 455 million) per year in the biosciences and the focus is on research in genomics, stem cell biology and bio-nanotechnology with applications in healthcare, food safety, plant and livestock breeding and bioprocessing. BBSRC supports research including postgraduate training in universities and research centres throughout the UK. BBSRC, 2007.
79 See Chapter 6 for more information and also RI (2007) and Babraham Institute (2007).
80 Edinburgh Research and Innovation, 2006.
81 The Molecular and Cellular Medicine Board (MCMB) is responsible for the MRC's research funding in the following fields: Cancer biology, Genetic mechanisms, Methodology development for gene therapy, Bioinformatics, Biotechnology and structural studies, Nanotechnology and Cell biology and Developmental and stem cell biology,

excluding neurobiology. The Board is in charge of the 'Stem Cell Initiative' as well as regenerative medicine and tissue engineering.
82 MRC is funded by the UK government via the Office of Science and Technology of the Department of Trade and Industry. In 2005/06, MRC supported nearly 3,300 researchers in universities and hospitals across the UK. It invested GBP 224 million (EUR 330 million) in research and training support in universities and teaching hospitals and nearly GBP 238 million (EUR 322 million) in their own units and institutes. Also, more than GBP 50 million (EUR 67.7 million) was spent on training researchers in universities and hospitals, through 350 fellowships, 30 so called New Investigator Awards and around 420 post-doctoral studentships (MRC, 2007).
83 In terms of technology transfer, the MRC has its own affiliated company, MRC Technology working with industry to translate the scientists' findings into health applications. The income from technology transfer licensing was GBP 34 million (EUR 46 million) in 2004/05.
84 It is the main government agency for funding research and training in engineering and the physical sciences and invests around GBP 740 million (EUR 1 billion) a year in a diverse set of subjects. Funding is available through responsive mode as well as specific calls for proposals. The focus is on using the information from advances in post genome research, such as structural biology and bioinformatics in relation to health by applying the techniques and reasoning of chemistry to problems in the health and life sciences (Engineering and Physical Sciences Research Council, 2007).
85 Department of Health, 2007.
86 The Bank operates under a Code of Practice drawn up by its Steering Committee. The code is an addition to the regulatory framework provided by EU cGMP as well as other EU Directives.
87 UK Stem Cell Bank, 2007.
88 Ibid.
89 The knowledge transfer networks were set up to establish interaction between the different scientific communities on the one hand and with scientists and the government on the other. The objective of Collaborative R&D is to enable the industry and research communities to work together on R&D projects in strategically important areas, with regenerative medicine technologies as one example.
90 Furthermore, a number of relevant but not TERM-specific funding initiatives by the UK government do exist, such as the UK Clinical Research Collaboration (UKCRC) where the goal is to combine laboratory and clinical, patient-based research and thus speed up the development of new treatments.
91 An independent charity fund and the largest non-governmental source of funds for biomedical research in the UK.
92 UKSCI, 2005.
93 A charitable foundation currently allocating approximately GBP 35 million (EUR 47 million) per year. The focus is on securing the required infrastructure for research at universities across the UK (The Wolfson Foundation, 2006).
94 British Tissue Engineering Network, 2007.
95 Also, MediTech links together academics, industries and clinicians conducting research in the areas of biomechanics, biomaterials and biomedical engineering. The network aims to support medical engineering and technology research, promotetechnology transfer and establish collaboration between academia and industries.
96 EuroStemCell, 2007.
97 ISCR, 2007.
98 Fridén (2005) states that in 2004, annual funding was almost EUR 109 million, not including infrastructure.
99 In fact, many of the Japanese initiatives described in this report have been initiated under the Millennium Project.
100 CDB, 2004.
101 See Stem Cell Project Japan (2004) (in Japanese).

102 Each COE receives JPY 30-250 million (EUR 18-151 million) annually. The COE is the responsibility of one university/faculty. The funding is partly used to support research conducted by young scientists and graduate students within the COE and can in some way be compared to similar schemes in Sweden (e.g. Ph.D schools or centres of excellence).
103 The budget was JPY 1,104 million for fiscal years 2001 and 2002 respectively and 993 for fiscal years 2003 and 2004 respectively.
104 An overview of some current research supported by MHLW (and also METI and MEXT) is found in the Journal Artificial Organ vol. 28 (1) 2004.
105 A complete list of ongoing programmes and projects can be fund at JST (2004).
106 METI organises 19 industrial clusters throughout Japan for the purpose of developing regional economy and supporting new businesses METI (2004).
107 In the development plan for medical industry in Kobe City (1999), the goal is for the biomedical cluster to employ 5,400 people in 2010 and 18,100 in 2020. The economic effects are predicted as a business output of JPY 100 billion (after 10 years) and JYP 330 billion (20 years).
108 BRI, 2007.
109 Knowledge Cluster Initiative, 2007.
110 This section is based on Fridén (2005).
111 Tokyo University, 2004.
112 Research themes include (1) creation of stem cells by reprogramming of somatic cells (nucleus); (2) in vitro studies of tissue formed from stem cells; (3) manipulation of stem cells outside of the body. The project uses cell biology, genetic and proteome level approaches.
113 Keio University, 2007a.
114 Tokyo Women's Medical University, 2007.
115 He is also a visiting professor at the Institute of Medical Science, University of Tokyo.
116 Kyoto University, 2004.
117 See Khamsi, R. (2005) and Kyoto University Hospital (2007)
118 Kyoto University, 2007.
119 Keio University, 2007.
120 NCVC (2004); International Medial Center of Japan (2007); NCH (2004).
121 Osaka University, 2004.
122 NIMS, 2007.
123 See also Kyushu University Hospital, Center for the Integration of Advanced Medicine and Innovative Technology (CAMIT, 2004).
124 Vogel and Holden, 2007.
125 Holden and Vogel, 2008.
126 Normile and Yamanaka, 2008.
127 For the development of its strategy for iPS cell research MEXT in January 2008 established a subcommittee on "strategy for stem cells and regenerative medicine". (http://www.lifescience.mext.go.jp/council/programlist_committee.html?id=16). Under the CSTP an "iPS cell research working group" has been working. (http://www8.cao.go.jp/cstp/project/ips/). At the time of writing, the latest document found on overall Japanese government policy for iPS cell research is by CSTP from 24 July 2008 (http://www8.cao.go.jp/cstp/siryo/haihu77/siryo4-2.pdf).
128 MEXT's budget request for FY 2008 for the program (submitted on August 31, 2007) was JPY 1.51 billion, a level which in all likelihood would not have been achieved had the breakthrough in iPS cell research not occurred. MEXT's budget request for the "project for realisation of regenerative medicine" for the FY 2009 is JPY 3.65 billion.
129 Daiwa Institute of Research, 2008.
130 MEXT, 2008.
131 http://www.icems.kyoto-u.ac.jp/cira/e/
132 http://www.icems.kyoto-u.ac.jp/
133 http://www.jsps.go.jp/english/e-toplevel/index.html
134 http://www.icems.kyoto-u.ac.jp/

135 One of the PRESTO-grants was a five year grant.
136 The projects are described on http://www.ipscc.jst.go.jp/english/researcher/index.html and http://www.ips-s.jst.go.jp/e/sakigake/saki_01.html
137 http://ips-cell.net/index.html
138 Besides MEXT, the Ministry of Health, Labor and Welfare (MHLW) and the Ministry for Economy, Trade and Industry (METI) already provide some support for iPS cell research and have asked for increasing resources for this purpose in their budget requests for FY 2009.
139 MHLW, 2008. The announcement contains no budgetary details. The selected projects already have some government funding. The selection represents a special approval by the Council for Science and Technology Policy (CSTP), which can be expected to facilitate the obtaining of further funds in the future as well as special attention in regulatory and other administrative processes.
140 McIntire et al., 2002, p.9. In relation to this, it is interesting that close to USD 4 B has been spent by the US private sector on regenerative medicine (HHS, 2005).
141 McIntire et al., 2002.
142 MATES IWG, 2007.
143 NIH, 2007; 2007a.
144 The theme 'New Pathways to Discovery' includes the topics: building blocks, biological pathways and networks; molecular libraries and imaging; structural biology; bioinformatics and computational biology; nanomedicine; human microbiome project; and epigenomics.
145 MATES IWG, 2007, p. 2.
146 It is organised under the Subcommittee on Biotechnology of the National Science and Technology Council of which the current members are the Departments of Commerce, Defense (Army, Navy, DARPA), Energy and Health and Human Services (NIH, FDA, CMS, CDC), the Environmental Protection Agency, the National Science Foundation, the National Aeronautics and Space Administration and the Office of Science and Technology Policy.
147 These included pancreatic development and regeneration: toward cellular therapies for diabetes; development of disease biomarkers; stem cells and cancer; testing stem cell therapy in mouse models of premature aging; developmental biology and regeneration of the liver; interactions between stem and progenitor cells and the microenvironment; directed stem cell differentiation for cell-based therapies for heart, lung, blood and aging diseases; immunology of biofilms; enabling technologies for tissue engineering and regenerative medicine; and bioengineering research grants (BRG). For example, the grant 'Enabling Technologies for Tissue Engineering and Regenerative Medicine' was developed as part of the MATES working group and has an award ceiling on USD 250,000. The focus was on the development of enabling technologies such as 3D fabrication technologies, bioreactors or quantitative, non-invasive tools to monitor structure, composition and function of engineered tissues in real time (Department of Health and Human Services, 2006).
148 Viola et al., 2003.
149 In total, this amounted to more than USD 70 million (EUR 45.8 million).
150 NIST, 2007.
151 In total, ATP gave the bio-technology sector USD 30 million in support in 2000, USD 58 million in 2001, USD 51 million in 2002, USD 26 million in 2003 and USD 29 million in 2004 NIST (2007).
152 The projects at the NASA/NIH centre include; HIV pathogenesis in human lymphoid tissue, study of progression of metaplasia to dysplasia and carcinoma, long-term maintenance of human prostate tissues, hematopoeitic stem cell culture for stem cell therapy in space, effect of microgravity on the immune function of human lymphoid tissues, modelling of Lyme disease, extracellular signals on differentiation of embryonic stem cells and culture of normal and metastatic breast stem cells.
153 NASA, 2007.

154 The Independent Citizens Oversight Committee (ICOC) was formed to oversee the CIRMs funding. This board consists of 29 members comprising players representing all involved stakeholders in fields such as science, medicine, business, education, as well as those concerned with patients' rights. The board decides where the resources go in public meetings and as a way to ensure members have the proper information before making decisions on fund allocation, the CIRM set up special advisory boards in the form of Scientific and Medical Working Groups.
155 Alliance for Stem Cell Research, 2007.
156 At federal level, the Senate passed a Stem Cell Bill on July 18th 2006 that would allow for funding of ESC in the US. The idea was that the bill would loosen the restrictions on federal funding of stem cell research imposed by President Bush in 2001. The result was 63-37 in favour of the Bill. However, President Bush vetoed funding of ESC, as was much expected. In order to overturn the veto, Congress needed two thirds majority voting for the Bill, but the Democrats were unsuccessful in achieving this. In response, on July 20th 2006 Governor Schwarzenegger answered by promising USD 150 million (EUR 106 million) in loans to stem cell research at the California Institute.
156 On 11th January, 2007, Congress passed the Stem Cell Research Enhancement Act of 2007, another attempt to remove the restriction on embryonic stem-cell research implemented by President Bush. The final vote was 253-174, 37 votes short of a veto-proof majority. President Bush vetoed the bill.
157 CIRM, 2007.
158 Ministry of Education and Research, 2008, A boost to research and innovation Research and innovation bill 2008/09:50
159 Co-funded by Invest in Sweden Agency, the Knowledge Foundation, the Vårdal Foundation, the Swedish Foundation for Strategic Research and the Knut and Alice Wallenberg Foundation.
160 The total funding from public players to firms in TERM-related fields in Sweden is difficult to estimate and has not been attempted.
161 Neumann (2006).
162 With the bibliometric analysis of stem cell research, a field broader than cell biology specifically aimed for TERM purposes is captured. However, it is difficult to narrow the search to include only TERM applications and the basic stem cell research is also likely to generate knowledge applicable to future TERM research.
163 If a country is found in the address field of the article one or more times, it is counted as one article from that country.
164 The areas of the circles are proportional to the number of articles of that country and the thickness of the lines are proportional to the number of co-authored articles between countries.
165 There are a few spelling variations among this group of organisations, e.g. Lund Univ and Univ Lund, but for most organisations, they lose very few publications in the statistics due to this.
166 PENN Medicine consists of the University of Pennsylvania School of Medicine and the University of Pennsylvania Health System. Penn's School of Medicine is ranked as 2nd in the nation for receipt of NIH research funds; and 3rd in the nation in the US News & World Report's most recent ranking of top research-orientated medical schools.
167 O'Brien, 2007.
168 Fridén, 2005.
169 McIntire et al., 2002.
170 In the second dataset, addresses with the word England, Scotland or Wales were changed to UK.
171 Swedish organisations are denoted in red.
172 The country publication volume is proportional to the area of the circles and the thickness of the lines to the number of co-authorship articles.
173 McIntire et al., 2002.
174 Pavitt, 1991; Carlsson & Jacobsson, 1997.

175 Ministry of Education and Research 20082008.Prop. 2008/09:50

176 VINNOVA, ITPS 2007 Neuroscience: Columbia University – Karolinska Institutet (Wikström ITPS Washington)

177 The datasets are extracted from Science Citation Index using the Web of Knowledge platform supplied by Thomson Scientific Inc.

178 Thomson Scientific focuses on journals that publish the full text in English or at very least, their bibliographic information in English, journals using a peer review process and the completeness of cited references. It is also recommended that each article in included journals should publish information on the funding source supporting the research presented.

179 Persson, 2007.

180 80% of all journals listed in the JCR Science Edition have self-citation rates less than or equal to 20%. However, significant deviation from this normal rate prompts an examination by Thomson Scientific to determine whether excessive self-citations are being used to artificially inflate the Impact Factor. If so, the journal's Impact Factor will not be published and the journal may be considered for de-selection from the Web of Science.

181 The impact factors were taken from Journal Citation Report, JCR, provided by Thompson Scientific.

182 McIntire et al., 2002; Bock et al., 2003; Bock et al., 2005; Williams, 2003.

183 Some biomaterial companies are also listed, both companies using stable materials and biodegradable ones.

184 The list includes both TERM companies and firms identified as being related to tissue engineering and regenerative medicine but do not fall under the strict definition used for the other focus countries. The companies included compared to other focus countries primarily develop biomaterial products.

VINNOVA´s publications

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VA 2009:

01 Svenska tekniker 1620 - 1920

04 Swedish possibilities within Tissue Engineering and Regenerative Medicine

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01 VINNOVAs Focus on Impact - A Joint Approach for Impact Logic Assessment, Monitoring, Evaluation and Impact Analysis

02 Svenskt deltagande i EU:s sjätte ramprogram för forskning och teknisk utveckling. *Only available as PDF*

03 Nanotechnology in Sweden - an Innovation System Approach to an Emerging Area. *For Swedish version see VA 2007:01*

04 The GSM Story - Effects of Research on Swedish Mobile Telephone Developments. *For brief version in Swedish or English see VA 2008:07 or VA 2008:06*

05 Effektanalys av ”offentlig såddfinansiering” 1994 - 2004

06 Summary - The GSM Story - Effects of Research on Swedish Mobile Telephone Developments. *Brief version of VA 2008:04, for brief version in Swedeish see VA 2008:07.*

07 Sammanfattning - Historien om GSM - Effekter av forskning i svensk mobiltelefoniutveckling. *Brief version of VA 2008:04, for brief version in English see VA 2008:06*

08 Statlig och offentlig FoU-finansiering i Norden

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VA 2007:

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02 Användningsdriven utveckling av IT i arbetslivet - Effektvärdering av tjugo års forskning och utveckling kring arbetslivets användning av IT. *For brief version in Swedish and English see VA 2007:03 and VA 2007:13*

03 Sammanfattning - Användningsdriven utveckling av IT i arbetslivet - Effektvärdering av tjugo års forskning och utveckling kring arbetslivets användning av IT. *Brief version of VA 2007:02, for brief version in English see VA 2007:13*

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05 Nationella och regionala klusterprofiler - Företag inom fordonsindustrin i Sverige 2006

06 Behovsmotiverade forskningsprogram i sektoriella innovationssystem. *For English version see VA 2007:15*

07 Effekter av den svenske trafikksikkerhetsforskningen 1971-2004. *For brief version in Swedish and English see VA 2007:08 and VA 2007:09*

08 Sammanfattning - Effekter av den svenska trafiksäkerhetsforskningen 1971-2004. *Brief version of VA 2007:07, for brief version in English see VA 2007:09*

09 Summary - Effects of Swedish traffic safety research 1971-2004. *Brief version of VA 2007:10, for brief version in Swedish see VA 2007:07.*

10 Effects of Swedish traffic safety research 1971-2004. *For brief version in Swedish and English see VA 2007:08 and VA 2007:09*

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VINNOVA´s mission is to promote sustainable growth
by funding needs-driven research
and developing effective innovation systems

VERKET FÖR INNOVATIONSSYSTEM – SWEDISH GOVERNMENTAL AGENCY FOR INNOVATION SYSTEMS

VINNOVA, SE-101 58 Stockholm, Sweden Besök/Office: Mäster Samuelsgatan 56
Tel: +46 (0)8 473 3000 Fax: +46 (0)8 473 3005
VINNOVA@VINNOVA.se www.VINNOVA.se