



## **Focus Report**

### **Nanotechnology in Regenerative Medicine**

**April 2010**

**Authors:**

Jörn Glökler, Nano & Micro Technology Consulting (NMTC); Matthias Werner, Nano & Micro Technology Consulting (NMTC); Richard Moore, Institute of Nanotechnology (IoN)

**Version:** April 2010

**Contact:** [richard.moore@nano.org.uk](mailto:richard.moore@nano.org.uk)

[www.observatorynano.eu](http://www.observatorynano.eu)

# Nanotechnology in Regenerative Medicine

## Executive Summary

Regenerative medicine is widely seen as one of the the next revolutions in medical treatment. It draws heavily from the fields of tissue science, biology, biochemistry, physics, chemistry, materials science, applied engineering and other fields and is a highly interdisciplinary new discipline. The general aim of regenerative medicine is to repair, replace or regenerate lost or damaged tissues and organs *in vivo* through techniques that stimulate them into healing themselves. Tissues and organs can also be grown *in vitro* for subsequent implantation into the body.

Regenerative medicine is considered to have the potential for developing new treatments for previously untreatable, or difficult to treat, diseases and conditions including diabetes, heart and vascular disease, renal failure, musculoskeletal defects and injuries, osteoporosis, and peripheral nerve and spinal cord injuries. Virtually any disease that results from malfunctioning, damaged, or failing tissues may have the potential to be treated through regenerative medicine techniques.

This report provides a brief overview of some of the key developments and approaches in regenerative medicine, together with profiles of some selected companies operating in the field.

A demographically-ageing population in the majority of Western countries means that there is an increasing incidence of diseases related to ageing such as cardiovascular disease, cancer, musculoskeletal and degenerative conditions. While there have been great advances in material science and in medical device design related to medical prostheses such as hip, knee and cardiovascular implants, which today often constitute part of the normal treatments for such conditions, such devices often have a finite life within the challenging environment of the body and can give rise to complications during revision surgery to replace them at the end of their working life..

Regenerative medicine offers a potential solution to many of these clinical needs and challenges in the sense that it seeks to replace, repair or otherwise stimulate the replacement of the patient's diseased or damaged tissues with new similar tissue, usually derived from the patient themselves, thereby restoring function. Unlike many pharmaceuticals which merely "manage" a condition, regenerative medicine aims to cure or repair rather than treat symptomatically

During the 1990s and early part of the current decade the main focus of research and development was in the field of tissue engineering in which scaffolds formed of suitable biomaterials were combined with cells (autologous or allogeneic, i.e. from the patient themselves or from another person) and growth factors *ex vivo*, grown in a suitable bioreactor, and then applied surgically to the patient. However, the lack of a suitable regulatory pathway in Europe and uncertainties over possible adverse effects such as tumourigenicity meant that few engineered human tissue products have been developed or brought to the market in Europe. While the the Advanced Therapy Medicinal Products Regulation came into force late in 2007 and now covers such the placing on the market in

Europe of such products, and while there is likely to be an important and growing market for such products, there is nevertheless likely to be a lengthy regulatory approval period before novel tissue engineered products begin to appear on the European market. In the US, the only products so far available on the market are first generation engineered skin and cartilage products although the US Department of Health and Human Services has estimated a future market of \$100 billion for regenerative medicine products.<sup>1</sup>

Over the past decade, there has been a shift in interest in many centres of research towards the regeneration of human tissues *in vivo*. Here, the focus is to design implantable biomaterial scaffolds that provide a suitable physicochemical environment in which cells can grow and differentiate and to use the body itself as a “bioreactor” to grow the desired replacement tissue. This offers many potential advantages in that the cells are the patient’s own, thereby avoiding risk of rejection or transmission of infectious agents, and a providing a potentially shorter regulatory route to the clinic. A further major focus of research has been on the role and use of stem cells in regenerative medicine and control of their differentiation into the desired tissue type. Cell and gene therapies are, like tissue engineering, covered by the European Advanced Therapy Medicinal Products Regulation but are, however, specialised topics in their own right and are not addressed in this report

This report provides an explanation of the novel technologies that comprise regenerative medicine together with some examples of products in development and company profiles. It provides an indication also of where knowledge at the nanoscale and nanotechnology are being actively applied to underpin and improve the performance of regenerative medicine processes and products.

While regenerative medicine, and the application of knowledge at the nanoscale to further underpin its processes and products, holds considerable promise from the perspective of meeting unmet clinical needs and patient benefit, and while the academic and research base in Europe is also strong, there are a number of important challenges and barriers to be overcome in relation to commercialisation and to clinical uptake which are highlighted in this report.

## **Introduction**

### ***Definition***

For the purposes of this report, the following simplified definition of regenerative medicine (adapted from that proposed by Mason and Dunnill, 2008<sup>2</sup>) has been adopted. This is a similar definition to that included in the previous ST report but is more inclusive.

***regenerative medicine:*** the replacement or regeneration of human cells, tissue or organs to restore or establish normal function.

### ***Keywords***

Regenerative medicine; tissue regeneration; tissue engineering; tissue repair; scaffold; advanced therapy medicinal products; human health

### ***Methodology***

Market figures have been quoted on the basis of available market data from press releases, company reports and internet websites as well as unpublished market research studies. However, it should be taken into account that reported market figures are only estimates.

Additionally, experts in the field have been consulted for the critical assessment of the current state of regenerative medicine and of the application of nanotechnology to support and improve its performance. Where appropriate, these assessments are indicated by annotation in the text of the report.

Some selected company profiles as included have been identified via various reports, conference proceedings and internet searches.

### **Science and technology aspects**

#### ***The state of R&D***

Although, to date, there are relatively few regenerative medicine products on the market, partially due to the early stage of development of the technology, lack of data relating to risks and efficacy and delays in establishing appropriate regulation for such products, a number of key methodologies integral to the success of regenerative medicine have become well-established including:

- techniques for sorting cells, cell expansion *in vitro*, and differentiation of cells (a vital aspect of growing or regenerating more complex tissues or organs which comprise multiple cell types and of achieving tissue functionality);
- techniques for growing cells on suitable three-dimensional scaffolds for subsequent surgical implantation;
- the design of a range of novel biomaterials, with or without nanoscale features, that can serve as structural scaffolds for tissue growth (e.g. medical devices that can create a permissive environment for regeneration *in-vivo*);
- development of bioreactors for the expansion and larger scale production of cells and tissues;
- the preservation of tissues;
- cell modelling techniques.

Use of these techniques, coupled with research on the engineering of relatively simple tissues such as skin and cartilage, have allowed researchers to gain a basic understanding of how cells,

biomaterials and growth factors function and interact to form tissues and more complex structures. Furthermore, increased understanding of the mechanical and physical environments that cells need in order to form functional tissues *in vivo* has contributed to research into developing biomaterials for scaffold, often with nanoscale features, that can provide a suitable environment for tissue growth.

### ***Additional demands for research***

Fundamental research continues to focus largely on achieving an understanding cell-to-cell signalling and cellular interactions with the extracellular environment at a micro and macro level, which can subsequently be applied to creating and integrating tissues *in vivo* with particular attention to interactions at the nano- level.

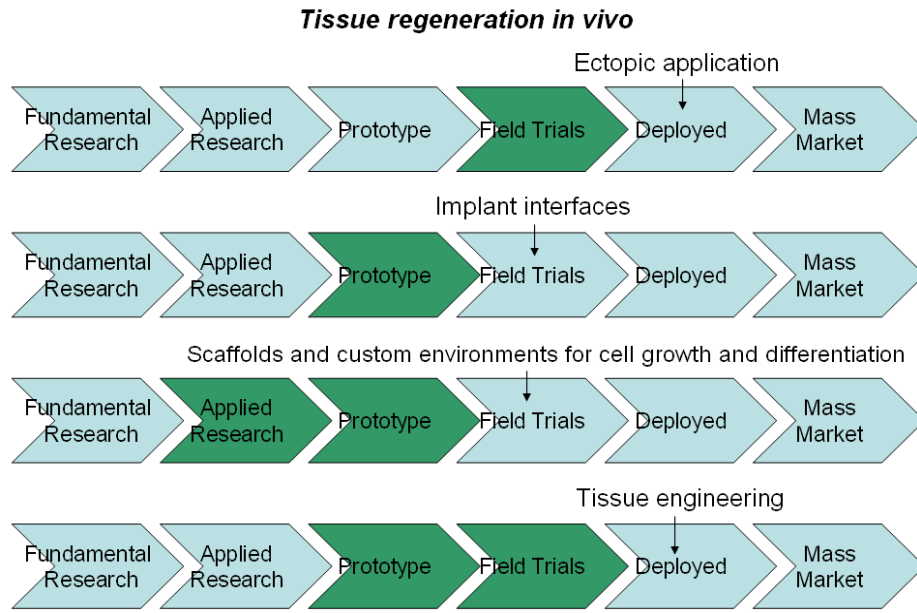
The US Department of Health and Human Services has identified the following as additional areas where further research is needed <sup>1</sup>:

- understanding the processes involved in mechanical signaling and cellular mechanotransduction (how cells and systems communicate with each other);
- improving control of tissue development and organogenesis;
- creating tissues *in vitro* and then bringing these tissues *in situ* (integration of laboratory-grown cells into living bodies);
- developing handling and storage procedures for regenerative medicine applications, in order to effectively manage and preserve tissue supplies;
- increasing scalability of engineered cells;
- developing tissue quality assurance procedures to ensure safety and consistency.

In addition, further research and data is needed concerning the safety aspects, e.g. biocompatibility, tumorigenicity, of regenerative medicine products and processes, and concerning the ability of cells to sense their surrounding environment.

### ***Applications and perspectives***

The most advanced regenerative medicine products in terms of market penetration are ectopically-applied substances for wound healing and scaffolds for *in vitro* tissue engineering. While many products are in early-stage development for regenerative medicine, nanomaterials are not often specifically mentioned as part of this development although they may frequently form part of components such as scaffolds.



**Figure 1: Estimation of Technology Readiness Levels. Arrows indicate front developments and mainly occupied stages are coloured in green.**

Regenerative medicine is a broad term covering a range of innovative medical therapies that are intended to enable the body to repair, replace, restore and regenerate damaged or diseased cells, tissues and organs. Regenerative medicine has a potential to extend healthy lifespans and improve the quality of life by supporting and activating the body’s natural healing mechanisms, or by creating an environment that mimics early development or that is more conducive for tissue regeneration. Some examples of clinical application areas of current research in regenerative medicine include

- replacement of skin for burns patients, wounds, pressure sores or diabetic foot ulcers
- bone and cartilage regeneration
- bladder repair
- vascular tissue engineering
- the use of stem cells in tissue regeneration
- repair of damaged heart muscle following heart attack
- restoration of peripheral nerve or spinal cord following injury, or of the CNS after tumour resection
- regeneration of pancreatic tissue to produce insulin for people with diabetes
- further early stage research on regeneration approaches to replace lost organ function
- the stabilization and maintenance of the viability of tissue prior to regeneration
- control of environmental contaminants
- preventing a tissue injury from deteriorating in either a controlled environment or in an uncontrolled setting, e.g. traumatic or shredding injury, burn, stroke, ischaemic disease, etc.
- interfaces between tissues and devices, including approaches intended to improve biocompatibility, and integration between cells and novel devices such as the artificial retina
- dynamically configurable materials, e.g. materials that self-assemble within the body
- the fate of biomaterials and implant materials within the environment of the body
- the interaction between cells and the morphology/topography of surfaces and coatings

A successful development of regenerative medicine centered on human cells could be a so-called 'disruptive technology' because it could potentially replace a number of major molecular pharmaceuticals and medical prostheses. For example, stem cell-derived  $\beta$ -islet cells can potentially replace a patient's requirement for insulin injections<sup>2</sup>.

### ***Some examples of current regenerative medicine applications***

Several regenerative medicine products or tissue-engineered products (a subcategory of regenerative medicine) are already available on the market for clinical applications in the areas of tissue engineered skin and cartilage, and in bone repair. One notable example is Apligraf (Organogenesis, USA), a tissue-engineered skin product, which has been used to treat over 250 000 patients for chronic leg ulcers. However, so far none of these products claim to be nanotechnology-based and those that do are not yet approved or widely available for the treatment of patients.

Because of the absence from the market of current products, this report details instead some of the more promising regenerative medicine developments, incorporating nanoscale features, that may enter the market in the near to medium future. Furthermore, due to the wide range of possible applications within the overall umbrella of regenerative medicine the report lists these in different categories.

### ***Implant interfaces incorporating nanomaterials***

Classical implants face problems like tissue rejection and poor mechanical integration. Much research amongst the orthopaedic implant sector focuses on increasing the biocompatibility of the inanimate implant material and on physical size vs molecular interaction and whether these may change over time. Examples include ultra-pure hydroxyapatite implant nanocoatings pioneered by Nano Interface Technology, Inc.<sup>3</sup> aimed at improving the interface between bone and implants and avoiding long-term problems such as poor fixation and tissue necrosis around the implant. These coatings are not yet on the market but are expected to gain FDA approval soon.



**Figure 2: Hip implant with nanocoating**  
(Nano Interface Technology Inc.)<sup>3</sup>

### ***The development of advanced scaffolds for regenerative medicine***

A scaffold is a structured environment that physically supports cell growth as part of a tissue repair or regeneration process. Scaffolds can be either active (e.g. they may incorporate materials or features that help influence or direct cell growth) or inert (e.g. they simply provide a shape and physical substrate for the final tissue construct). There are many different types of scaffold materials including:

- scaffolds derived from natural or biological material, for example following purification or decellularisation
- scaffolds formed from synthetic materials, either bioresorbable or non-degradable

Ideally, a scaffold used in regenerative medicine should as far as possible mimic conditions, including a variety of physical and chemical cues at the nanoscale and especially in the extra-cellular matrix (ECM), that cells need to form tissues resembling those found naturally in the body.

Cells may be harvested from the patient (autologous), or another person (allogeneic), cultured and seeded onto the scaffold *in-vitro* with suitable growth factors, grown and expanded in a bioreactor until of suitable bulk or shape, and then re-implanted into the patient. Increasingly, an alternative approach in which the patient's cells are persuaded to grow into the scaffold *in-vivo* and populate its interstitial spaces from the surrounding tissues or ECM is being adopted. Over a period of time the synthetic scaffold, or matrix, is resorbed into the body and replaced by extra-cellular matrix produced by the cells themselves.

One particular challenge in producing three dimensional tissue structures, e.g. for use in reconstructive surgery or to fill bone voids, or in engineering artificial organs, is that of transporting nutrients and oxygen to the growing cells and removing waste products as engineered tissues lack an initial blood supply.

Taking these needs into account, the key requirements for a scaffold to be effective in promoting three-dimensional cell growth and vascularisation, and assembly of a tissue (or ultimately an organ) include:

- good biocompatibility;
- the ability to degrade into non-toxic components that can be eliminated from the body as the synthetic scaffold is replaced by new extracellular matrix produced by the cells;
- the ability to exert an effect at molecular level;
- the ability to incorporate cell-specific recognition factors such as adhesive proteins or functional domains in ECM components that promote cell binding to the scaffold;
- the ability to include and sequentially target biomolecules that promote cell growth and differentiation into the desired tissue thereby achieving the reparative process;
- the ability to enable diffusion of cell nutrients and cell-produced biomolecules on demand and in a timely manner;

- the ability to react to external inputs in a controlled and predictive manner where needed;
- the ability, where appropriate, to be chemically attracting to endogenous progenitor cells;
- the ability to react and adapt to changes in physiological parameters;
- structural characteristics, particularly in a three-dimensional scaffold, such as a high and interconnected porosity that facilitates the vascularization and innervation of the new tissue, high surface area for cell population and adhesion, and suitable mechanical integrity and physical properties depending on the type of tissue to be produced. The modulus must also be compatible with the surrounding tissue and also with the stage of regeneration.

For example, engineered cartilage will only become fully functional when grown in a matrix that allows physical movement such as compression and decompression during growth of the chondrocytes. In addition chondrocytes prefer a fibrous scaffold material in order to lay down their collagen type 2 matrix. The optimal porosity, pore interconnectivity and chemical and mechanical characteristics of scaffolds will also vary according to cell type and intended engineered tissue type. These characteristics comprise a combination of microscale structure and nanoscale surface and functionalization features in any given scaffold.

Some examples of commonly-used scaffold materials that either include nanoscale features or that can be functionalized at the nanoscale to provide characteristics suitable to support cell growth include

- collagen and collagen-based materials
- fibrin
- chitosan
- keratin
- peptides
- glycosaminoglycans, e.g. hyaluronic acid
- hydrogels
- silk proteins
- hydroxyapatite
- tri-calcium phosphate
- commonly-used and regulatory-approved medical polymers with known biocompatibility, e.g.
  - polylactic acid (PLA)
  - polyglycolic acid (PGA)
  - poly DL lactic-co-glycolic acid (PLGA)
  - polycaprolactone (PCL)

Scaffolds that are currently being used include approved components like biocompatible and degradable polymers that can imitate the extracellular matrix. Examples include FDA-approved polymers such as poly(D,L -lactide-co-glycolide) (PLGA) and polylactide (PLA). However, these are not yet applied as nanoscale products outside the field of research. Many other polymers based on biological building blocks are being developed; most of these are still going through clinical trials and awaiting approval.

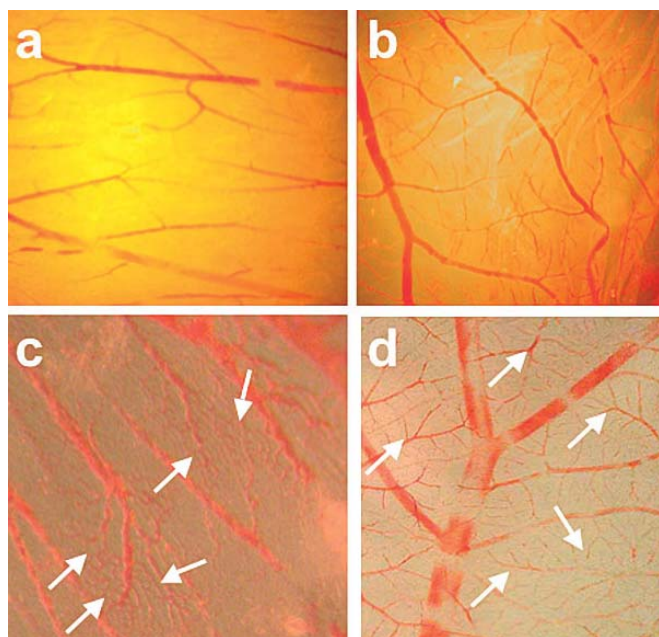
### Ex-vivo tissue engineering

Autologous, allogeneic, or xenogeneic tissue can be engineered and expanded *ex-vivo*, and introduced to replace damaged tissue *in vivo*. To this end suitable cells or tissues need to be obtained, from the patient him/herself (autologous), from another person (allogeneic) or from an animal (xenogeneic), tested (e.g. to identify and eliminate any transmissible agents), sorted, expanded (in the case of human cells), processed and manipulated *ex vivo*, and incorporated into a suitable scaffold with suitable growth factors, to generate new engineered tissues ready for surgical implanting into the patient.

Scaffolds for *ex-vivo* tissue engineering face similar problems as those for *in vivo* regeneration. However, if the scaffold is biodegradable, fewer obstacles exist for the final tissue (re-)implant. Notable examples include PuraMatrixGMP™ from 3DM<sup>4</sup>, a self-assembling hydrogel that is available in clinical-grade quality for orthopaedics, bioproduction, and drug delivery applications and which has entered a clinical trial for use as a scaffold material in dental bone regeneration in 2008; and a nanostructured material developed by Arch Therapeutics, Inc. that promotes almost instantaneous haemostasis when applied by syringe onto a wound.(2008)..

### Ectopic applications

So far, wound healing products are amongst the more advanced nanotechnological materials in the sector. Examples can be found in products developed by OmegaGenesis<sup>5</sup> or Altrazeal™ from ULURU Inc<sup>6</sup>. The latter, especially, has advanced and has completed the first clinical trial successfully<sup>7</sup>.



**Figure 3: Chick CAM assay demonstrating sprouting. (a) Treated with vehicle, (b) VEGF, (c and d) 1 and 10 µg nanorods (taken from OmegaGenesis<sup>8</sup>)**

### Cell therapy and gene therapy

Besides human tissue engineering products, cell therapy and gene therapy are the two other main application areas addressed by the Advanced Therapy Medicinal Products Regulation in the European Union. While both are important areas, with potentially significant clinical impact and in which knowledge and technology at the nanoscale are being applied at research level, they are outside the scope of the current report due to their specialist nature and specific sets of challenges.

### Tissue regeneration in-vivo

Increasingly, the trend in regenerative medicine is likely to progress from using active biomaterials seeded with cells and growth factors *in-vitro* toward the development of “intelligent” biomaterials functionalised with bioactive molecules that promote cell homing to the implanted scaffold *in-vivo*. One such example currently in the research phase involves growing healthy new bone in patients by implanting a gel that supports bone growth beneath the periosteum of long bones and then later harvesting this healthy natural bone for use in reconstructive or repair surgery elsewhere in the body, thereby avoiding the traditional method of using bone from the iliac crest which often leaves patients with severe pain<sup>9</sup>.

Other applications in development include

- the regeneration of skin *in vivo*;
- the arrest of further deterioration of neural or other tissues by the formation of a barrier or environment that will facilitate normal repair.

## **Economic aspects**

### ***General market description***

The market for regenerative medicine products is still in its infancy and, to date, a modest number of products are available. A recent report by Life Science Intelligence Inc.<sup>10</sup> suggests that the worldwide market for tissue engineered and regenerative medicine products was close to \$1.8 billion in 2008 and the same report predicted that there would be a projected market growth of 16.2% compound annual rate from 2008 to 2013 with the worldwide market approaching \$3.2 billion by 2013. However some experts consider that this figure may be underestimated by a factor of up to x10 (personal communication by a reviewer to the authors).

Relatively few large multinational companies are currently active in the field of regenerative medicine and fewer still have declared their interest in the application of nanotechnology to the field as a supporting technology. Current development in the field is largely represented by specialist, small to medium-sized companies. However, progressing regenerative medicine products to market is likely to require substantial financial resource and this aspect is further explored in the section below on “Economic information and analysis”.

The potential for regenerative medicine to become part of mainstream medical practice undoubtedly is high, as described in a previous part of this report, but considerable technical and commercial challenges remain. Some of the non-technical barriers are described in the following sections of this report.

### ***Drivers and barriers***

A demographic shift towards an increasingly ageing population is a feature of the majority of Western nations. By 2060, it is estimated that the EU will move from having four working-age people (aged 15-64) for every person aged over 65 to a ratio of only two to one. The largest decrease is expected to occur during the period 2015-2035 when the baby-boom cohorts will be entering retirement<sup>11</sup>. These demographic changes will have a dramatic effect on the society in which we live. With this demographically ageing population also come new clinical challenges in relation to diseases associated with the elderly such as arthritis, osteoporosis and other orthopaedic conditions, neurodegenerative diseases, deafness and macular degeneration. Furthermore, modern lifestyles are resulting in an increased prevalence of “lifestyle-related” conditions and diseases such as obesity, cardiovascular disease and diabetes. Additionally, increases in life expectancy are not always matched by an extension of health so more people will spend an increasing number of their later years in poor health and with chronic diseases. In addition, if conditions such as obesity are not urgently addressed many people may enter this unhealthy state at an even earlier age.

This means that the market for clinical approaches that address these challenges is likely to expand, and is furthermore likely to continue to do so for the foreseeable future as older citizens increasingly wish to remain active into an extended retirement. Moreover, another feature of this demographic shift is that an increasingly smaller proportion of the total population will be of working age, thereby reducing the overall tax and national insurance base and thereby providing a growing economic challenge for healthcare systems.

In this context, the growing clinical need for the healing or replacement of damaged or diseased tissues and organs in an ageing population is obvious. Medical technology has, for many decades, addressed this need by the development of new generations of medical devices, such as orthopaedic or cardiovascular implants and this market is currently large and mature. However, even with the application of novel technologies such as nanotechnology to further improve the performance of these products, they still have a finite life within the harsh environment of the human body and explantation and replacement can be costly, traumatic for the patient and sometimes unsatisfactory in clinical outcome. This has led to increased focus on technologies and clinical approaches that can help the body to repair itself or to regenerate new tissue. These approaches are collectively termed regenerative medicine. In the longer term, regenerative medicine may be expected to lead to the creation of fully biological or biohybrid tissues and organs that can replace or regenerate tissues and organs damaged by disease, injury, or congenital anomaly, although such development is currently in its early stages.

Tissue engineering, one of the main areas under the umbrella term “regenerative medicine” has been considered a promising medical technology for over a decade but its development and impact on the market in Europe was somewhat held back by the lack of a European regulation covering the placing of such products on the market in the EU prior to the coming into force of the Advanced

Therapy Medicinal Products Regulation<sup>12</sup> on 30 December 2007 (which was due to be implemented in Member States by 30 December 2008). The ATMP Regulation covers gene therapy, somatic cell therapy and tissue engineered products. While there are therefore relatively few tissue engineered products currently on the market in Europe, a number are in the developmental pipeline.

In a research study funded by the UK Engineering and Physical Sciences Research Council on barriers to commercialisation and utilisation of regenerative medicine in the UK, Rowley and Martin<sup>13</sup> noted that

“...while the underlying science of regenerative medicine has grown exponentially over recent years, this has not been translated into a successful, commercial enterprise.”

In further analysing the situation, they suggested that

“Data demonstrates that UK academic regenerative medicine is thriving. Unfortunately, lack of access to capital, regulatory hurdles, a dearth of clinical evidence on (cost) effectiveness is leading to problems with utilisation and reimbursement. This is compounded by an NHS culture that is considered to be unsupportive in utilising innovative products, and does not provide an attractive environment for the commercialisation of regenerative medicine products. These have all been suggested as having contributed to hindering the progress that the science has made thus far.”

“In general, product acceptance by patients, clinicians and the public was not seen to be problematic. However, companies had, and continued to encounter, difficulties in achieving widespread clinical adoption and utility of their products.”

“The utilisation of regenerative medicine products is likely to demand a conceptual shift in the working practices of clinicians, as therapies are anticipated to offer a step-change in care. This will be a very difficult barrier to overcome, with clinicians known to favour particular techniques that they have had success with. Training and education will need to be provided by the manufacturer, and should be targeted at the appropriate level for all staff that will come into contact with the product.”

“There are a number of significant barriers to the emergence of regenerative medicine in the UK. The industry does not yet have a clear identity and visibility, as there are no exemplars of the conversion of emerging regenerative medicine businesses into major public companies. The complex nature of the science and engineering involved, combined with a weak venture finance climate, means it is difficult for new companies to attract investment and to develop the manufacturing capability required to bring regenerative medicine products to the market. The technical demands placed on developing regenerative medicine companies are very high; they need to be ‘polymaths’, spanning biology, engineering and materials science. Finally, the regulatory environment is still evolving, and reimbursement and investment models have yet to emerge.”

While the study was focused on the UK and takes account of the structure of public healthcare provision in the UK, it is likely that many of these observations will be applicable also to the scenario and outlook elsewhere in Europe for regenerative medicine.

A distinction should furthermore be made between therapeutics and so-called molecular medical devices (MMDs) which have quite different regulatory pathways.

### ***Economic information and analysis***

Mason and Manzotti<sup>14</sup> state that “cell therapies (Authors’ note. For the purposes of this report cell therapies that are covered under the Advanced Therapy Medicinal Products Regulation are meant rather than already widespread therapies such as those for leukaemia or based on blood transfusions which are excluded from the scope of this report) are undoubtedly a disruptive technology requiring not only novel discovery, development, manufacture and marketing of living products, but also an entire service infrastructure to support their deployment in the market, including appropriate regulation, reimbursement and clinical expertise. In addition, new business models need devising in order to capture the value of cell- and tissue-engineered products. Unfortunately, current pharma and biotech models do not seem to be adaptable to cellular therapies. In part this is due to the final living product and its manufacturing process being totally inseparable, coupled to the spectrum of opportunity ranging from patient-specific therapies that are service orientated, through to universal commercial products that are more capable of scalable manufacture.”

Mason and Dunnill<sup>2</sup> suggest that, for the more sophisticated products of regenerative medicine research, it is likely that most start-ups will require the deep pockets of major pharmaceutical, healthcare or device companies in order to commercialise their products. In this context they consider that the engineering of human cells is a rather alien concept to pharmaceutical companies more used to the development of molecular medicines although biopharmaceutical companies developing protein drugs may have more familiarity with some aspects of the process. They furthermore suggest that some pharmaceutical companies might struggle with a business concept in which cells may only be required once for lasting benefit compared with the majority of protein therapeutics, and that the situation for cells is more akin to the business case for some medical devices noting that a few device companies concerned with acellular repair are already active in collaborations with regenerative medicine start-ups.

Despite the fact that extensive research is being conducted in the field, no large companies are yet selling any nanoproducts associated with regenerative medicine. Some companies even openly declare the absence of nanotechnology in their products<sup>15</sup>. The key players are still, in the main, small companies like 3DM which are trying to push their products toward clinical application with the help of larger companies.

The volume of the current market is low and many of the involved companies are still engaged in early stage development. However, some big pharmaceutical players such as Bayer have a key interest in research concerning regenerative medicine. Despite this interest, the company itself does not divulge within its business communication as to which extent nanotechnology is involved

(personal communication). Thus any estimations regarding projected market share, number of employees involved and volumes for regenerative medicine products would, at this stage, remain highly speculative.

One important reason for the slow market penetration of regenerative medicine products to date is the length of time needed from the initial research stages until the final approval for product release on to the market. Generally, it takes more than a decade from initial inception until a medicinal product reaches the market although regulatory approval of a regenerative medicine product that falls under the definition of a medical device, e.g. an implantable biomaterial without addition of cells or growth factors, could be expected to be much more rapid.

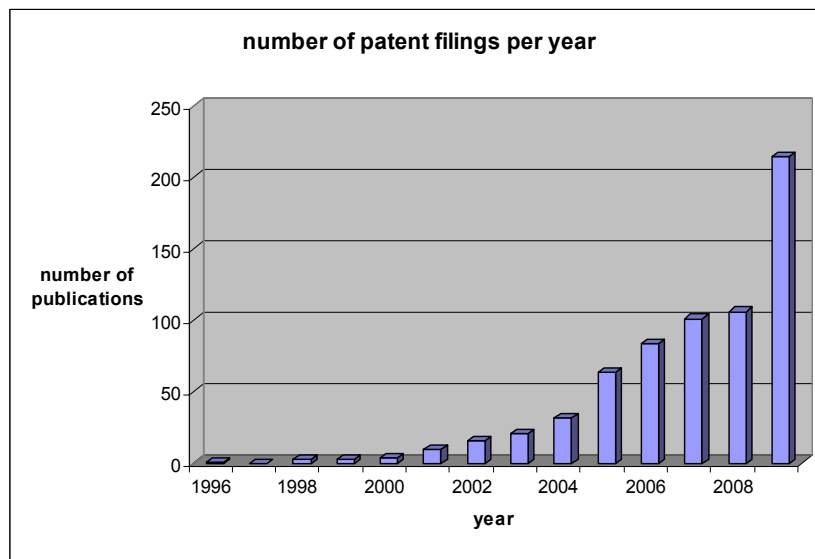


Figure 4: Patent search with biomaterials, nano and implant keywords. Development of patent filings in the field.

If the patent situation can be used as an indicator, it is suggestive that many products for regenerative medicine are in development and should begin to enter the market in the coming years.

Next to the USA, Europe is the principal source for patents in the sector of regenerative medicine.

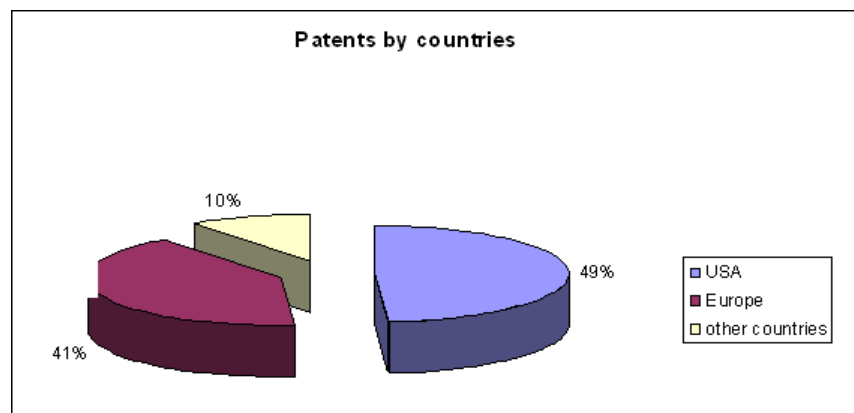


Figure 5: Patent search with biomaterials, nano and implant keywords. Geographic distribution of patent filings.

### ***Boundary conditions***

An important issue for regenerative medicine is the compatibility and long term integration of nanomaterials *in vivo*. Although some inorganic materials have been shown to serve as colonisable scaffolds for implants<sup>16</sup>, little is known about their long term effects. It is likely, however, that more well-studied biodegradable polymers that could potentially serve as transient, resorbable scaffolds may be less problematic.

All these products need the approval of the relevant health regulatory agencies in Europe or elsewhere according to which regulatory path they have to follow, i.e. Advanced Therapy Medicinal Products Regulation or Medical Device Directive, according to principal intended mode of action. For companies that want to sell their products in the USA, for example, the most important agency is the Food and Drug Administration (FDA). The process of FDA approval for medicinal products usually takes more than a decade and includes several clinical trial stages. Since nanomaterials are generally used in order to take account of their particular novel characteristics, these will be evaluated thoroughly before any regulatory approval is granted. However, the review process for regenerative medicine products containing nanomaterials is expected to broadly follow the same paths as those used for other products that do not claim to contain nanomaterials<sup>17</sup>.

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has stated: "*Experts are of the unanimous opinion that the adverse effects of nanoparticles cannot be predicted (or derived) from the known toxicity of material of macroscopic size, which obey the laws of classical physics.*"<sup>18</sup> This lends weight to the probability that a specific evaluation of the hazards and associated risks of individual nanomaterials applied in regenerative medicine will become necessary.

Recent studies describe the behaviour of some forms of carbon nanotubes (CNTs) as being similar to known hazardous materials like asbestos<sup>19 20</sup>. Already the German Umweltbundesamt has issued a warning on nanotechnology<sup>21</sup>. These may eventually halt developments to use CNTs for medicinal purposes in Germany and could possibly lead to a negative perception of other nanomaterials amongst the general public.

This possibility has already led to reluctance by some larger companies to openly endorse nanotechnology in healthcare. Several products in the developmental pipeline are reported to have been shelved as negative reports concerning safety of the nanotechnologies involved have surfaced (personal communication). However, protein-based nanomaterials that are broken down and excreted in a similar way to other proteins are expected to pose lower hazards, e.g. collagen, hyaluronan, peptides.

### ***Selected company profiles***

The following are examples of companies that are active in the field of regenerative medicine. While in some cases the application of nanotechnology is not necessarily claimed in their products, e.g.

materials used in scaffolds, there is an underlying trend towards the formulation of materials at the nanoscale to provide the consistency, performance or characteristics desirable for regenerative medicine purposes.

### **Arch Therapeutics, Inc.**

Arch Therapeutics is a life science company developing and commercializing nanostructured compositions that promptly stop or control bleeding (haemostasis). It has concluded a license agreement with the Massachusetts Institute of Technology for development of the technology into commercial products.

The license provides Arch Therapeutics exclusive and non-exclusive commercialization rights to a range of patents and applications for technology that includes a family of compositions to control bleeding and the movement of other bodily substances.

Arch Therapeutics' compositions are clear, water-like, non-sticky materials that can be easily squirted through a syringe onto a bleeding wound. Arch Therapeutics expects the compositions to improve results in both surgical and trauma settings. The compositions should improve general outcomes for patients, decrease morbidity and mortality, and provide productivity and economic benefits in hospital environments and other settings. In early animal tests, the material has been used successfully to stop bleeding in the liver, spleen, femoral artery, eye and brain.

[www.archtherapeutics.com](http://www.archtherapeutics.com)

### **Bayer Schering AG**

Schering AG was a research-centred pharmaceutical company founded in 1851 that merged with Bayer in December 2006. At that time the company employed more than 26,000 people in 140 subsidiaries all over the world. The company's headquarters are in Berlin, Germany.

Schering's annual gross revenue was nearly €5 billion (2003). To Schering's key businesses belong the areas of gynaecology, andrology and oncology. Their best-known products are combined oral contraceptive pills. The company was also involved in special therapeutics, diagnostic devices & nuclear medicine. The company's founder was Ernst Schering (1824-1889). The largest German manufacturing facility is located in Bergkamen. Schering used the Berlex Laboratories brand in the USA. On March 13, 2006, Merck KGaA announced a €14.6 billion bid for Schering. The offer document was due to be issued in early April 2006.

Merck's takeover bid was surpassed by Bayer's €16.2 Billion bid for Schering on March 23, 2006. In June 2006 Bayer finally bought the majority of shares, over 90%. A domination agreement using the code name "Step One" was used for the take-over. As a result of the take, Bayer Schering Pharma is one of the ten largest specialty pharmaceutical companies in the world and the company's goal is a leading market position in each of its specialist fields. With its distinctive expertise in research, the company develops new medicines and therapies which make an essential contribution toward improving patient's quality of life.

As a research-oriented company, Bayer Schering Pharma has focussed on nanotechnology at an early point in time. For example, in diagnostic imaging, contrast agents based on nanoparticles have optimized the quality of pictures taken.<sup>22</sup>

### **Fidia Advanced Biopolymers**

Fidia Advanced Biopolymers s.r.l. (FAB) was formed in Italy in 1992. It is an independent company operating in the advanced biomedical field.

The company utilizes its integrated R&D capabilities to develop devices of novel conception, which are designed to offer advanced solutions to specific clinical needs.

FAB research produced HYAFF, hyaluronic acid in solid form, a totally biocompatible and biodegradable biomaterial and forerunner of a vast series of biopolymers used in diverse applications, the most sophisticated of which is tissue engineering.

FAB research has produced innovative technologies that enable human tissues such as cartilage and skin to be regenerated in a laboratory. The process originated from the idea of using hyaluronic acid to create a scaffold which would provide the ideal conditions for body cells, such as keratinocytes, fibroblasts and chondrocytes, to proliferate and form healthy tissue.

The result is advanced technology by which highly functional, autologous tissues can be recreated and grafted onto cartilage lesions or diabetic ulcers.

FAB products for tissue repair include:

- Genaid: (*Hydeal-D ester of hyaluronic acid formulated as a gingival gel*)
- Hyal-System: (*hyaluronic acid sodium salt solution for intra-dermal administration*)
- Hyal-System ACP: (*auto cross-linked hyaluronic acid solution for intra-dermal administration*)
- Hyalofemme: (*Hydeal-D ester of hyaluronic acid formulated as a vaginal bioequilibrant gel*)
- Hyalosilver: (*hyaluronic acid sodium salt 0.2% + colloidal silver 2% spray*)
- Jaloplast: (*hyaluronic acid sodium salt formulated as 0.2% cream, 0.2% topical gel, cream-impregnated gauze pads for topical use, 0.2% topical spray solution*)
- Jaloplast Plus (*hyaluronic acid sodium salt 0.2% + Silver sulfadiazine 1% formulated as cream-impregnated gauze pads for topical use*)

### **Genzyme Biosurgery**

Genzyme Biosurgery is a subsidiary of one of the world's leading biotechnology companies, Genzyme Corporation, headquartered in Cambridge, Massachusetts, USA. Genzyme has grown from a small start-up to a diversified enterprise with more than 11,000 employees in locations spanning the globe and 2008 revenues of \$4.6 billion.

Genzyme Biosurgery offers two advanced products to treat joint problems: Synvisc® (Hylan G-F 20) for Osteoarthritis of the knee and hip and Carticel® (autologous cultured chondrocytes) for knee cartilage damage.

### **Integra**

Integra LifeSciences Holdings Corporation of the USA acquired IsoTis of the Netherlands in October 2007. The combined company offers some of the most advanced technologies to address surgeons' needs and Integra is now one of the largest companies in the world focused on advanced technology in orthobiologics. It has a product portfolio encompassing some of the most trusted orthobiologic brands, such as INTEGRA(R) Dermal Regeneration Template, DuraGen(R) Dural Graft Matrix, Integra Mozaik(TM) Osteoconductive Scaffold, NeuraGen(R) Nerve Guide and the Accell family of demineralized bone matrix products, DynaGraft(R) II and OrthoBlast(R) II. The combined company has operations in North America and Europe with more than 2,000 employees, including approximately 300 sales and service professionals and over 500 employees in Europe.

### **Nano Interface Technology Inc.**

Nano Interface Technology Inc (NITI) is a private company categorized under Dental Equipment and Supplies and located in Lorton, Virginia, USA. It was established in 1998 and incorporated in Florida. Its mission is "Innovation in the Nano-biotechnology and Nanotechnology." NITI has a mix of the technical, scientific and business professionals. The company's scientific advisory board consists of Biochemist, Cardiologist, Colloid Scientist, Dentist, Internist, Materials Scientist, Pharmacist, and Polymer Scientist. The products and technologies developed by the NITI can be put to variety of uses. The target market has been chosen as the applications in the life sciences market. This market has been chosen in view of its relevance, ease of entry and potential size. The main focus is on the development of the hydroxyapatite (HA) – used extensively as the latest material for the coating of the implants for the human body. The usage of HA synthesized by this process is expected to decrease the failures of the implants, reduce the costs of the insurance and decrease the patient's trauma.

### **Neotherix**

Neotherix is a regenerative medicine company based in the UK specialising in the development of novel bioresorbable scaffolds for tissue regeneration and repair.

The company develops innovative products for soft tissue repair and therapy in specific, selected applications where there is a clear clinical need. It applies and exploits a unique knowledge of polymer electrospinning technology combined with wound healing biology to develop bioresorbable scaffold materials.

The scaffolds possess a non-woven three-dimensional architecture, comprising nano/micro-scale synthetic bioresorbable polymer fibres. The highly porous scaffold structure supports the migration and proliferation of fibroblast cells from surrounding healthy skin tissue in order to facilitate healing of the wound.

As fibroblasts populate the scaffold and begin to generate new tissue, the bioresorbable fibres are gradually broken down by hydrolysis. After 7-10 days the material ceases to provide a scaffold architecture to the cells and is completely degraded after 3 weeks *in situ*. The by-products of hydrolysis are metabolised by normal biochemical pathways, ultimately being lost during respiration as carbon dioxide and water.

The bioresorbable nature of the scaffold means that it does not require subsequent removal, but acts as a temporary support for cells involved in the healing process until its eventual replacement by new tissue. Blood vessel formation follows, ensuring good tissue viability.

### **OmegaGenesis Inc.**

The company was founded in 2008 to bring Mayo Clinic-proprietary nanomaterial technology to the marketplace. It is now based in California and Minnesota, USA. The company is the market innovator in nanotechnology-based angiogenesis and imaging solutions. Its solutions promote the growth of new blood vessels where needed to improve human health. The technology and products are based on the idea that controlling blood-vessel growth will improve human body management for a diverse set of medical applications, ranging from common wound healing to tissue reactivation.

OmegaGenesis is the pioneer in using nutrient enhancement through new capillary growth to heal wounds and activate dormant cells. Its research has led to production of nano-scale materials that work on the cellular and sub-cellular level to promote or inhibit angiogenesis, the growth of new blood vessels.

### **Orthomimetics**

Orthomimetics, based in the UK, is a trans-Atlantic collaboration between two world-leading academic institutions, the University of Cambridge and the Massachusetts Institute of Technology (MIT), who have each contributed 30 years of experience to the repair of bone and soft tissues, respectively. Its products combine groundbreaking regenerative medical technology with state-of-the-art minimally invasive delivery methods to provide long-lasting solutions that restore joint mobility following sports injuries and other orthopaedic trauma and reduce the risk of osteoarthritis. In December 2009, Orthomimetics was acquired by TiGenix, a regenerative medicine company based in Leuven, Belgium (see below).

### **RTI Biologics, Inc.**

RTI Biologics Inc. (Alachua, Florida, US) is a leading provider of sterile biological implants for surgeries around the world, with a commitment to advancing science, safety and innovation. RTI prepares donated human tissue and bovine tissue for transplantation through extensive testing and screening, precision shaping and proprietary, validated sterilization processes. These allograft and xenograft implants are used in spine, sports medicine, orthopedic, dental and other surgical specialties.

## TiGenix

TiGenix is a biomedical company that focuses on innovative local treatments for damaged and osteoarthritic joints. Based in Leuven, Belgium, TiGenix was founded in 2000 by Professor Frank P. Luyten, rheumatologist, and scientist and bioengineer Gil Beyen.

TiGenix is built on technologies developed at the universities of Leuven and Ghent. The company's scientific background and expertise has concentrated on the developmental biology of cartilage, bone and other connective tissues. The insights TiGenix' scientific founders gained into the biology of cartilage have subsequently led to the development of a technology platform focused on finding solutions for damaged and diseased cartilage.

## ULURU Inc.

ULURU Inc. was founded in 1987 and has its headquarters in Dallas/Fort Worth, USA. It is a specialty pharmaceutical company focused on the development of a portfolio of wound management and oral care products to provide patients and consumers improved clinical outcomes through controlled delivery utilizing its innovative Nanoflex™ Aggregate technology and OraDisc™ transmucosal delivery system. ULURU Inc. developed and commercializes Altrazeal™, a transforming powder dressing with proprietary Nanoflex™ technology, for the management of exuding wounds.

## 3DM Inc.<sup>23</sup>

3DM Inc. was founded in 2001 to commercialise biotech R&D started already in 1994. Its business strategy is to establish and maintain a position as the leading synthetic cell culture scaffold for bioproduction, life science R&D and stem cell therapies, through a worldwide marketing and distribution partnership with Becton Dickinson (BDBiosciences). 3DM is developing a pipeline of medical devices for orthopedic and cardiac therapies with industry-leading companies. R & D includes stem cell expansion and delivery, bioproduction, and tissue engineering. The main product on the market is Puramatrix.

## References

<sup>1</sup> 2020: *A New Vision - A Future for Regenerative Medicine*, US Department of Health and Human Services, March 2006, [www.hhs.gov/reference/newfuture.shtml](http://www.hhs.gov/reference/newfuture.shtml)

<sup>2</sup> Chris Mason Peter Dunnill *A brief definition of regenerative medicine*, *Regenerative Medicine*, January 2008, Vol. 3, No. 1, Pages 1-5 , DOI 10.2217/17460751.3.1.1

<sup>3</sup> NanoInterface website [www.nanointerfacetech.com/index.html](http://www.nanointerfacetech.com/index.html) and [www.nanointerfacetech.com/NanoInterfaceTechwebsite.pdf](http://www.nanointerfacetech.com/NanoInterfaceTechwebsite.pdf)

<sup>4</sup> 3DM, Inc. Puramatrix synthetic peptide hydrogels - cell culture, bioproduction, medical devices. Available at: [www.puramatrix.com/](http://www.puramatrix.com/)

<sup>5</sup> OmegaGenesis - Home. Available at: [www.omegagenesis.com/index.html](http://www.omegagenesis.com/index.html)

<sup>6</sup> ULURU Inc. - Altrazeal™ [www.altrazeal.com](http://www.altrazeal.com). Available at: [www.uluruinc.com/altrazeal.htm](http://www.uluruinc.com/altrazeal.htm)

<sup>7</sup> ULURU Inc. to present Altrazeal clinical evidence at the AMPA Annual Scientific Meeting [www.uluruinc.com/press\\_releases/ULURU\\_Inc\\_to\\_Present\\_Altrazeal\\_Clinical\\_Evidence\\_at\\_the\\_AMPA\\_Annual\\_Scientific\\_Meeting.pdf](http://www.uluruinc.com/press_releases/ULURU_Inc_to_Present_Altrazeal_Clinical_Evidence_at_the_AMPA_Annual_Scientific_Meeting.pdf)

- <sup>8</sup> OmegaGenesis Product Overview - Wound Healing.pdf  
[www.omegagenesis.com/resources/pdfs/OmegaGenesis%20Product%20Overview%20-%20Wound%20Healing.pdf](http://www.omegagenesis.com/resources/pdfs/OmegaGenesis%20Product%20Overview%20-%20Wound%20Healing.pdf)
- <sup>9</sup> Molly M. Stevens, Robert P. Marini, Dirk Schaefer, Joshua Aronson, Robert Langer, and V. Prasad Shastri, *In-vivo engineering of organs: The bone bioreactor*, Proc Natl. Acad. Sci. USA. 2005 August 9; 102(32): 11450–11455
- <sup>10</sup> Worldwide Markets and Emerging Technologies for Tissue Engineering and Regenerative Medicine, Life Science Intelligence Inc., [www.lifescienceintelligence.com/market-reports-page.php?id=IL600](http://www.lifescienceintelligence.com/market-reports-page.php?id=IL600)
- <sup>11</sup> Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Dealing with the impact of an ageing population in the EU (2009 Ageing Report)*, Commission of the European Communities, Brussels, 29.4.2009 COM(2009) 180 final
- <sup>12</sup> Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, Official Journal of the European Communities, L 324/121, 10.12.2007
- <sup>13</sup> Barriers to the Commercialisation & Utilisation of Regenerative Medicine in the UK, Emma Rowley and Paul Martin, April 2009, [www.nottingham.ac.uk/iss/research/Current-Research-Projects/Staff\\_projects/regenmed/reports\\_publications.htm](http://www.nottingham.ac.uk/iss/research/Current-Research-Projects/Staff_projects/regenmed/reports_publications.htm)
- <sup>14</sup> Chis Mason and Elisa Manzotti, *Regen: the industry responsible for cell-based therapies*, Regenerative Medicine, November 2009, Vol. 4, No. 6, Pages 783-785
- <sup>15</sup> GSK Public Policy Position Statement on Nanomaterials [www.gsk.com/policies/Public-Position-on-Nanomaterials.pdf](http://www.gsk.com/policies/Public-Position-on-Nanomaterials.pdf)
- <sup>16</sup> Chun YW, Webster TJ. The role of nanomedicine in growing tissues. *Ann Biomed Eng.* 2009;37(10):2034-2047.
- <sup>17</sup> FDA Considerations for regulation of nanomaterial-containing products (Presentation), Nakissa Sadrieh, Ph.D., Office of Pharmaceutical Science, CDER, FDA. Available at: [www.mhra.gov.uk/home/idcplg?ldcService=GET\\_FILE&dDocName=CON2022823&RevisionSelectionMethod=Latest](http://www.mhra.gov.uk/home/idcplg?ldcService=GET_FILE&dDocName=CON2022823&RevisionSelectionMethod=Latest)
- <sup>18</sup> Scientific Committee on Emerging and Newly Identified Health Risks (SCENHIR), Request for a scientific opinion: on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies, Available at: [http://ec.europa.eu/health/ph\\_risk/committees/04\\_scenihir/docs/scenihir\\_q\\_003.pdf](http://ec.europa.eu/health/ph_risk/committees/04_scenihir/docs/scenihir_q_003.pdf)
- <sup>19</sup> Poland CA, Duffin R, Kinloch I, u. a. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nano.* 2008; 3(7):423-428.
- <sup>20</sup> Ma-Hock L, Treumann S, Strauss V, u. a. *Inhalation toxicity of Multi-wall carbon nanotubes in rats exposed for three months.* Toxicol. Sci. 2009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19584127>
- <sup>21</sup> UBA - Press Releases 2009 Nanotechnology for mankind and environment – Seize upon opportunities, reduce risks. Available at: [http://www.umweltbundesamt.de/uba-info-presse-e/2009/pe09-075\\_nanotechnology\\_for\\_mankind\\_and\\_environment\\_seize\\_upon\\_opportunities\\_reduce\\_risks.htm](http://www.umweltbundesamt.de/uba-info-presse-e/2009/pe09-075_nanotechnology_for_mankind_and_environment_seize_upon_opportunities_reduce_risks.htm)
- <sup>22</sup> Innovation & Ethics - Bayer Schering Pharma. Available at: [www.bayerscheringpharma.de/scripts/pages/en/research\\_and\\_development/innovation\\_ethics/index.php](http://www.bayerscheringpharma.de/scripts/pages/en/research_and_development/innovation_ethics/index.php)
- <sup>23</sup> Industrial Biotechnology StatReport, p. 14. Available at: [www.medicaldevicedaily.com/img/IndustrialStatReport.pdf](http://www.medicaldevicedaily.com/img/IndustrialStatReport.pdf)