nanomedicine
EUROPEAN TECHNOLOGY PLATFORM

# ROADMAPS IN NANOMEDICINE TOWARDS 2020

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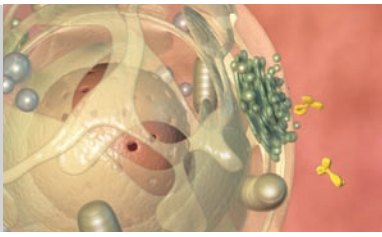


# Content

# 1. Executive Summary

The first Strategic Research Agenda of the ETPN Nanomedicine was drafted in 2006 with a broad range of options highlighted. Over the intervening years it has become increasingly clear to the industrial sector that an academic driven or *laissez-faire* approach to Nanomedicines will be an inefficient process. It is recognised that it is now time to make more detailed specific recommendations, using experts from academia and especially industry to draft industry driven roadmaps[1] and recommendations for R&D in nanomedicine.

Consequently, together with the European Commission, the ETPN initiated a roadmapping process in early 2009 with two objectives: firstly, to identify translatable trends in research and understand their expected impact on applications, products, and markets and secondly, to fine-tune and target research funding on areas with greater commercial potential and most importantly, that will help patients.
This focus is especially important in view of reduced public funding and the resulting need for public/private funding of research.

The three areas addressed, Nano-diagnostics, Nanopharmaceutics and Regenerative Medicine are represented by the three scientific areas of the ETPN. The key findings of the roadmapping process can be summarised as follows:

Successful translation of research results from academia into products has been identified to be one of the major challenges in this innovative science based area. Strategies to foster and initiate this translatability must be developed and implemented to help European research and industries remain competitive in the global market. In some other European industrial sectors this productive symbiosis between the industrial and academic sectors is in existence; failure to achieve this here will disadvantage all stakeholders.

In the diagnostics field nanotechnology already plays a crucial role. In nano-diagnostics two areas have been thoroughly investigated, namely *in vivo* imaging and *in vitro* diagnostics, in which nanotechnology is considered to be the major enabler. Four prime contributions are expected in the future:

- The improvement of current and future imaging systems
- The design of new contrast agents
- In the in vitro diagnostic area, nanotechnology is expected to improve diagnosis in general
- Enable real point-of-care applications

[1]The term "Roadmap" in the context of this report is referring to envisioned industrial R&D strategies addressing the whole value chain starting with researching of basic technologies and leading to the development of e.g. a prototype of a future application.

Therapeutics have already been impacted by nano-thinking and as the theoretical science base improves, the delivery of both existing and breakthrough drugs for difficult diseases will significantly be improved. The nano-pharmaceutics part of the roadmapping process revealed some areas where breakthroughs are envisaged or expected. The pharmaceutics or galenics of molecules will be heavily reliant on advances in nanotechnology; in effect this is an extension of micro-delivery systems into the nano-realm. Some breakthroughs or radical innovations are expected in the area of activatable nanomedicines using external non-invasive forces. Equally important will be the improvement of nano-enabled devices for the delivery of medicines / drugs provided that cost is kept within limits.

The application of nano-technologies in regenerative medicine has and will herald in new types of products for damaged tissues or untreatable diseases with benefits for patients, clinicians, and the economy. Research is still in a very early stage and as a result it has proven to be difficult to identify product driven roadmaps. Nevertheless, it is very important to establish a sound regulatory framework in this area and insure the translatability of research results into products. Particular products and applications are expected in the area of smart nano-enabled biomaterials that can either improve medical instrumentation, or e.g. facilitate the regeneration of damaged tissue by themselves.

A second field of products is expected to be in the area of cell therapies where nanotechnologies will aid the production and transplantation of cells. A frontrunner in the commercialisation of stem cells will be the identification of existing cell differentiation agents using novel (nano)technology.

Common to all three priorities is the need for a well thought out regulatory environment, fostering scientific research and enabling competitive product development. An essential and in most cases missing element is the open communication of commercial knowledge on markets and diseases to European researchers.

This report aims at consolidating the findings of all the discussions and presentations held during the ETPN's roadmapping process. Ultimately, the goal of this process is to identify those developments that are perceived as critical for the clinical uses of Nanomedicines and target efforts in those areas by improving public funding as well as engaging in a dialogue with industry.

# 2. Introduction

Patients´ needs are the driver for future opportunities for European research in Nanomedicines. Therefore, the prioritisation of research activities in Europe should be driven by the main unmet causes of mortality and morbidity in our population. Indeed, this principle underpinned the strategy that was adopted in 2006 during the preparation of the Strategic Research Agenda of the ETP Nanomedicine[2].

Globally, healthcare costs have been increasing due to the costs associated with healthcare development in a heavily regulated environment and higher patient expectations. Costeffective technologies and cutting-edge treatments, seeking early minimal intervention rather than invasive therapies, are therefore mandatory. Nanomedicine as a translational science has the goal to provide cost effective novel therapies and diagnostics using the expanding world of Nanotechnology. To reach this goal the process of translating research results from academic labs to the clinic has to be greatly improved. The industrial nature of the ETP provides the platform for its industrial members to articulate and explain the development pathway mandated in this heavily regulated sector to the research community. Regulation changes from year to year and few outside the pharmaceutical- or diagnostic sectors understand the stringent requirements before a product can be made available to patients. These requirements far exceed those required for publication in peer reviewed journals. Here, industry has a difficult task in bridging the need for breakthrough treatments with the often non-translatable output from academic labs.

Today, the healthcare sector is experiencing a time of radical change and is more open to outside ideas now than at any period in its history. Globalisation also means that ideas can come from anywhere and scientists wishing to play a part in this exciting era must be aware of the complex environment in which they operate. Globally, there is much confusion over what is basic research and translatable research; both of course, have their place. Nationally or EU funded nanomedicine programmes must be industrially credible from its inception and have a clear route to proof of concept to provide the drugs and diagnostics that patients need and expect.

### Economic considerations

Healthcare research is not only hindered by the relatively high costs associated with the discovery of nanomedicine products, but also because of financial issues caused by short exclusivity periods and reimbursement policies. Nevertheless, technological innovation at European level remains the major competitive factor in the medical device market. Technology plays an important role in the purchasing decisions concerning many medical devices, justifying the increasing investments by manufacturers. A major challenge for medical device manufacturers is the cost-containment policies that have already been implemented in several European countries.

The medical device, drug delivery and regenerative medicine industries today are highly research oriented. State-of-the-art technology has often been perceived as a key purchasing factor by hospitals, as well as an important differentiation factor by medical device manufacturers. Considerable investments in R&D are characteristic of the industry, which reflects the high rate of innovation as well as the shortening product life cycles. Only through innovation can a company become a technology leader.

[2]www.etp-nanomedicine.eu

## Roadmapping Process

The first expert workshop to tackle the outlined challenges, jointly organised by the ETP Nanomedicine and the European Commission, took place on February 19 & 20 2009. The intention of this workshop was to consolidate and extend the understanding of the topic "Nanomedicine" and to particularly identify industrial, application driven roadmaps that will help to focus future requirements in the European Research Framework Programme FP7 and beyond. The information collated was further augmented by the ETP's General Assembly in Münster in May 2009, where additional new areas and topics were discussed and missing issues were identified and integrated.

The workshop comprised six round table sessions on the application of nanotechnologies in the areas "Diagnostics", "Drug Delivery" and "Regenerative Medicine". Approximately 50 invited experts from academia and industry presented their views on application and product driven industrial roadmaps that they foresee as being of interest to research & industry stakeholders. By this process, the ETP was able to gather a huge amount of information on topics expected to play a decisive role in Nanomedicine. In particular, the experts were asked to comment on the following key issues:

- Application areas and products that have to or will be addressed in the future
- Clinical and economic benefits
- Markets targeted, projected market sizes
- Technology breakthrough areas
- Key characteristics of products and technologies

## General Findings & Considerations

A common denominator across the different presentations and viewpoints at the workshop was the need to provide continuity to the commitment of the EC towards translational research. The experts positively responded to the request for a product-driven agenda, but critically highlighted those obstacles which will need to be eliminated towards the achievement of breakthrough technologies.

One important prerequisite for the successful implementation of the identified roadmaps will be an improved knowledge and communication between academics, SMEs, and especially large industry. The discovery of breakthrough products for patients today is hampered by a lack of good communication between stakeholders, especially in Europe.

Good communication is necessary for "Open Innovation" and requires knowledgeable academics and SMEs working on translatable projects to transfer to industry. Whilst such projects are not completely absent, there is often ignorance on the process to get to the clinic and to some extent, also an unwillingness to accept the process required by global regulatory authorities. In this respect, the experts shared the view that relevant academic departments and individual researchers involved in healthcare should develop an industrial liaison policy to improve their global competitiveness and knowledge. Beyond that the importance of spin-offs and technology transfer companies was stressed as these companies are often the ideal environment for the development of the early stages of nanomedicine products.

Some ideas and recommendations are given below as on how the various stakeholders could be able to improve their impact:

### Public Authorities

- Improve industrial peer review of applied research proposals
- Where possible give a tranche of money to universities and ask them to invest it in their research as a portfolio. There would then be an incentive to choose and fund the best projects. There are experiments in the UK on this
- Request assessment of safety, healthcare impact and industrial relevance in research proposals
- Strengthen IP protection issues by implementing policies and guidelines that facilitate the interests of both industrial and research partners

### Industry

- Increase the efficiency of industrial contacts with universities
- Increase involvement of industrialists with the activities of major research departments (academia)
- Promote a higher number of sabbaticals at academic research organisations
- Create "reverse symposia" on what industry needs or what they are unaware of
- Provide detailed sources of information on industrial priorities
- Share specialised industry technologies and expertise
- Speed up decision making by increasing contact with patients or patient groups

### Academia

- Change the academic culture towards encouraging and rewarding real innovation and entrepreneurship in Europe
- Involve experienced recently retired industrial experts in evaluation
- Require both industrial liaison policy and industrial liaison offices as prerequisites to participate in funded programmes
- Plug in to industry news-flows using widely available internet websites
- Understand the implications of the "Open Innovation" concept
- Train academics with an understanding of drug discovery

Thus far, many projects are initiated without taking many of the above aspects into account and often are underpinned by a misinterpretation of the industrial (i.e. commercial, IP and regulatory) needs and thus the consequences of "laissez faire" are that current research projects are often based on wrong industrial assumptions.

Researchers, for example, frequently confuse market costs with cost of goods which are always lower. Nucleic acid based therapeutics for example are promoted as having lower costs than protein based therapeutics, whereas in reality their costs are likely to be higher. Nucleic acid therapeutics will play a decisive role and it is thus even more important to understand their real advantages. Similarly, projects on molecularly imprinted polymers frequently are falsely claimed to have lower production costs than antibodies.

Furthermore, it is essential to understand the pharmacology, metabolism, pharmacokinetics, immunology and toxicology of all nanomedicines. This is an absolute prerequisite.

As in any radically new drug there will be major uncertainties. The starting point for a drug's development is that it should do no harm; that is a major objective of a phase one clinical trial. Nanomedicines are no exception to this rule. Whilst not so attractive from an academic perspective, it is essential before starting on expensive applied research that this safety information, formally acquired in phase one, is seriously considered at the outset or at least its acquisition is planned in the near future. However, very few projects yet have sufficient regard to these parameters. It is certainly essential that analytical methods exist to detect nanomedical components *in-vivo* or *ex-vivo*. It is very unlikely, that any company will develop a nanomedicine which contains potentially toxic or non-metabolisable components such as cadmium, silica, cobalt, copper or gold unless such valid safety data is available. Consequently, as costs of drug development are so high, these concerns will lead to an inadequately researched modality staying in academic laboratories for ever. It is not enough to declare a material inert *in vivo*, this being rarely the case.  Nanomaterials which are not eliminated from the body are not acceptable to industry and regulators; this is a common and predictable cause of project failure and projects that do not seriously address this issue should not be funded as applied research, this especially includes DMPK data.

## Conclusions

The success of "Open Innovation" in Europe requires transparency and open communication between stakeholders which is currently not always the case. The ETP Nanomedicine provides a unique network for communication between industry, SMEs, academics, clinicians, and patients and should be used accordingly by its members and the external bodies such as policy makers and regulatory agencies. Thus, it is crucial to involve the medical community in the platform as well as in newly established research projects to enhance chances for a market launch of developed products.

The opinions of public or private health care insurances are also essential, either directly or indirectly *via* industry experts. Reimbursement covers cost but other factors are also important such as understandung the route of at ministration.

The following sections now report the summarised experts' view on the different areas of nanomedicine. Within each section, the description of the topic and the identified roadmaps are followed by an overview of estimated market sizes for the individual area. As also indicated in the text, these findings are only indicative and rely on the individual knowledge and insight of the source.

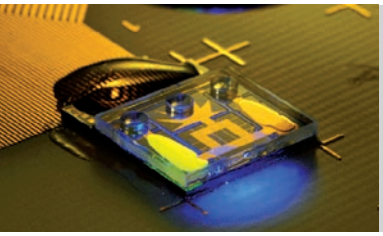
Furthermore, specific industrially relevant roadmaps and/or targeted applications identified during the expert workshop are listed in a separate table. For each roadmap or application the key R&D priorities as well as required technologies, potential challenges and targeted diseases are listed in the columns.

Tentative timelines for each section are presented in the appendix in the order of the chapters. They are thought to be helpful to get an overview on which technology areas and application / product roadmaps will be relevant for R&D at a point of time.

### Disclaimer

## Market Figures

The market figures listed in this report are indicative assumptions only. They have been proposed by the individual experts based on their individual knowledge and experience. Thus, the figures may vary according to the level of detail of the source. Furthermore, they are not normalised. Hence, market figures may not be compared between the different nanomedicine areas, but are intended to provide an indication of expected market developments in the future.



# 3. Diagnostics

The area of diagnostics can be divided into "in vivo" and "in vitro" technologies. In both areas the goal is to detect diseases as early as possible even to the point of detecting single defective cells or biomarkers predicting the onset or initiation of a disease. Major objectives are the development of:

- Devices for combined structural and functional imaging
- Portable point-of-care devices (POC)
- Devices for multi-parameter measurement (multiplexing)
- Devices for monitoring therapy and personalised medicine

The two round tables on diagnostics showed the way that academia and industry understood the common issues, indicating the high "industrialisation" of this area. This is partly due to the fact that the regulatory framework for medical devices allows a quicker market launch compared to pharmaceutical products or the even more complex area of regenerative medicine. The only exception in this regard is the development of imaging agents, which are treated as pharmaceutical products and are thus sub-ject to stronger regulatory requirements.

A topic equally important to the two sections is that of biomarkers. These are specific molecules or particles which are able to locate important biological targets. This research area is crucial in the imaging and also in the diagnostic area. However, identification and validation of biomarkers is challenging and more research and development in this area is essential. The very same argument holds true for the use of biomarkers in drug delivery as well.

### 3.1 In vivo imaging

In the *"in vivo"* - imaging area some substantial challenges have been identified. One of the foremost obstacles is the difficulty in obtaining the approval of new and innovative contrast agents. Equally challenging is the improvement of the imaging equipment , not forgetting the training of operators. Nanotechnology can contribute to the development of the *in vivo* imaging area by two means:

- Improving the existing and/or discovering new quantitative imaging systems
- Developing new contrast agents

The benefits expected from nanotechnology are mainly based on the physical and chemical properties of novel materials at the nanoscale. However, the development of nanotech-based *in vivo* imaging also depends on several non-technical parameters like:

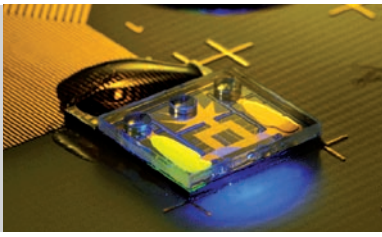
- Regulatory approval of contrast agents
- Education and training of healthcare providers
- Healthcare reimbursement policies

#### 3.1.1 Imaging modalities

Some conventional imaging modalities like PET[3], MRI[4], SPECT[5], US[6], and optical are revisited by nanotech in developing targeted and multimodal nanoparticles based contrast agents. Besides these improvements, some new imaging modalities like the MPI[7] method (from Philips) are currently under development. The trend here is clearly on implementing these imaging modalities alone or in combinations.

MPI is a completely new modality which offers excellent temporal and spatial resolution. It also promises high sensitivity (two orders of magnitude better than MRI, though less than PET) and can reside completely under an interventional table.

[3]PET: Positron Emission Tomography, [4]MRI : Magnetic Resonance Imaging, [5]SPECT: Single Photon Emission Computed Tomography,
[6]US : Ultra Sound, [7]MPI : Magnetic Particle Imaging



The principle can also be used for highly focused hyperthermia for a better therapeutic outcome. Imaging systems are under development but suitable contrast agents are needed to get the best results.

Miniaturisation of imaging devices and improvement of technical specifications of existing imaging systems can be achieved thanks to nanotechnology. In the perspective of developing a lightweight, small footprint CT[8] system, a proposed disruptive technology uses carbon nanotube based X-Ray sources in CT to shrink the size of the systems. This would bring CT to the doctor's offices or even to ambulances.

Also in ultrasound technology, developments of miniaturised transducer technology will enable to perform imaging inside the body with improved resolution at low cost. The Image quality of future ultrasound will improve towards "molecular imaging" and make the modality suitable for *in vivo* diagnostics and therapy monitoring. The low costs, safety and portability of ultrasound technology make it suitable also for non-expert de-centralised usage.

*In vivo* imaging can also be used for guiding therapy with MR, PET, Optical and X-ray/ CT, MRgFUS[9] for targeted biopsy and localised drug release. Targeted therapy is expected to lead to improved quality of healthcare, in reducing treatments with unsatisfactory patient outcome or with adverse effects.

### 3.1.2 Contrast agents

Reducing the concentration of contrast agents is one means to reduce costs and adverse effects on the patient in diagnostics. The characteristics of contrast agents (size, composition, coating, and physical properties) can be adjusted to respond efficiently to design requirements, for instance for a better sensitivity and specificity.

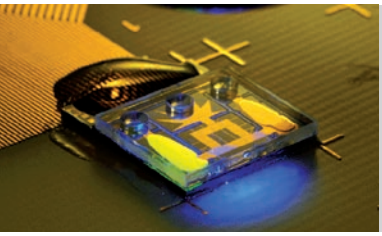
Another option is to design or develop a contrast medium capable of addressing several modalities at the same time. This could consequently also reduce the volumes and reinjection rates. In fact, these contrast agents that can be used in different modalities separately or combined in a multi-modality approach are highly desirable. However, their development is challenging due to the greatly varying characteristics of the imaging modalities, and importantly, their interaction with contrast agents as well.

A strong focus is suggested on magnetic particles either for MPI or MRI using (U)SPIO[10]. The latter can improve sensitivity or specificity in MRI depending on the applications and the anatomy. An example for this technology is macrophage imaging. Such an approach could be beneficial in either delivering a better diagnosis or a better evaluation of the treatment for several diseases. Such technologies could be particularly useful for diagnosing e.g. multiple sclerosis, degenerative or inflammatory diseases such as arteriosclerosis, arthritis, etc.

Further new types of carriers for contrast agents are envisaged such as magnetic nanoparticles or even empty viruses or magnetic bacteria. Magnetic particles could offer higher efficiency due to narrower characteristic distribution (magnetic, geometry, size, etc.), precise control of magnetic properties, and an inherent potential for lower costs. The production of magnetic nanoparticles could also be envisaged by biomimetic templating. Another category of nanoscale particles are crystalline nanoparticles used for therapeutic purposes or for diagnostic applications in combination with external devices such as MRI, Laser, Radiotherapy, CT Scan, Ultrasound, HF, etc.

In particular the up-scaling of the production methods for contrast agents has great economic potential. The nano particles to be used as carriers for imaging agents should possess no toxicity and have to be metabolised by the human body; their biodistribution, and clearance should be extensively tested before going into development.

[8]CT: Computed Tomography, [9]MRgFUS: Magnetic Resonance guided Focused Ultra Sound,
[10]USPIO: Ultra small Super Paramagnetic Iron Oxide particles



One example would be the development of a contrast agent against amyloid plaques detectable by magnetic resonance imaging. Alzheimer´s Disease (AD) is a neurodegenerative disease characterised by the extracellular deposition of amyloid plaques. Currently, there is no *in vivo* diagnostic technique for Alzheimer´s Disease (AD) apart from memory testing, which is mostly limited to advanced AD patients. Early detection of AD would be necessary for early treatment of this disease. Targeting the extracellular amyloid plaques with specific and biofunctionalised contrast agents, detectable by magnetic resonance imaging (MRI), would provide a more accurate diagnosis of AD. The biofunction-alised contrast agents will be very useful for monitoring therapeutic effects of the treatment response as well.

### 3.1.3 Non technical aspects

Regulatory approval is the biggest hurdle in the development of imaging agents, besides the proof of benefit for patients (early diagnosis, risk stratification, follow up of treatment efficacy) and the training or education of radiologists (images reading / interpretation).Obtaining an approval of new and innovative contrast agents (regulatory aspect, feasibility of clinical development/ trials, development costs) is a major challenge.

In this area, the concept of temporary approval (i.e. for a 5 years period) as it exists in the USA regulations, could be a useful approach in Europe on the basis of a green line for safety.

The market for nanotechnology based *in vivo* imaging is not clear because the benefit for patient or society has not been properly measured so far. No reduction in healthcare cost is expected regarding *in vivo* imaging but an improvement in providing more effective i.e. cheaper healthcare may be possible. Reimbursement policy will be a key factor for the approval of new contrast agents.
With respect to the innovation cycle in nanomedicine, the improvement process will start in academia and SME's, who will probably make the initial discoveries; then the major industries will pick up the successful developments and integrate them with their existing strategies.

**Table 3-1: Global Market Size – In vivo imaging**

| Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Clinical Imager (MPI Instrumentation only) | - | 50 | 700 |
| Tumour Therapy Delivery System (MPI Instrumentation only) | 1 | 20 | 100 |
| SPIO/ USPIO | 10 | 100 | 1000 |
| Nano structures as carriers plus drug release | - | 10 | 100 |

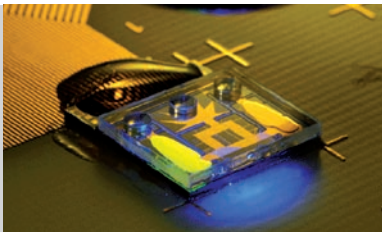
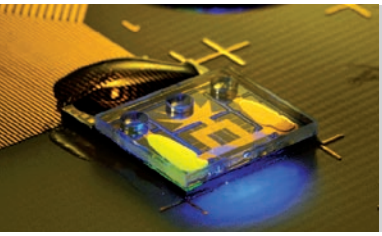
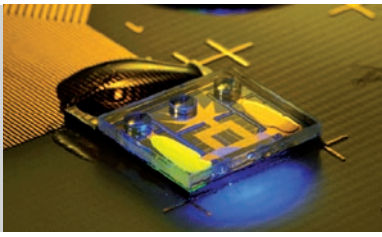


**Table 3-2: Specific Roadmaps / Applications and R&D challenges – In vivo imaging**

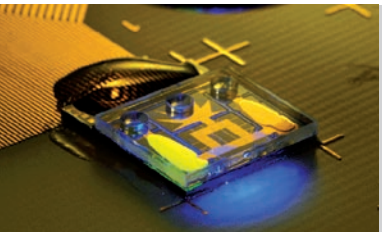
| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Magnetic Particle Imaging (MPI) | • Instrumentation for Imaging and Therapy<br>• Focused Thermal Ablation Unit for Tumour Therapy<br>• Interventional procedures (including use of particle-coated instruments) | • Hi-temp. superconductive novel magnets<br>• System geometries which fit under a table for interventions<br>• RF send/receive components and<br>• High Power Amplifiers<br>• Transducer technology<br>• new image processing and reconstruction<br>• Imaging Systems – Simulation and Development | • New contrast agent is a crucial requirement<br>• Real-time computing<br>• Nanoparticle characterisation, toxicity analysis, coating chemistry<br>• Optimizing combination contrast medium/ imaging modality<br>• Reliable preparation control at industrial level of coated nanostructures with narrow size distribution<br>• New nanostructures to optimise relaxation signals<br>• Tumour detection at the milli/micro scale | • Cardiovascular diseases<br>• Neurodegenerative diseases<br>• Cancer |
| MRI, MPI Contrast Agents | • Contrast media based on nano-structures<br>• Magnetic nanoparticles produced by biomimetic templating<br>• Novel routes to magnetic nanoparticles, adapted to the new imaging modalities<br>• Contrast agents useful for hyperthermia (theranostics) | • USPIO (Ultrasmall Superparamagnetic Iron Oxide nanoparticles)<br>• Protein markers | • Activated nanoparticles<br>• Adapt properties (size, composition, coating, physical properties<br>• Up-scaling of biomimetic production,<br>• Pharmacological approval | • E.g. Lymph nodes characterization<br>• Cell tracking<br>• Tumour and plaque targeting<br>• Functional imaging, e.g. quantitative perfusion |



| | | | | |
|---|---|---|---|---|
| Magnetic particles for drug targeting | • Guidance / retention of therapeutic particles in tissues or fluids<br>• Focalization of magnetic nanoparticles | • Microwave and RF waveform patterning<br>• Ultrasound waveform patterning | • Control of the position and movement of magnetic nanoparticles inside the body<br>• Placement of high concentration of nanoparticles in specific sites inside the body<br>• High payload of drug | • CNS<br>• Cancer<br>• Toxics removal |
| Hyperthermia applications | • MRgFUS / MPI<br>• Hyperthermia and Focused Hyperthermia approaches and instruments for Tumour Therapy<br>• Remote (thermal) triggering of genetic therapy or local drug release, e.g. from liposomes | • MRI / MPI<br>• New remote excitation approaches and devices<br>• Synchronous non invasive monitoring of applied hyperthermia | • Optimise NP materials, size, excitation frequency and energy<br>• Control of heat release in living tissues by controlling the hyperthermia mechanisms action | • Cancer<br>• Antibiotic resistant diseases<br>• Theranostics |
| Computed Tomography with small equipment footprint and less weight | • Instrumentation for Imaging and Therapy<br>• Mobile equipment | • Cold electron sources based e.g. on carbon nanotube (CNT) technology<br>• System geometries with the small X-ray sources distributed over 360 degrees plus corresponding detector technology | • (CNT based) small X-ray sources<br>• CMOS technology: Super-fast imaging detectors for CT<br>• Specialized batteries and power conversion | • Cancer<br>• Various |
| Luminescence based optical contrast agents | • Contrast media based on tuneable nano-luminophores<br>• Mixed luminescent and magnetic nanomaterials, localized thermal therapies<br>• Biocompatibility, biodegrability<br>• Luminescence probes guided biopsy and therapy | • Sol-gel, hydrothermal based synthesis methods<br>• Surface chemistry for bio-targeting and biocompatibility, high bio-specificity | • Biocompatible properties of the nanolabels, high-bio-specificity<br>• Imaging devices dedicated for in vivo luminescence detection, imaging and quantitative analysis | • Cancer diagnosis and therapy<br>• Luminescence based engineered assays for screening |



| | | | | |
|---|---|---|---|---|
| Targeted therapy and local drug release | • Image guided therapy<br>• Image-guided, remote (thermal) triggering of genetic therapy or local drug release, e.g. from liposomes | • MR,<br>• PET,<br>• Optical and X-ray<br>• CT, MRgFUS for drug release | • NP remote focusing by means of static and RF magnetic fields | • Multiple (Theranostics) |
| Microfluidics for PET synthesis and tracer development | • Personalized doses in PET imaging | • Microfluidics<br>• Tracer synthesis | • Miniaturization / simplification of the whole PET tracer production<br>• Regulatory issues: risk contra benefit<br>• Validation period long and very costly | • Multiple |
| Molecular Optical Imaging [e.g. Molecular Fluorescence Imaging] | • Nanotechnology-based Optical Imaging Contrast Agents<br>• Optical Image Processing<br>• Optical Imaging Systems Development<br>• Clinical Trials Phase I & II | • Laser, LED, Optical Fiber Catheters<br>• Nanoparticles with Optical Properties [e.g. Fluorescence Properties]<br>• Optical Image Processing Software & Hardware | • Increase Sensitivity and Specificity<br>• Molecular Structural Imaging<br>• Molecular Functional Imaging<br>• Molecular Monitoring of the Response to Therapy<br>• Non-Invasive Imaging<br>• Minimally Invasive Imaging | • Cardiovascular<br>• Cancer<br>• CNS<br>• Inflammatory<br>• Infectious |



### 3.2 In vitro Diagnostics

Most technological investments on *in vitro* diagnostics have focused on central analytical labs. However, there is a trend towards decentralisation of *in vitro* diagnostics (IVD) and thus towards point-of-care diagnostics (POC). Analysis will become multiplexed to offer doctors or patients a more comprehensive and personalised diagnosis. Simultaneously, biomarkers have to be validated for routine clinical use. It is expected that the development of new drugs will go alongside the simultaneous development of companion diagnostics tests specific to the drug. The major technical challenges here are related to proof of concept as well as routine and precise analysis of biomarkers in biological samples.

Besides the technical evolution, the trend towards point-of-care reveals new ethical, social, economical and regulatory issues to be addressed for the development of IVD.

#### 3.2.1 Evolution of in vitro diagnostics

At the moment point-of-care is not the main focus of IVD industry which concentrates and earns the most money in central clinical labs. However, in the long term the capacity of central lab diagnostics will probably saturate, which will likely result in an increased need for POC diagnostics. The trend towards simple diagnostics tests in the physician's office and ultimately the home of the patient becomes inevitable. This trend however requires more robust systems, easy to operate without technical training, offering fast response and the delivery of easily analysable data to the practitioner.

#### 3.2.2 Scientific and technological challenges

Another trend is to provide the doctor with a diagnosis result based on a multi-parameter analysis and not just a number for concentration values of a single parameter. To really make this happen, a multiplex[11] analysis system will require some integrated data processing capability able to perform sophisticated algorithms.

The corresponding challenges to overcome are:

- Lab quality results within minutes (sensitivity and speed)
- Robust, 'fool-proof', results under all circumstances (precision)
- High accuracy of predictions and reliability
- Less invasive sample taking (finger-prick blood, saliva, urine)
- Integration into healthcare systems

Within the prospect of the development of POC diagnostics, sample preparation becomes a key challenge in particular to go from the micro- to the nano-scale.

As stated before, there is a lack of clinically applicable biomarkers, the main issue being the difficulty to screen and validate them. It is worth mentioning that the screening of biomarkers will also assist future drug clinical development. In consequence IVD is taking the lead to push drug development in co-developing a (companion) diagnostics test specific to a drug. This co-development of pharmaceuticals and diagnostics tests represents a driving force for the next stages of biomarker research.

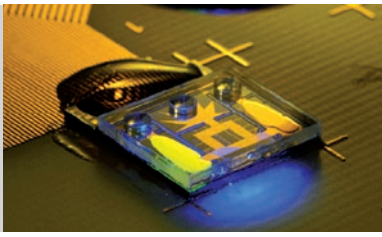
The corresponding challenges are:

- Identification of biomarkers
- Validation of biomarkers
- To overcome assay interferences

Breakthrough elements that have been identified are to:

- Design new non-isotopic reporters with adequate sensitivity (transducers)

[11]Multiplexing means the simultaneous detection of multiple different markers for the unambiguous diagnosis of a specific disease.



- Design sensitive reporters to monitor interactions between biomolecules
- Design new technologies to deliver proper analytical reagents into cells and sub-cellular compartments
- Design new technologies to tag specifically proteins of interest in living cells
- Design new bioprobes

As a new player in the field, semiconductor companies can contribute their expertise in automation and miniaturisation gained in the traditional semiconductor manufacturing. However, their access to biological expertise is currently a bottleneck which considerably limits them in producing relevant POC devices.

Within the perspective of discovery of new biomarkers, mass spectrometry MS looks like the most efficient analytical technique for proteomic. The size reduction combined with adequate software and data treatment represents the main challenges. Some new techniques are ways to measure quantitatively the interaction between proteins and other molecules including proteins. They can potentially revolutionise the field. Such approaches will probably be deployed on a micro or nano fluidics format and have come about because of the push to measure protein-protein contacts. They potentially offer a universal diagnostics platform.

In summary, the challenging question here is whether a new generation of molecular probes could be designed to trigger cellular metabolism and/or extra-cellular secretion of molecules that will be analysed, when circulating in the body fluids, with a better sensitivity, at lower cost, and with possible multi-parametric analysis.

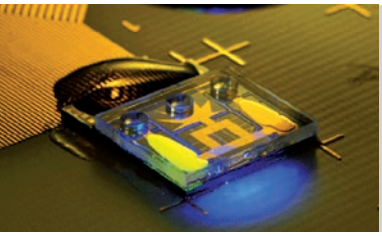
### 3.2.3 Miniaturised devices

The development of nanoscale sensors, either mechanical, or electrical or optical, and their integration into microscale devices offers enormous potential for cheap, point-of-care diagnostic devices with high sensitivity. For example the integration of nanowires into transistor devices could deliver single event detection of target molecules bound to the wire. Other areas could include integrated optics for surface plasmon based sensing or patterned nanocrystal surfaces such as ZnO mats capable of providing electro-mechanical sensing of nanometre deflections driven by Piconewton forces. The integration of unique sensing modalities arising from nanoscale manipulation of matter with mature, high volume, low-cost manufacturing common to the electronics and opto-electronics industries is envisaged to provide a route for nanotechnology from the lab to the patient.

### 3.2.4 Volume manufacturing

There are a series of challenges associated with manufacturing and in particular low cost fabrication, which includes process optimisation, quality assessment, consistency and quality assurance. These are highlighted in several thematic areas including nanodevices (chapter 4.2), multifunctional extra-cellular matrix analogues (chapter 5.1.1) and of course *in vitro* diagnostics. The challenge of going from lab scale prototypes to full manufacturing while still having to create an affordable solution is quite common. However, no strategies have been implemented and thus novel solutions have to be identified.

Volume manufacturing should be seen as an essential part of the development of nanomedicine. As well as the issues of production at the nanoscale and the understanding of the surface chemistry issues, there is a need to develop macro technologies, such as printing, to enable the practical realisation of these devices on a human (macro) scale at reasonable costs with sufficient volume to meet demand.



Given the limitations of ink jet in terms of speed, high shear rate and reliability, it will be necessary to select printing technologies appropriate for volume production. The research challenges for printing of macro devices based on nanotechnology are:

- Rheology of complex multi-phase fluids
- Impact of stress during the printing process on the efficacy of the sensing medium and the viability of live cultures after printing
- Configuration of devices linked to manufacture
- Manufacturing tolerances to retain control of dimensions and deposition volume

### 3.2.5 Issues related to IVD

The trend towards POC diagnostics creates new societal, ethical and regulatory issues that will have to be addressed. How will e.g. POC change the doctor-patient-relationship? The POC devices will not be an over-the-counter business but rather help and support doctors to diagnose or monitor patients and patients to monitor their treatment progress at home.

The movement of healthcare systems towards POC, especially its reimbursement policy will dramatically determine the emergence and growth of this industry.

**Table 3-3: Global Market Size – In vitro diagnostics**

In vitro diagnostics markets are quite difficult to assess. In particular its evolution will heavily depend on the regulatory decisions mentioned above.

| Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Hospital | 200 | 700 | 1.500 |
| Physician office (PoC) | - | 1.000 | 1.500 |
| Home | - | - | 1.500 |

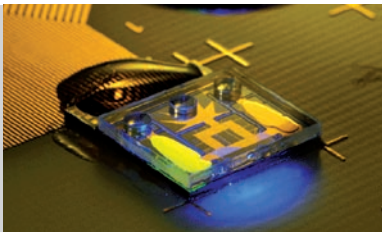
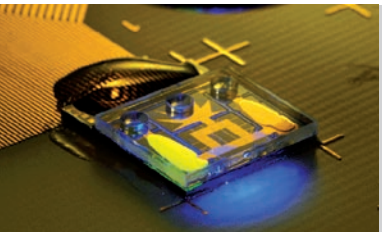


**Table 3-4: Specific Roadmaps / Applications and R&D challenges – In vitro diagnostics**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| In-vitro diagnostic decentralized testing applications (POC) | • Coupling chemistries<br>• Assay formats<br>• Capture probes | • Magnetic label biosensor platform<br>• Luminescence label biosensors<br>• Device technologies, sensors, based on biosensing elements (proteins or nucleic acids)<br>• Microfluidics<br>• Electrokinetics<br>• Detection<br>• Sample preparation (nanoscale reagents – handling, storage, stability)<br>• Surface engineering / surface patterning | • Sampling speed<br>• Multiplexing capability<br>• Sample volume<br>• High sensitivity<br>• Integration<br>• Manufacturing costs<br>• Fast antibiograms<br>• Breath, sweat and saliva analysis<br>• Analysis on micro-biopsy<br>• Biomarkers<br>• Continuous flow monitoring<br>• New sampling modes: 1) whole body sampling or 2) new samples …<br>• Sample preparation: 1) Very high concentration methods or 2) very small samples | • Oncology, infectious disease, HIV<br>• Chronic disease<br>• Neurodegenerative diseases<br>• Inflammation process (macrophags) |
| Multi-Parameter Testing<br>Multiplexing | • Multiplex detection<br>• Manufacturing of test | • Protein, DNA Arrays, etc. | • High Precision<br>• High Sensitivity<br>• High Predictability and Reliablity<br>• Overcome Assay interferences | • Oncology<br>• Understand the relationship between the patient (circulating biomarkers) and its tumour (biopsy)<br>• intensive care |
| Theranostics, Therapeutic monitoring | • Individual Therapy (personalised)<br>• Continuous monitoring of drug delivery and its therapeutic effect | • Micropumps<br>• Biocompatibility<br>• In vivo sensors<br>• Miniaturization<br>• Integration<br>• Energy saving<br>• Communication networks | • Coupling high sensitivity and controlled release<br>• Continuous, in vivo diagnostics<br>• Associated biomarkers | • Chronic diseases: Diabetes, Respiratory diseases<br>• Oncology |



| | | | | |
|---|---|---|---|---|
| (glyco) Proteom / RNA / Epigenom Map | • Development of molecular X ray | • Nano MS<br>• Quantitative MS | • Affordable, extremely high degree of multiplex detection (e.g. Maldi-TOF)<br>• Algorithms for complex data analysis of proteom map | |
| (Quantitative) Biopsies | • Analysis and characterisation of tissue (potentially on the cellular level) | • Single cell PCR<br>• 3D imaging<br>• 3D tissue mapping<br>• Optical, luminescence | • Automation (sample prep, imaging and identification)<br>• Molecular single cell imaging and tomography<br>• Single cell molecule extraction<br>• Multianalyte extraction (DNA, RNA, Protein, metabolites… all in the same few cells) | • Oncology<br>• Wound management |
| Genomic based diagnostics | • Early detection / screening of population for major cancers, and major infectious diseases threats | • Sample preparation / collection devices (body fluids: blood / urine / saliva, other)<br>• Filtration devices, micro-nano supports (beads, others)<br>• Microfluidics, surface chemistry<br>• Technologies to manufacture those sequencers: nanopores, activated pores, fixed polymerase on cantilevers | • Concentration of analytes (RNA, DNA, cells, single molecules)<br>• Stabilization of analytes<br>• Pricing below 1 € a piece<br>• No amplification<br>• Low cost<br>• Massively parallel long reads (300-400 bases)<br>• Speed for infectious disease | • Cancer<br>• Infectious diseases |
| Proteomic based diagnostics | • Amplification-free / direct (multi) detection system | • Protein array tests<br>• Signal processing<br>• Nano LC<br>• Biomarkers validation<br>• Sample collection | • New sensors<br>• Single molecule sensitivity<br>• Marker discovery & validation<br>• Mass Spec miniaturisation<br>• New sample biomarker inventory | • Cancer early detection<br>• Inflammatory process<br>• Infectious diseases (Identification and antibiotic susceptibility) |

# 4. Drug Delivery[12]

Today, the pharmaceutical sector is experiencing major changes triggered by challenges from generics companies, competition from an emerging biopharmaceuticals sector and a more difficult reimbursement environment. The pharmaceutical industry is looking for radical innovation, both for new small molecule approaches and especially to expand the market for biologicals, which should also include *inter alia* nucleic acid therapeutics. In addition, there are many therapeutic classes which lie in between large and small molecules. Many of these novel entities provoke significant delivery challenges (due to their polarity and size) which nanomedicine technology should be able to address.

These intellectual property opportunities have been recognised globally, especially in China. It is now time for Europe to focus its resources on producing the new nano-based drugs that patients need and expect.

### Funding the right translatable nanomedicine programmes

The initial enthusiasm for nanomedicines research has led to significant funding for non-translatable research and manufacturing, which we can no longer afford and which unsurprisingly has not attracted industrial involvement. It is hoped that aligning research programmes with real industrial priorities will encourage the pharmaceutical sector to participate. It will be argued that this will detract from more radical nanomedicines on the longer term, but it should be born in mind that even these shorter term objectives will take over 10 years to get to patients.

Nevertheless, nanopharmaceuticals are an emerging sector which offers new therapeutic approaches to patients and a prospect of profitable drugs against a background of generic competition and difficult regulatory and reimbursement environments.

Bearing this in mind the round tables during the expert workshop were faced with the challenge of finding answers and defining roadmaps to improve research on these topics.

At the expert workshop the therapeutic area was divided into two sections namely "Nanopharmaceuticals" and "Nano-enabled devices" which will be reported on below. There was some inevitable confusion at the round tables on the technical distinction between nano-enabled devices and nano-pharmaceuticals. However, both potentially offer ways to deliver macromolecules or molecules not currently "druggable" to the mass market. With respect to disease areas the approaches presented were and are applicable to a wide range of diseases and the experts thus saw no reason that such challenging programmes should be focused on specific diseases.

The topic of nanopharmaceuticals has been broken down into 3 sections that are reported on below. These sections are titled "Delivery of Macromolecules", "Radical Innovation based Nanomedicines" and "Targeting drugs to facilitate cell differentiation". The first section here is a variant of a more standard application for nanoparticles in drug delivery. The latter two are rather novel and highly innovative areas that could potentially receive more attention in the coming years as they offer the potential for disruptive treatments.

### Computational Chemistry

One enabling technology area that was highlighted at the round tables is computational chemistry. This very complex field has a comparatively low commercial value but supports a large number of sectors. It is a highly interdisciplinary activity which lies between funding silos but would benefit from a European initiative. It underpins healthcare, material sciences and basic sciences and involves theoretical chemistry, ultrafast computing hardware and software design. A key requirement is biological data from the real world to validate and predict any advances.

[12]In the SRA of the ETP Nanomedicine this area of Nanomedicine was originally labelled using its historical terminology – "Drug Delivery". However this term does not include areas where no traditional drug is delivered and thus, the preferred title of this section of Nanomedicine should rather be changed to "Nanopharmaceuticals".

Molecular recognition is essential for the design of self-assembling nanostructures and currently there are no adequate tools. This area warrants a detailed and an imaginative study to find out what could possibly be done. Currently the graphic interfaces are a lot better than the computational predictions. Success in this area would speed up the process of bringing (nano)drugs on the market and ultimately could reduce animal experimentation.

## 4.1 Nanopharmaceuticals

### 4.1.1 Delivery of Macromolecules

One area identified as being crucial for future breakthroughs is the area of nano-encapsulation or nano-delivery systems. These systems have to be able to provide a significant therapeutic payload and must be capable of being transported through biological barriers. Furthermore, the delivery particles have to be biocompatible and acceptable to regulatory agencies i.e. they should not be retained in the body, even if inert themselves. Ultimately therapeutic particles should be inexpensive, manufacturable, acceptable to regulators, and stable to store.

Another related topic will be that of technologies promoting the movement of drugs across biological membranes, tissues or organs aided by nanoparticles and exhibiting transport rates in such way that therapy can be effective. For proteins for example this lies in the range of 10mg per day orally with the bioavailability of the macromolecules or APIs being greater than 10%.

The choice of the delivery route or the barriers to be crossed by a nanomedicine will be crucial – of particular interest are e.g. Intra-cellular, Dermal, Oral, Pulmonary and across the Blood Brain Barrier (BBB). Much will depend on the specific case, but ideally a non-invasive route would be preferred and an oral route would be commercially the most desirable for some indications. For CNS delivery this may be a step too far as the BBB is a major challenge in its own right and an injectable nanomedicine may be acceptable at least initially.

The choice of the therapeutic entity could include proteins, antibodies, nucleic acids, antigens, peptide mimetics, PNAs, foldamers, "non-Lipinski" molecules (large polar molecules) and materials that require some external secondary activation such as ultrasound, radiation or EMFs. Small molecules could also be included but they normally already have a good bioavailability and expensive delivery technologies may not be reimbursed, making them commercially probably a lower priority. This is unless the pharmaceutics contribution is low-cost and/or there is a significant targeting of a disease lesion of, say cancer. Another exception for small molecules would be the use of nanotechnology to deliver drugs to the brain where in some instances existing traditional medicinal chemistry has failed.

With respect to theranostics[13] whilst this was mentioned in the SRA of the ETP Nanomedicine, it is currently thought that such an entity would require unacceptable compromises on both the diagnostics and the therapeutics side. Thus, for the moment theranostics are not seen as a high industrial priority.

#### Clinical Benefit

Nanomedicine will offer the possibility to bring new therapeutic modalities, therapeutic entities such as nucleic acids on the market or to expand the current clinical uses of biologicals. Such new therapeutic classes should offer radical improvements in the treatment of difficult diseases. These high information content drugs will be highly specific and have lower side effects than current drugs. It is hoped that this may permit macromolecule delivery by non-invasive means, possibly including also intra-cellular drug targets. Furthermore, nanomedicines could enable the use of macromolecules or even small polar molecules in the CNS for untreatable conditions.

#### Economic benefit

Therapeutics is a changing market currently valued at €820bn in 2009 but challenged by generic competition and patent expiries. By 2015 the generics sector could grow dramatically from €270bn to

[13]Theranostics is the term used to describe the proposed process of diagnostic therapy for individual patients - to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results. (Wikipedia)

€500bn. The pharmaceutical industry in Europe has always been a highly profitable industry and a strongly science based employer. However, in order to be competitive, the industry must innovate and change more radically than at any time in its past.
To do so it is required to operate in an open innovation framework using European and global inputs at a time when there is a truly global competition.

Nanomedicines will be a key component as companies seek new drugs composed of nucleic acid and try to expand the established markets for protein based therapeutics. For the European sector to survive as an employer, the industry must tackle the challenges of nanodelivery of macromolecular drugs.

**Table 4-1: Global Market Size – Nanopharmaceuticals**
The table below provides an estimate on the expected market sizes of the different areas taking a 10 year development cycle for new drugs into account.

| Expected Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Non-invasive[14] delivery of protein nanomedicines | 0 | 10.000±5.000 | 20.000±10.000 |
| Non-invasive[14] delivery of DNA based nanomedicines | 0 | 5.000±2.000 | 10.000±5.000 |
| Non-invasive[14] delivery of "Non-Lipinski molecule" | 0 | 2.000±2.000 | 4.000±2.000 |
| (Enabler) Computational Tools | 15 | 20 | 40 |

**Table 4-2: Specific Roadmaps / Applications and R&D challenges - Nanopharmaceuticals**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Therapeutic nanoparticles and polymers | • Synthesis<br>• (Multifunctional)<br>• Surface Engineering<br>• Nano/micro emulsion processes<br>• Biodegradable, biocompatible and non-toxic materials<br>• Up-scaling and standardisation<br>• Polymer pharmacology and safety | • Nucleic acid based molecule packaging<br>• "Non-Lipinski" molecules<br>• Small molecules<br>• Protein chemistry<br>• mAb's (monoclonal antibodies)<br>• Injectable NanoVectors for directed (Targeted / Personalized) Therapy | • Increase payload<br>• Delivery Pathways: non-invasive delivery (CNS, Oral, Nasal, buccal, Inhaled, Pulmonary)<br>• Cellular uptake & recycling, bio-compatibility<br>• Transport across biobarriers | • NS<br>• Infectious<br>• Inflammatory<br>• Cancer<br>• Cardiovascular |

[14]Includes parenteral CNS macromolecule therapeutics

| | | | | |
|---|---|---|---|---|
| | | • Nanovaccines<br>• Multifunctional nanoparticles and polymers | • Encapsulation & Stabilisation of protein based therapeutics<br>• Encapsulation of plasmid DNA<br>• Nanoformulation of antigens<br>• Behaviour of drugs in confined environments<br>• Standardized, reproducible industrial production to an affordable price<br>• Immunogenicity | |
| Nanocarriers & Transporter molecules / particles | • Moving therapeutic particles across barriers<br>• Improve therapeutic outcome<br>• Guidance/retention of therapeutic particles in tissues or fluids<br>• Localisation of magnetic nanoparticles | • Nanoencapsulation<br>• Virus like particles<br>• Enzymatic degradation of extracellular matrix – encapsulated enzymes combined with drugs<br>• Ultrasound – acoustic active capsules<br>• Hyperthermia – thermosensitive liposomes<br>• Ionizing radiation – alfa-particles conjugated antibodies | • Transport across biobarriers<br>• Extravasation, penetration through extracellular matrix<br>• Inducing transvascular and interstitial pressure gradients<br>• Increase diffusion through extracellular matrix<br>• Control of the position and movement of magnetic nanoparticles<br>• Placement of high concentration of nanoparticles in specific sites | • Cardiovascular<br>• Cancer<br>• CNS<br>• Inflammatory<br>• Infectious |
| Computational Tools | • Self-assembly prediction | | • Free energy calculation<br>• Computational prediction | • Horizontal |

### 4.1.2 Radical Innovation Nanomedicines

Currently, there are very many new concepts being evaluated. However, they must be developable into therapeutics under current or future regulatory environments. To achieve this, there must be some information available before funding or early in the preclinical research programme to clearly indicate that this is possible. Ideally, the aim would be a transition of the nanomedicine into a phase I clinical study. The researchers must have support from a company or clinical research group with clinical experience to ensure that the research monies help patients. Examples might be the targeting of a disease using the EPR effect[15] or the activation of a nanomedicine using an external source or medical device. However, it is suggested, that projects with no quantitative in vivo data on distribution and elimination results, should not be funded.

Activatable nanoparticles are generally inactive, inert and biocompatible and can subsequently be activated with an external device (MRI, Focused Ultrasound, Radiotherapy, Laser …) in order to locally deliver the intended therapeutic effect. Activatable nanoparticles for therapy is an emerging field mainly focused on by SMEs. Such approaches are clinically applied with hopefully benefits for patients.

Another promising area would be bridging the area between small molecules and large molecules. Such synthetic constructs could be nano in scale ranging from foldamers to synthetic "antibodies" based for example on dendrimer chemistry. It may be future drugs will occupy new and larger chemical space than tradition "Lipinski" molecules. These may or may not require nanodelivery technology.

#### Clinical Benefit

To introduce radical innovation based therapeutic modalities to the market, such new therapeutic classes should offer radical improvements in the treatment of difficult diseases.

Those nanotherapeutics should provide new modalities for clinicians compared to existing macroscopic (e.g. surgery) or molecular (e.g. drugs, biologics) approaches.

Further efforts in the above areas may ensure Europe's competitiveness.

#### Economic benefit

In order to remain competitive, European industry must keep innovating and bringing unique products on to market. It is difficult to estimate what the market size for such unproven entities will be. Nevertheless, it is advisable to establish roadmaps to provide an indication of future developments.

**Table 4-3: Global Market Size - Radical Innovation Nanomedicines**

| Expected Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Radical Innovation based Nanomedicines | 0 | 1.000 | 3.000 |
| Activated Nanoparticles devices for X-ray modality[16] | >500 | >2.000 | |

[16] Nanobiotix market estimation; this does not include other uses of nanoparticles that are utilised in combination with laser or alternative magnetic field, etc.
[15] The Enhanced Permeation and Retention (EPR) effect is the property by which certain sizes of mol-ecules, typically liposomes or macromolecular drugs, tend to accumulate in tumour tissue much more than they do in normal tissues (Wikipedia)

**Table 4-4: Specific Roadmaps / Applications and R&D challenges - Radical Innovation Nanomedicines**

Specific roadmaps related to radically innovative nanomedicines are difficult to identify as the concepts are still very much prospective. One very promising roadmap however seems to be the development of activatable (nano)-particles that have the capability of releasing their payload at the target location after an external signal (e.g. MRI, PET, US, X-ray etc…).

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Therapeutic Nanoparticles | • Safety and toxicology | • Extremely varied | • Acceptable to regulators<br>• Acceptable to industry | • CNS<br>• Infectious<br>• Inflammatory<br>• Cancer<br>• Cardiovascular |
| Activatable Therapeutic and / or Theranostic Nanoparticles | • Activatable Composite Nanoparticles<br>• Synthesis<br>• Surface Engineering<br>• Targeting<br>• Moving across barriers<br>• Clinical Trials Phase I & II | • Use of external radiation / energy / electromagnetic sources for activation of nanoparticles<br>• Laser, LED, Optical Fiber Catheters<br>• MRI<br>• MPI<br>• CT<br>• PET<br>• X-ray<br>• Ultrasound | • Increase Safety and Efficacy<br>• Switch on / Switch off Mode of Action by Activation<br>• Non-Invasive Activation<br>• Minimally-Invasive Activation<br>• Regulatory Challenges from the Interaction of Nanopharmaceuticals with Medical Devices | • Cardiovascular Cancer, CNS, Inflammatory, Infectious |
| Activatable Nanoparticle devices | • Preclinical Development<br>• Clinical Development<br>• Interaction energy / nanoparticles | • Inorganic crystalline NPs (nanophosphors)<br>• Metallic NPs | • Activated nanoparticles<br>• Adapted properties<br>- physical properties<br>- size<br>- composition<br>- coating chemistry<br>• Nanoparticle characterization<br>• Nanoparticles toxicity analysis | • Cancer:<br>- breast,<br>- prostate,<br>- colon |

### 4.1.3 Targeting drugs to facilitate cell differentiation

The development of targeted drugs to facilitate cell differentiation, described in further detail in chap-ter 5.2, perhaps provides the quickest way to commercialise stem cell technology. Many companies have libraries of compounds which could impact the way mature cells or progenitor cell differentiate or de-differentiate. There are two problem areas however - how to optimise such compounds given the lack of knowledge of the target(s) and how to deliver the drug to the appropriate target organ (a clear overlap with nano-delivery devices is given here). Another option would be the incorporation of such molecules in biocompatible materials. Such activities bridge regenerative medicine and drug delivery and show possibilities of synergies between quite divergent fields.

#### Clinical benefit

Cell based therapies offer an alternative treatment modality for diseases which are currently poorly treated with large and small molecules.
Some of the envisioned therapies may even offer a cure rather than a treatment for the symptoms or stop the progression of the disease.

#### Economic benefit

Some drugs on the market or under research already work by such methods so there is precedence. What is anticipated in this area is converting an ad hoc process built on random discovery into something more organised or more susceptible to shorter term industrialisation,that could help strengthening European competitiveness. It would highlight the area and lead to a greater understanding of cell differentiation and its applications outside academia, if only a limited number of new drugs were discovered and delivered.

**Table 4-5: Global Market Size – Targeting drugs to facilitate cell differentiation**

The table below provides an estimate on the expected market sizes of the different areas taking a 10 year development cycle for new drugs into account.

| Expected Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Targeting drugs to facilitate cell differentiation | 0 | 2.000 | 6.000 |

**Table 4-6: Specific Roadmaps / Applications and R&D challenges – Targeting drugs to facilitate cell differentiation**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Targeting drugs to facilitate cell differentiation | • Optimisation of the drug compounds<br>• Delivery to the appropriate target | • HT assays for differentiation<br>• Assays for SAR<br>• Delivery Technologies<br>• Target identification strategies | • Optimising leads<br>• Targeting | • CNS<br>• Inflammatory<br>• Cancer<br>• Cardiovascular |

## 4.2 Nanodevices

The topic "nanodevices" has to be seen closely related to the field of nanopharmaceuticals. Nanodevices may potentially provide another pathway to deliver drugs / pharmaceuticals to the targeted location. For example nanodevices could be needle arrays to deliver drugs transdermally. This might greatly simplify medication of patients, as such devices could be designed to be painless, cheap and very easy to use. However, nanodevices could also be micro- or nano-sized carrier devices that actively (or passively) dispense drugs over a period of time to a specific target in the patient`s body.

Moving from designing drugs in an increasingly generic world to designing products with real benefits for patients in terms of convenience or better dosing is an ongoing challenge. It should be recognised that there is an overlap between the device area, enabling the delivery of therapeutics, and nano-therapeutics. The drugs to be delivered could be small molecules or macromolecules given that the device is the main differentiating factor for therapy in this case.

### 4.2.1 Challenges

Nano-based delivery of medicines will involve a variety of pharmaceutic techniques. A straight forward approach, but using innovative technology, is to use needles that are built of hollow nano-needle arrays. This could enable no-pain transdermal delivery of drugs into target tissue. Further approaches could also involve potentially needleless technologies, e.g nanoparticles that encapsulate drugs and can be targeted at specific disease areas in the body such as tumours, inflammations, plaques in arteries or the brain such as in Alzheimer's Disease etc. Very important in this respect is the development of reliable metering systems to verify the delivery of the correct amount of agent.

A common issue for all nanodevices applied to deliver medicines to the patient is the topic of immunogenicity and biocompatibility of the device itself as well as the contents stability

Ultimately, devices that could allow for an integrated monitoring of therapy either by external or internal devices are envisioned. This would include the development of micro/nano (electronic) systems for e.g. disease control.

Besides their diagnostic function, sophisticated external positioning and activation devices for MRI and focused ultrasound could also play a therapeutic role. Such technologies obviously might imply regulatory challenges since they have to be considered and treated as drug / device combinations.

On a technological level, biocompatibility, reliability etc. are clearly major challenges for the development and the application of in-vivo nanodevices. Key challenges here are related to the low cost fabrication of such devices in order that they will be reimbursed.

### 4.2.2 Clinical benefit

The clinical benefits are obvious as low cost systems (~2 Euros) could offer pain-free, safe delivery of macromolecules at home or point-of-care.

The closed loop, integrated monitoring systems would offer ease of use and reduce the impact of hospitalisation of patients.

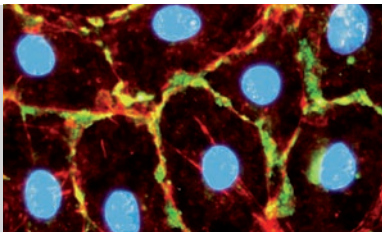
**Table 4-7: Global Market Size – Nanodevices**

| Market Size (M€) | 2015 | 2020 | 2025 |
|---|---|---|---|
| Focused Ultrasound Therapy System (includes ablation), equipment only, see below for total market | 175 | 350 M€ | 500 |
| Linked MRI, equipment only, see below for total market | 175 | 350 M€ | 500 |
| Pressure & Thermosensitive Drugs | 90 | 350 M€ | 750 |
| Targeted therapies in Oncology | 30.000 | | |
| Anti inflammatory diseases | 0 | 5.000 | 8.000 |
| CNS diseases | 0 | 0 | 2.000 |

**Table 4-8: Specific Roadmaps / Applications and R&D challenges – Nanodevices**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Devices for drug delivery | • Biocompatible and non-toxic materials<br>• Miniaturised systems for long-term delivery of accurate drug doses | • Metering systems for drug delivery<br>• NEMS<br>• Nanocapsules, carriers, devices, polymeric NC & NP[17]<br>• Multifunctional nanocarriers (NC)<br>• Intelligent implants for controlled time release of therapy | • Stability of drug payload<br>• Immunogenicity / biocompatibility of device and contents<br>• New polymer chemistry | • CNS (neurological)<br>• Cancer<br>• Inflammatory<br>• Diabetes<br>• Cardiovascular<br>• Pain relief<br>• Osteoporosis |
| Minimally invasive, microneedle based transdermal drug delivery systems | • Closed loop TDD<br>• Non-closed loop | • Micro needles<br>• Low cost nano-hollow needle arrays<br>• Miniaturised biophotonics | • Delivery accuracy<br>• No pain, potentially needle-less | • Diabetes<br>• Cardiovascular<br>• Vaccines<br>• CNS |
| Localised Therapy | • MRI-guided non-invasive localized delivery of pressure or thermosensitive drug and other biologic compounds with Focused Ultrasound (FU) | • External positioning and activation devices MRI/FU[18]<br>• FU sensitive imageable carriers<br>• MR compatible robotics<br>• Novel ultrasound transducers | • Regulatory challenges of device and drug | • Cancer (tumour) |

[17]NP: Nanoparticle
[18]FU: Focused Ultrasound



# 5. Regenerative Medicine

Regenerative Medicine addresses the repair, replacement or regeneration of damaged tissues or organs via a combination of technological approaches. They can be divided into two sub-areas: smart biomaterials (RT1) and advanced cell therapy (RT2). Ultimately, it is envisaged as being able to cure specific diseases or repairing damaged tissues, such as cartilage, bone, teeth, muscle, or nerves.

Academia is the driver for regenerative medicine with industry still lagging behind in terms of translation of research findings into products. The academic push unfortunately often lacks the industrial knowledge of where the real market opportunities are with the result that comparatively few products are being developed by fully integrated larger companies. This mirrors the inevitably slow introduction of new modalities, such as biological therapeutics, to a heavily regulated sector. Despite the successful and exciting results in recent years, academic research often stops at the first step in product development- demonstration of a proof of concept in a small animal model. Long term safety, standardisation and cost-effectiveness of the proposed solution are often not investigated. This misalignment between knowledge generated in academia and knowledge needed for the clinical, industrial and therapeutic translation is partly responsible, for the lack of regenerative medicine products.

The key challenges that have to be addressed to aid translation into profitable products are:

- The validation of product manufacturing processes to meet the high technical and quality standards required for regulatory approval
- The proof of long term safety and efficacy
- The minimization of costs through the scale-up and the automation of the manufacturing process itself (process optimization)
- Understanding the profitability of these new drugs, e.g. the reimbursement schemes envisaged
- The training of professionals for a more effective clinical adoption

With these observations in mind the ETP is currently investigating procedures and strategies to overcome the described hurdles. In the process of identifying industrially relevant roadmaps four general prerequisites for successful translation of research results towards "industrialisation" have been identified: Firstly, the entire process should follow an application focused approach. Secondly, academia, industry and end users, each having individual needs and targets, need to jointly drive the process. Thirdly, regulatory requirements that will become relevant for applying products in health care have to be considered early on in the process. And fourthly, a consistent funding strategy has to be established to guarantee the translation of the most innovative and useful ideas into products to serve the patients needs.

### Clinical and Societal Needs

There is a consensus that regenerative medicine products will have a potentially disruptive impact on the healthcare system but with high costs. While scientific breakthrough is advocated by the EC policy, industrial competitiveness is perceived as a key driver for nanomedicine.

Research needs to be focused on major diseases with poor clinical solutions and high healthcare costs. Most of the data are available for the US market but they only can be a rough guide to the European one.

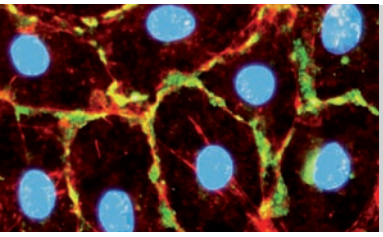
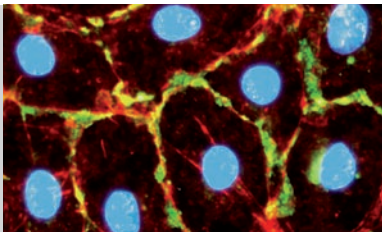


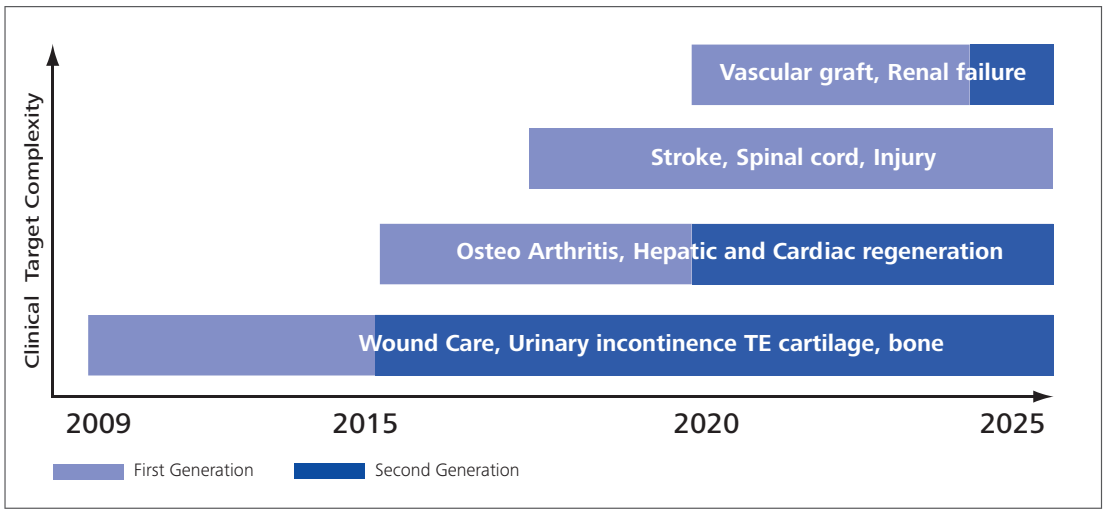
**Table 5-1: Disease related healthcare costs**

| Area | N° Patients (millions) | Costs for patients | US healthcare costs B$ | Source |
|---|---|---|---|---|
| Wound healing | | | 31 | The National Institute of General Medical Sciences |
| Urinary incontinence | 25 | | 26 | National Association for Continence [NACF], 2007 |
| Osteoathritis | | | 86 | US Department of Health and Uman Service |
| Diabetes | 5,8 | 21 | 125 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |
| Heart Failure | 5,2 | 53 | 277 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |
| Coronary heart disease | | | 165 | American Heart Association (report 2009) |
| Renal failure | 0,47 | 119 | 56 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |
| Stroke | 5,7 | 11 | 62 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |
| Parkinson Disease | 0,65 | 35 | 23 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |
| Spinal cord injury | 0,25 | 148,8 | 37 | C.Merrill & P.Dunnill, Reg.Med (2008), 3(3), 251-253 |



The competitive scenario shows that orthopaedics and wound healing products have been the easiest to enter in the market. Beyond these advanced areas which are now focused on industrialization and optimization of the clinical procedure with cheaper and less invasive solutions, others (such as the regeneration of cardiac, spine, neuronal tissue) are still dealing with major fundamental research. The figure below shows a timeline for the delivery of first effective smart biomaterials or cell therapies for spinal cord injury, cardiovascular diseases or osteoarthritis.

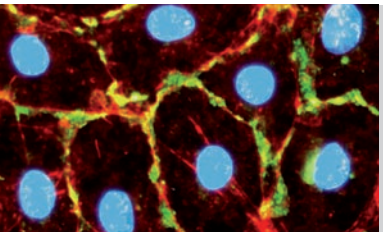
**Figure 1: Time-lines for clinical translation of increasingly complex tissue targets**




The following chapters will now further detail the findings from the expert discussions. It was felt that a fair balance between the success of both, breakthrough and competitiveness, could be found in shared research goals based on class of products based on robust scientific and technological platforms. The following paragraphs provide some detailed insights into the roadmap process and elucidate a few classes of products that are perceived of being instrumental in bringing clinically relevant applications on the market.

### 5.1 Smart Biomaterials

Research efforts have recently moved from the development of inert polymers which mimic the biomechanical properties of native tissue to bioactive materials which promote the tissue self healing. The design of these smart biomaterials has to be accompanied by intensive studies of the biology of the targeted tissue to gain a better understanding and control of tissue-biomaterial interaction. Today, research focuses on developing new biomaterials which can be used in non-invasive clinical protocols. Those materials target the regeneration of damaged tissue through the use of injectable, self-assembled and switchable biomaterials compounds.



Being biocompatible is only the first critical requirement for a biomaterial. Tissue cells respond with a biunivocal relation to specific mechanical and chemical anisotropy which characterizes the natural tissue. Since most of the extracellular matrix features are on the nanometre scale, advanced bio-inspired materials should incorporate nanometre surface features on biomaterials to reproduce the complex *in vivo* signals in a multifunctional Extracellular Matrix Analogues (EMA). In order to optimize the design of biomaterials for regenerative medicine, it will be necessary to understand not only how cells sense a biomaterial, but also the downstream consequences on fibrosis and immune rejection. Inflammation dictates important physiological outcomes. Unlike past research, investigators have recently been recognising that, rather than being inhibited, inflammation needs to be controlled and directed towards a regenerative pathway.

Therefore, there is a high clinical demand for therapeutic tools able to

- control inflammation following the implantation of a medical device by directing it towards a physiological pathway of tissue repair

- jump-start the extracellular matrix production by endogenous and/or transplanted cells.
  For example a cellular matrix-bound ligand that enhances the mobilization, recruitment and therapeutic effects of circulating progenitor cells after myocardial injury.

Two classes of multifunctional extracellular matrix analogues (EMA) are foreseen: Nanoarchitectured EMA and Synthetic Pro-morphogens EMA. In this direction, advanced technologies, such as high throughput nanoscreening devices or cues delivery shapers, will speed up the research toward a clinical application. These classes of products and enabling technologies will become a robust technological platform which will be adaptable to many clinical applications and gradually achieve pioneering treatments in the most challenging clinical scenarios.

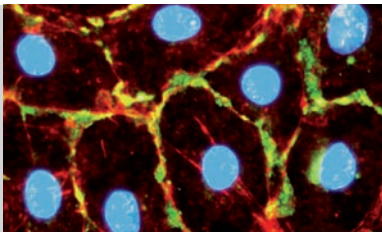
### 5.1.1 Nano-architectured EMA: drive regeneration with physical cues

Bio-mimicking tissue and organ systems involve the development of 3D engineered or self-assembled scaffolds which primarily reproduce the architecture of the native ECM. Several micro-nano fabrication techniques (electrospinning, rapid prototyping, soft lithography…) have been developed to control scaffold size, shape, mechanical strength, network interconnectivity, geometry, and orientation. Moreover, the possibility of obtaining bioactive and self-adaptative materials which modify their responsive properties in relation to environmental changes (smart material or self adjusting) could provide the right tools to address the complexity of tissue regeneration.

Biocompatible nanomaterials and composites could be designed to be sensitive to thermo, photonic, electrical, magnetic, chemical stimuli to express "on demand" the required bioactive functionalities related to adaptive, switchable stimuli. Such materials will be capable of performing nano-scale stimulation such as stretching, on demand drug release and cell localisation. Functionalised Nanoparticles (NPs), Nanowires (NWs) and Carbon NanoTubes (CNTs) could be used to build composite multitasking nanomaterials.

### 5.1.2 Synthetic Pro-Morphogens EMA: drive regeneration with biochemical cues

The name of Pro-Morphogen recalls the Pro-Drug concept working as enhancement of the bioavailability and the selectivity of the biochemical key (morphogen) for tissue regeneration. Nanoarchitectured EMA coupled with synthetic morphogens (bioactive analogues of growth factors and hormones) may become therapeutically active biomaterials able to present a specific biochemical signal to either the inflammatory cells or tissue cells in a controllable fashion. Pro-morphogens will be nanostructured biomaterials integrating morphogens in their structure of an appropriate presentation to the cells for extracellular (e.g. dendrimeric systems presenting bioligands, nanobeads carrying growth factor ana-



logues) or intracellular cues (e.g. nanoparticles able to both recognize and bind specific cell cycle markers (gene, mRNA or proteins). The level of control will be given by the correct orientation of the morphogens in the 3D space (e.g. coatings or self-setting nanomaterials able to present morphogens while creating their stable binding to tissue), by the establishment of appropriate gradients and by the timing of delivery.

It is envisaged that pro-morphogen kits will be specifically developed for the main tissue degeneration conditions (e.g. osteoarthritis damages, cartilage damages, neural damages, myocardial damages) in the form of molecularly-driven nano-gel gradients and nano-patches. The development of these therapeutically-active products will be accompanied by nanomaterial science progress to ensure their accurate delivery by the clinician during intervention. For this purpose, visco-elastic properties, thermo-responsive behaviour, pH sensitivity and self-assembly properties will be studied in relation to the physico-chemical properties and changes of tissues during their phases of inflammation and regeneration as well as in consideration of the cell surface and cytosolic conditions.

In order to reach the market at a competitive price level, the products will have to pass several intermediate development steps which include: 1) standardisation of the process and materials properties; 2) scaling up of the fabrication, 3) assessment of biocompatibility and toxicity (from cell-based assays in vitro to in vivo small animal models, 4) preclinical validation. A parallel technological development of the methodology platform should also be supported to deliver fully validated products.

### 5.1.3 Enabling technologies

The study of functional impact of nanomaterials on cell cycle progression and differentiation will be enabled by advanced technologies, such as High throughput nanoscreening devices, which will monitor tissue complexity providing a platform of quantitative information exchanged between cells and material. Reproducible and affordable cost solutions (e.g., biomedical microelectromechanical, 3D high content screening and analysis (HCSA) and nanoelectromechanical systems) have been proposed in this direction. Similarly, efforts are now undertaken to use nanostructures, as optic and magnetic sensors, to monitor in vivo the production and properties of specific biomolecules or to assess the material biohazard with high throughput approach.

The ability to manufacture products with the potential of patient-tailored assembly in the surgical theatre will require the development of easy-to-handle devices. Similarly, the need for a high-precision delivery in the damaged tissue during the different phases of regeneration will need to be considered in the development of cues delivery shapers. These enabling technologies may be divided in:

- Nanogradient generators: could lead to the production of material for the controlled delivery of growth factors and anti-inflammatory drugs (e.g. nano-extruders able to drive the assembly of different materials or coaxial electrospinning could be employed for this scope)

- In situ patch shapers (e.g. miniaturized extruders and spatulas able to deliver, shape and stabilize therapeutic patches for the tissue regeneration of osteochondral defects, infracted myocardium, severed nerves and spine, ocular tissues)

- Cell delivery catheters (e.g. high precision catheters able to provide delivery of cell suspension and cell/gels constructs, see section entitled cell therapy)

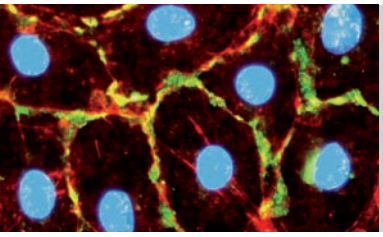


**Table 5-2: Global Market Size – Smart Biomaterials**

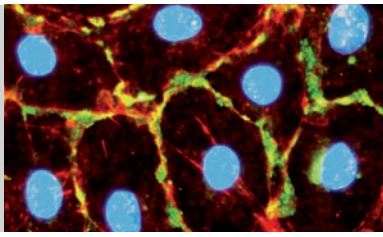
The subsequent table summarizes the expected market size for each disease ranked for research complexity. Since most of these diseases are age-related they are projected to grow with the increase of senior citizen population.

| Market Size (M€) | 2006 | 2009 | 2012 | 2015 | 2020 | 2025 | Source |
|---|---|---|---|---|---|---|---|
| Spine | 3.800 | - | - | 5.000 | 7.000 | 9.000 | Health-point Capital |
| Biocompatible Biomaterials | 20.000 (8.15% p.a.) | - | - | 35.000 | 43.000 | 52.000 | Global Analyst [19] |
| Wound Care (active dressing) | - | 3.500 (US:23% p.a.) | - | 5.000 | 12.000 | 17.000 | Global Analyst |
| Bone fillers | 115 (12% p.a.) | - | - | 240 | 300 | 380 | Global Analyst |
| Orthopedic Biomaterial | 180 | 200 | 230 | 260 | 320 | 430 | Data research |

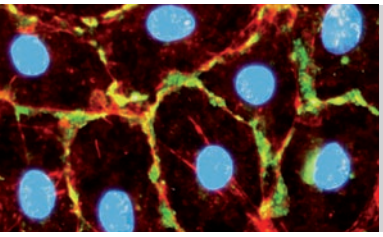
**Table 5-3: Specific Roadmaps / Applications and R&D challenges – Smart Biomaterials**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Nano-architectured EMA | • Bio-mimicking tissue and organ systems architecture<br>• Adaptive-switchable physical signals | • Micro and nanotechnology fabrication techniques for engineering 3D architecture of scaffold<br>• Bioactive and self-adaptative materials<br>• Composite multitasking materials which react to electrical, magnetic, thermal changes<br>• Analysis of the cell-biologic effects in vitro in cell culture models | • To tune the physical properties of nano-composite material "on demand" for a specific application<br>• Reproduce the physical nanofeatures of native ECM<br>• Reduce costs<br>• Assessment of toxicity<br>• Scale up<br>• To control the batch to batch variability | • Wound healing<br>• Osteoarthritis<br>• Cardiac injury<br>• Vascular disease<br>• Spinal cord injury<br>• Nerve injury |

[19]Global Analyst Inc figures and growth rates were delivered in 2006. Projections according to the Global Analyst were translated up to 2025 by the ETP experts.



| | | | | |
|---|---|---|---|---|
| Synthetic Promorphogens EMA | • Enhance the bioavailability and the selectivity of the biochemical clues in nanostructured materials<br>• Multitasking nanomaterials | • Nanocomposites materials including dendrimers, nanoparticles (NPs) and nanowires (NWs) and CNTs<br>• Coatings on biomaterials to reproduce the complex in vivo signals<br>• Analysis of the cell-biologic effects in vitro in cell culture models | • Anchor nano/micro pro-morphogens to biomaterials<br>• Produce standardized and scalable 3D nano-patterned materials<br>• To control the batch to batch variability of nanomaterials<br>• Inhibit immune reaction and control inflammation<br>• Assessment of toxicity<br>• Scale up<br>• Reduce costs | • Osteoarthritis<br>• Cardiac injury<br>• Vascular disease<br>• Spinal cord injury<br>• Nerve injury |
| High throughput nanoscreening devices | • Multi-parametric evaluation of functional properties of materials | • Microfabrication techniques<br>• High content screening (2D and 3D)<br>• Biomedical microelectromechanical systems<br>• Nanostructures as sensors for specific biomolecules | • Quantitative evaluation of cell signaling<br>• Low cost<br>• Automation<br>• Reproducibility and validation | • Enabling technologies for EMA developement |
| Cues delivery shapers | • Develop easy-to-handle fabrication devices<br>• High precisely controlled delivery of chemical clue | • Nanoestruders (Coaxial electrospinning)<br>• In situ patch shapers<br>• Device to deliver tissue by catheters | • Correlate the material quality with the process parameter<br>• Automation<br>• Reproducibility and validation | • Enabling technologies for EMA developement |



## 5.2 Cell therapies

The novel concept of cells as "living drugs" has changed the vision of tissue engineering and cell therapies. There are many potential forms of cell therapy including:

1) the transplantation of stem cells that are autologous (from the patient) or allogeneic (from another donor)

2) the transplantation of fully differentiated, functional cells

3) the transplantation of in vitro engineered tissues

These innovative approaches have proven to have positive and promising effects in critical diseases, such as healing of invalidating wounds, cartilage degeneration, heart failure, etc. Increasingly, stem cells are being proposed as agents for cell-based therapies due to their plasticity, established isolation/generation procedures, and capacity for ex vivo expansion. However, the mode of action of cells and their interaction with the tissue remains unclear. Moreover, to date the available technologies are hindered by the low percentage of live cells which reach the target site. Therefore, understanding the cell biology is a first necessary step toward the identification of the best strategies for tissue engineered products (TEP) and cells produced for cell therapy. The use of animal models aids not only in the discovery of which stem cell population is the most efficacious, but also in determining the stem cell mode of action, optimal cell dose and timing.
The development of an effective cell therapy will include the minimization of costs and the satisfaction of regulatory requirements on quality and safety with highly controllable and reproducible manufacturing processes. The minimization of costs (re-agents, time, and operator requirements) should be simultaneously coupled with the maximization of product yield (target cells/day, TEP/day) and quality (cell purity, functionality, sterility, etc.).

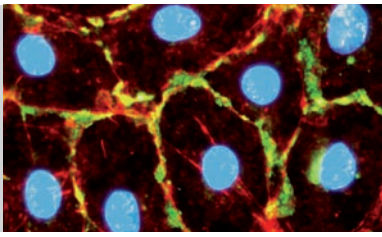
Two classes of products for cell therapies are envisaged:

- Delivery systems for cell transplantation
  - Delivery vehicles
  - Tissue engineered product
- Cells

Furthermore, the translation into clinical practice requires to address key issues, such as comparison between cell sources, optimal cell dose, timing and mode of delivery, biodistribution and demonstration of long-term safety and efficacy outcomes. Toxicology assessment and quality control for therapeutic delivery of the cell product need also to be addressed. Research efforts should be focused on automation and integration of existing enabling technologies, such as Advanced Cell Production Systems and Quality and safety control assays.

### 5.2.1 Product class 1: Materials for Cell Transplantation

Although the precise mode of action of cell-mediated regeneration is largely unclear, the control of cell delivery has been identified as a key parameter for the development of an effective cell based therapy. More information is needed to understand the process of in vivo tissue regeneration. The cell mode of action can include donor cells engraftment and differentiation or the release of paracrine factors, such as growth factors and cytokines, which are released from endogenous cells in damaged tissue (after myocardial infarction or in osteoarthritis for example). In this perspective, efficient cell transplantation is a key parameter in stem cell therapies. Research on biomaterials has been focused on the design of safe and manufacturable technologies for the local and systemic delivery of therapeutic molecules from the enclosed cells. Two classes of delivery systems for cell transplantation may be identified.



- Delivery vehicles designed to work as "cell reservoir" where cells are immobilised within polymeric and biocompatible devices and secrete in vivo while the biomaterial is degraded. Development of innovative and efficient manufacturing process and non invasive surgical procedures is crucial to design repeatable and economically acceptable therapeutic approach. This product class will be based on biomaterials able to act also as immunoprotectant material (such as protective immune-stealth coronas) minimizing immune response to allogenic cells transplantation and enhance the rate of survival of transplanted cells. A specific example would be nanostructured biomaterials able to surround pancreatic islets during their transplantation and grafting into the portal vein. Currently, after transplantation most of the pancreatic islets are attacked by the host immunosystem and do not survive in therapeutically suitable numbers in the patient`s body.

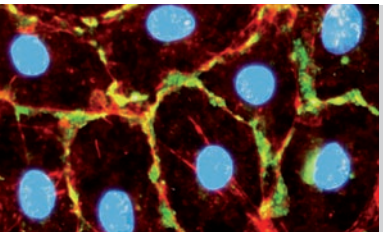
- Tissue engineered product (TEP) designed to replace the damaged tissue with in vivo process of integration and remodelling. Three-dimensional (3D) multifunctional materials have been proposed as scaffolds for cell culture during the development in vitro of functional engineered tissue replacement. Scaffold should prove a constant mechanical stability and structural integrity comparable to the native tissue. During the culture, the cell-biomaterial compound can be subjected to physical/physicochemical cues that mimic in vivo conditions and induce the tissue maturation. Translating the promising product into therapies requires overcoming significant tissue engineering manufacturing challenges, such as the identification of the best isolation and optimal culture protocol to promote cell expansion (adult and stem) or differentiation, as recalled in the following paragraph.

  The widespread use of TEP requires the compliancy of the regulatory requirements and the design of novel patient-tailored solutions with minimally invasive delivery systems. Long term safety and effectiveness, and prove of the mode of action (engraftment, paracrine factors release, disease modification) need also to be studied.

### 5.2.2 Product class 2: Cells

The utility of a cell therapy product is ultimately based on its function in the human patient. In this direction the first major challenge for the development of a new therapy is the identification of the best cell source and optimal culture protocol to guide the in vivo therapeutic regeneration. Both, the autologous or allogenic approach may be envisaged for major indications such as osteoarthritis, myocardial infarction, diabetes. The shortcomings of autologous therapy include the time required to culture the cells to adequate numbers and the unpredictable patient to patient variability on cell features. The provision of allogeneic, "ready-to-use", cells could overcome these disadvantages but individual immune response may need to be further investigated.

Thus, cellular therapeutics include engineering and manufacturing of both "patient-specific" versus "off-the-shelf" cell-based products. Once the process conditions are defined, strategies for implementing them at large scale and at a lower cost need to be implemented. In principle, scalability of patient-specific or off-the-shelf solutions can be implemented by increasing the culture volume or replicating the same controlled process in many sites. However, the culturing of cells or tissue engineered products are still characterised by a high variability and poor efficiency of the results. Optimization of cell-based products for clinical application process include the definition of a safe, robust and cost-effective manufacturing process which uses animal-free, chemically defined suitable medium.



### 5.2.3 Enabling technologies

Controlling, monitoring, and evaluating the impact of culture parameters on target cell output is the key to reduce the cost related to cell therapies, thus increasing their potential availability. Bioprocess engineering fundamentals, including bioreactor design and process control, have been proposed as solutions to reduce the manufacturing costs and increase the production volume for stem cell expansion or tissue engineered product manufacturing. The synergy between experimental and computational approach could lead to adaptive bioreactors, such as modular solutions, which comply with the regulation framework. The ultimate goal will be the establishment of economically viable tissue manufacturing systems.

The lack of robust in vitro assays which correlate with in vivo safety and efficacy of cell therapy products without significant processing, large cell numbers, or longer analytical time frames, currently preclude real-time monitoring of the manufacturing process. In the long term the identification of quantitative non destructive analytical methods will give the possibility of documenting online the identity, reproducibility, potency, and safety of cell therapy products and will guide bioprocess optimization and validation. Large animal studies have been proposed for the assessment of long term safety - the availability of reliable animal models that may reflect the chronic pathologies that are a major target for cell based therapies would be a critical element enabling effective development of these technologies.

**Table 5-4: Global Market Size – Cell therapies**

| Market Size (M€) | 2015 | 2020 | 2025 | Source |
|---|---|---|---|---|
| Non stem cell-based therapies (driven by wound healing, orthopaedics) | 1.000 | 2.500 | | Jain Pharmabiotech (2006) |
| Tissue Engineering (driven by orthopaedics, wound healing, cardiac, neurological) | 10.000 | 20.000 | | Jain Pharmabiotech (2006) |
| Stem cell therapies (driven by cardiovascular, diabetes) | 1.000 | 7.000 | | Jain Pharmabiotech (2006) |
| Supporting technologies | 3.500 | 8.000 | | Jain Pharmabiotech (2006) |

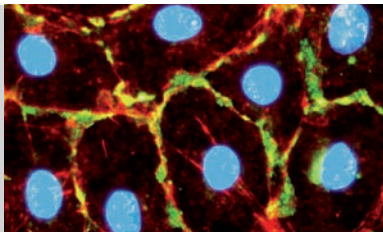
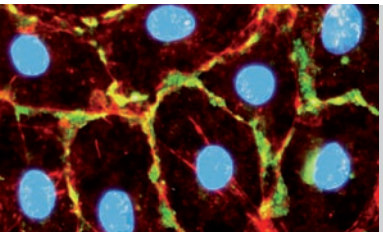


**Table 5-5: Specific Roadmaps / Applications and R&D challenges - Cell therapies**

| Roadmaps / Targeted Applications | Key R&D Priorities | Technologies | Challenges | Targeted Diseases |
|---|---|---|---|---|
| Delivery vehicles | • Cell-biomaterial fate in vivo, in long term cell engraftment<br>• Understand cell mode of action<br>• Minimization of immune response after implantation | • Self-assemblying, functionalized particles for in vivo control of cell distribution and alignment<br>• Non invasive cell traceability methods<br>• Optimization of culture methods<br>• In vivo optimized reproducible surgical procedures<br>• Stable anchoring or cell encapsulation in selective permeability biomaterial<br>• Functionalized microspheres and injectable multifunctional hydrogels for cell delivery and culture | • Immunoisolation barriers<br>• Off-the-shelf availability<br>• Patient-tailored cell therapy<br>• Scale up<br>• Reproducibility<br>• Long term safety and effectiveness | • Osteoarthritis<br>• Cardiac Injury<br>• Spinal cord injury<br>• Diabetes<br>• Retinal degeneration |
| Tissue Engineered Products | • Progenitor cell characterization and culturing<br>• Cell-biomaterial fate in vivo, in long term cell engraftment<br>• In vitro functional tissue generation<br>• In vivo engineered tissue integration | • Nanostructured scaffolds for complex tissues generation<br>• Controlled chemical environments for cell culture<br>• Modular, disposable bioreactor design<br>• In vivo optimized reproducible surgical procedures | • Off-the-shelf availability<br>• Patient-tailored cell therapy<br>• Minimally invasive delivery systems<br>• Scale up<br>• Reproducibility<br>• Long term safety and effectiveness of the TEP therapy | • Wound healing<br>• Osteoarthritis<br>• Cardiac Injury<br>• Vascular disease<br>• Heart Valve Replacement<br>• Retinal Degeneration |



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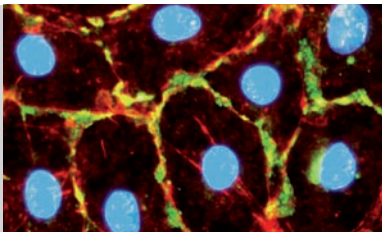
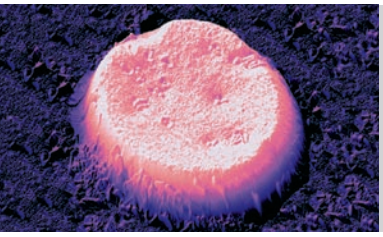
| Tissue Engineered Products | | • Cryopreservation techniques | • Prove of the mode of action (engraftment, paracrine, disease modification)<br>• Being compliant with the regulation | |
| Cells | • Optimal protocol for cell isolation<br>• Definition of optimal cell expansion protocols | • Integration of actuators and bioreactor designs for environmental control<br>• Animal-free, chemical defined medium<br>• Cryopreservation techniques<br>• Auto-adaptive bioprocess control systems<br>• In vivo optimized reproducible surgical procedures | • Identification of the best donor<br>• Low production - maintenance costs<br>• Quality control of cell source<br>• Reproducibility<br>• Long term safety and effectiveness of the cell therapy<br>• Reliable animal models of chronic diseases<br>• Prove of the mode of action (engraftment, paracrine, disease modification)<br>• Minimally invasive delivery systems<br>• Being compliant with the regulation | • Spinal Cord traumatic injury<br>• Multiple Sclerosis<br>• Parkinson's Disease<br>• Huntington's Disease<br>• Alzheimer's Disease<br>• Stroke<br>• Cardiac Injury<br>• Retinal Degeneration<br>• Diabetes |
| Bioreactors | • Implementation of chemical/physical environmental cues for 3D tissue culture<br>• Monitoring and control sensors and systems | • Integration of actuators and bioreactor designs for environmental control<br>• Modular, disposable bioreactor design<br>• Quantitative, non invasive sensors<br>• Auto-adaptive bioprocess control systems | • Device scalability and process automation<br>• Low production - maintenance costs<br>• User friendly<br>• Reproducibility | • Enabling technologies for the development of cell therapies |



| | | | | |
|---|---|---|---|---|
| In vitro assays | • Identification of predictive markers of cell potential<br>• Identification of quantitative markers for product quality and cell characterization<br>• Minimization and control of batch-to-batch variability<br>• Validation of cell and tissue cryopreservation methods | • Cell specific, chemically defined, safe culture media equivalents<br>• Microfluidic sampling and analysis systems<br>• Non destructive analytical methods for product quality definition<br>• Safety and quality monitoring markers and devices | • Real-time, on-line implementation<br>• Assay integration and unification<br>• Portable, miniaturized systems | • Enabling technologies for the development of cell therapies |



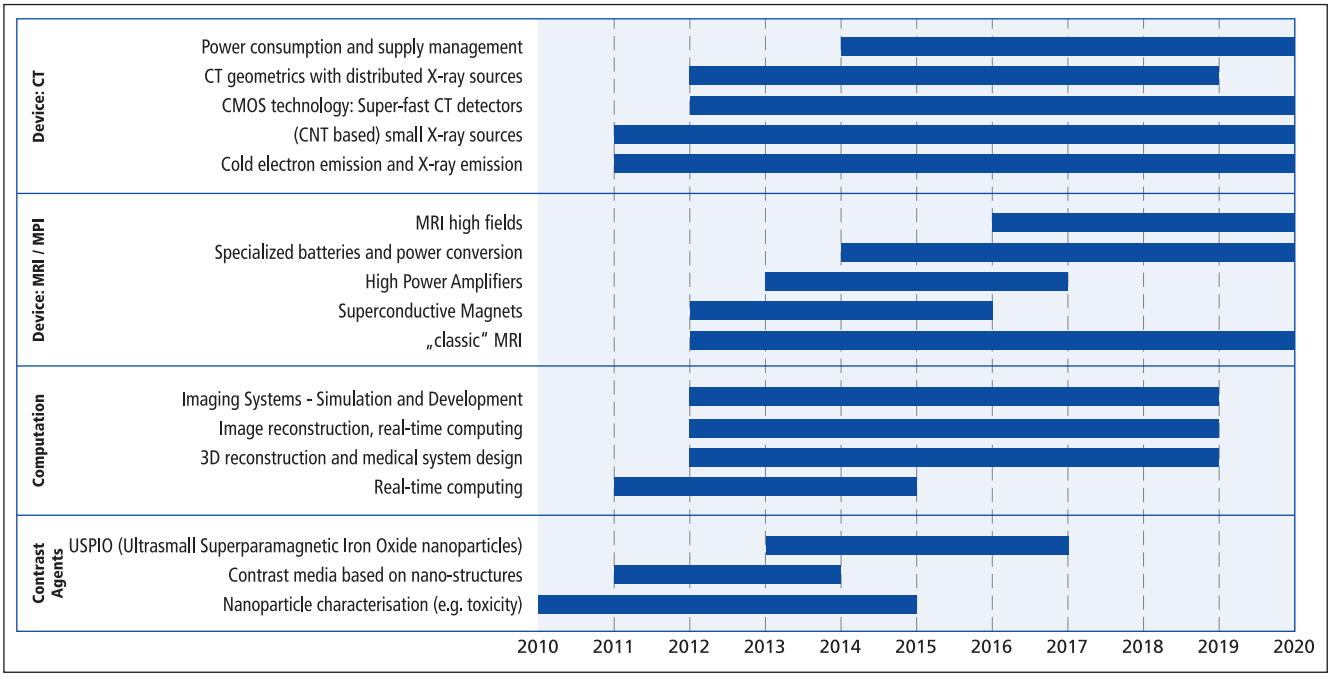
# 6. Appendix

The timelines presented below were extracted from the roadmap presentations of the experts. They have been consolidated, filtered for duplicate entries, grouped according to topics and arranged in proper order. They neither claim to be comprehensive nor complete. Many of the listed research topics are of course already under investigation in academic research labs today.
The timelines however are supposed to roughly present an estimate at what point in time the specific topic is expected to become relevant for industrial R&D.

## 6.1 Diagnostics

### 6.1.1 Timelines – In Vivo Diagnostics

**Figure 2: In Vivo Diagnostics – Technology**



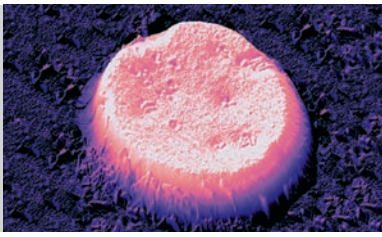
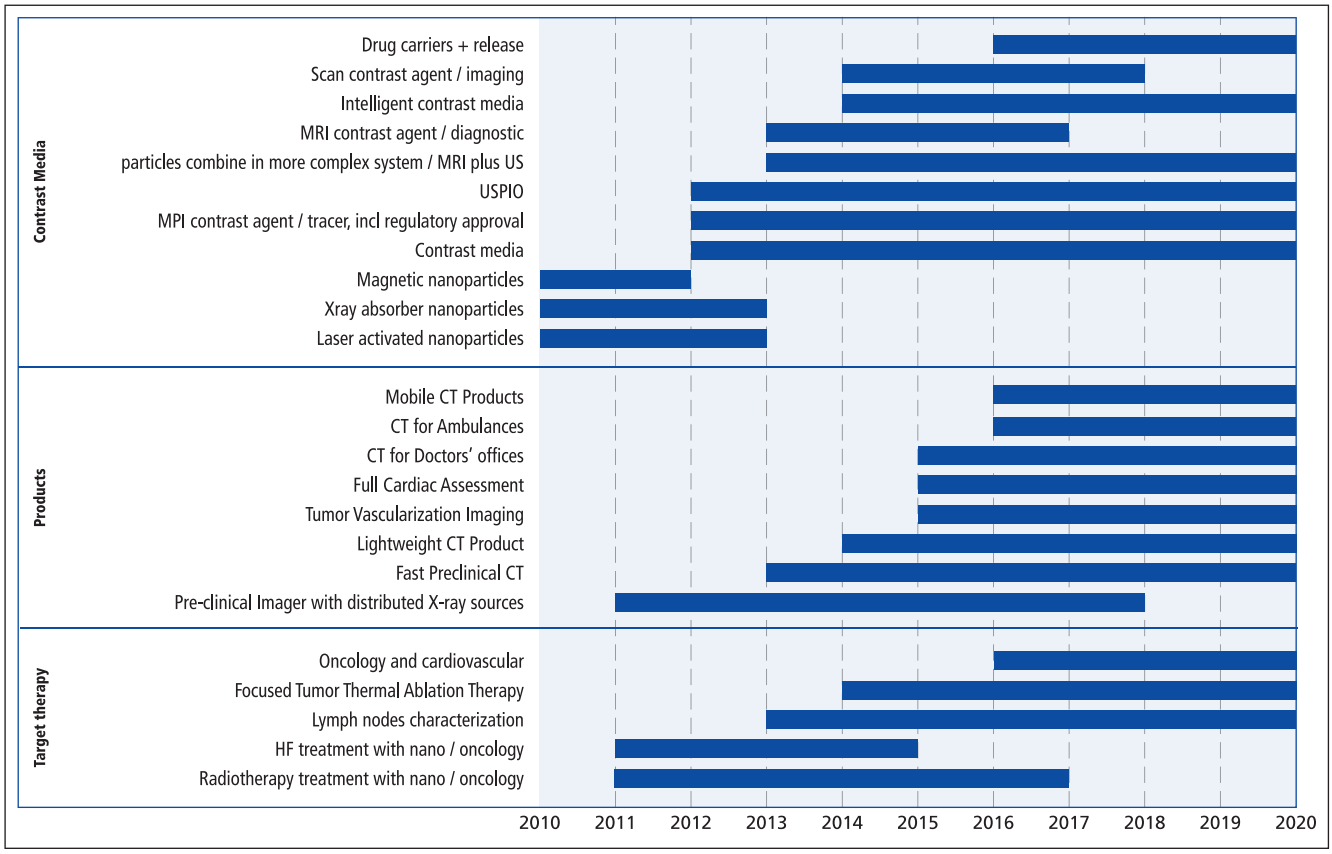
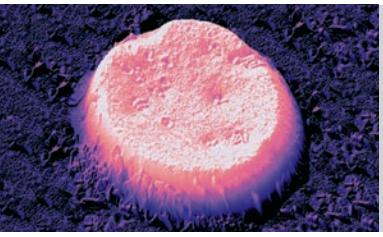


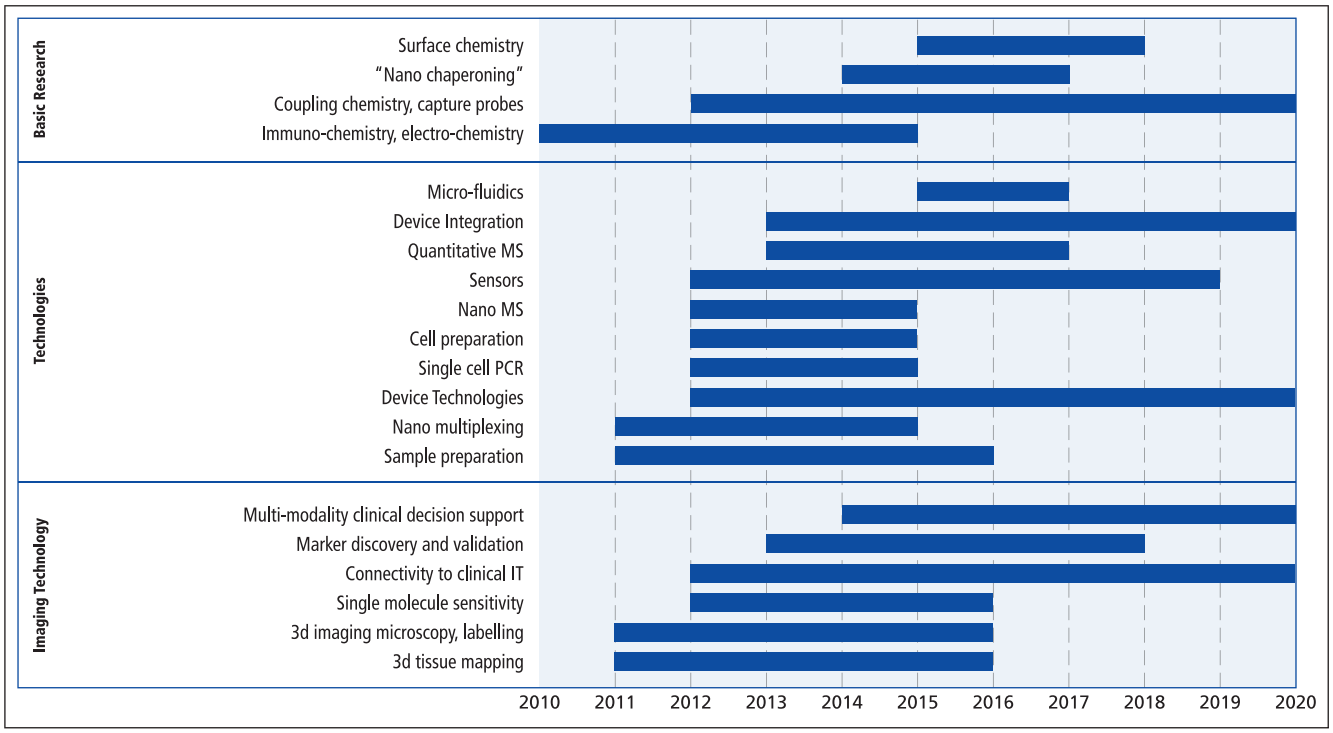
**Figure 3: In Vivo Diagnostics - Products & Applications**





### 6.1.2 Timelines – In Vitro Diagnostics

**Figure 4: In Vitro Diagnostics – Technology**



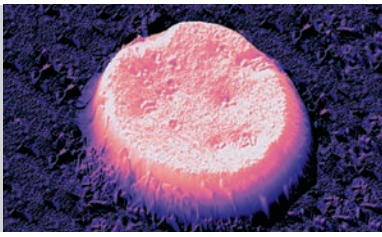
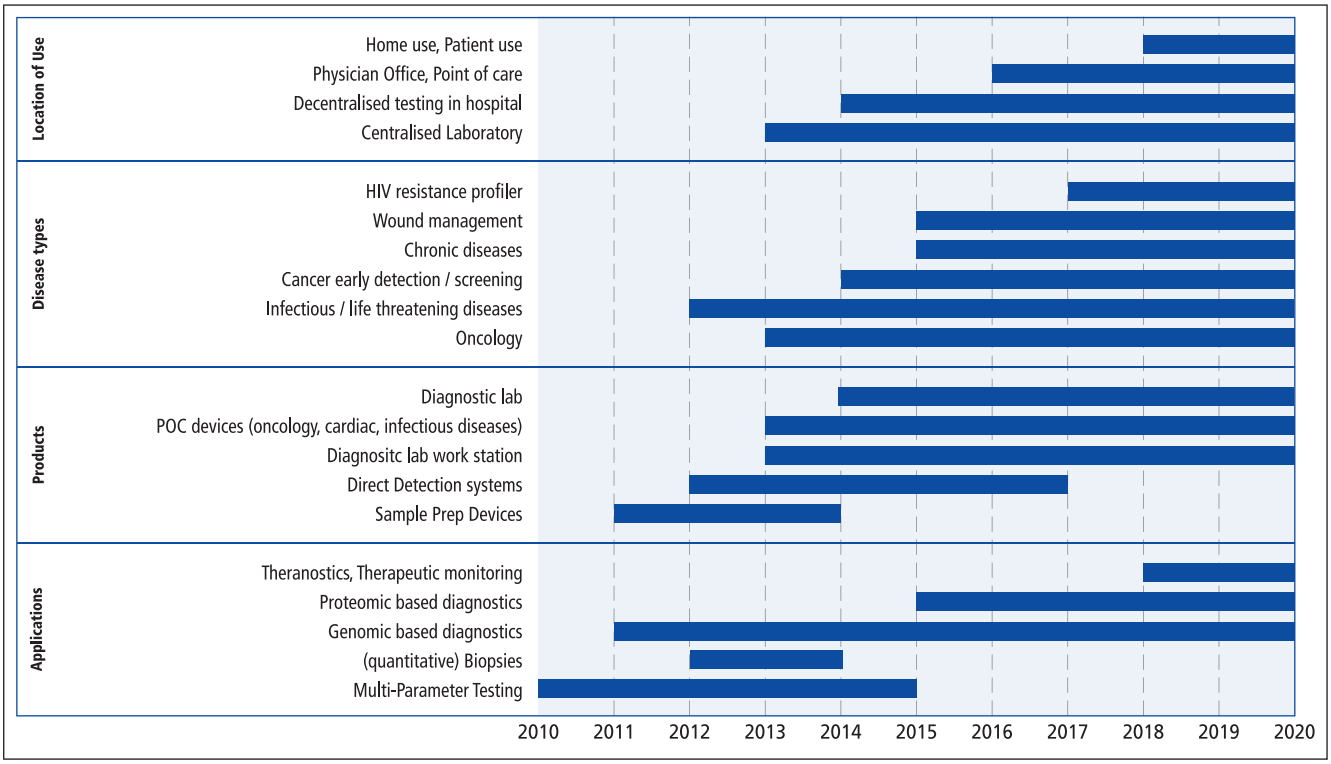
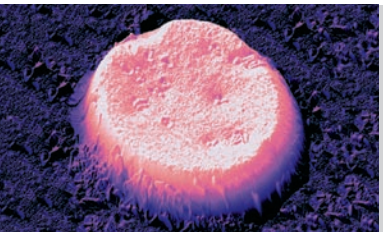


**Figure 5: In Vitro Diagnostics - Products & Applications**





## 6.2 Drug Delivery

### 6.2.1 Timelines - Nanopharmaceuticals

**Figure 6: Nanopharmaceuticals – Technology**

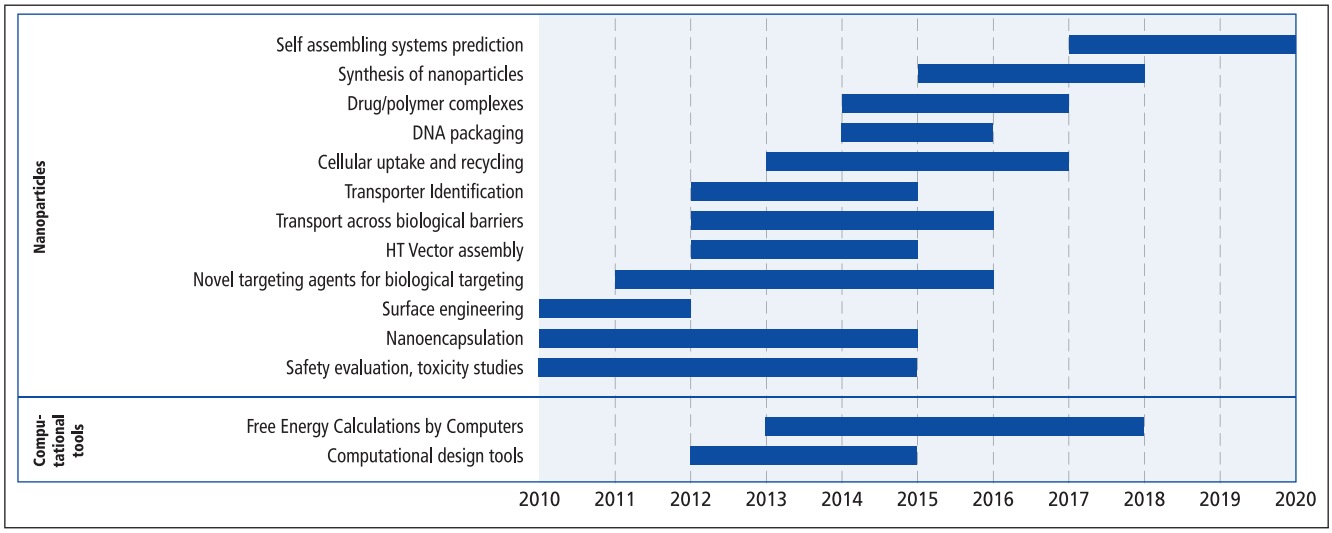
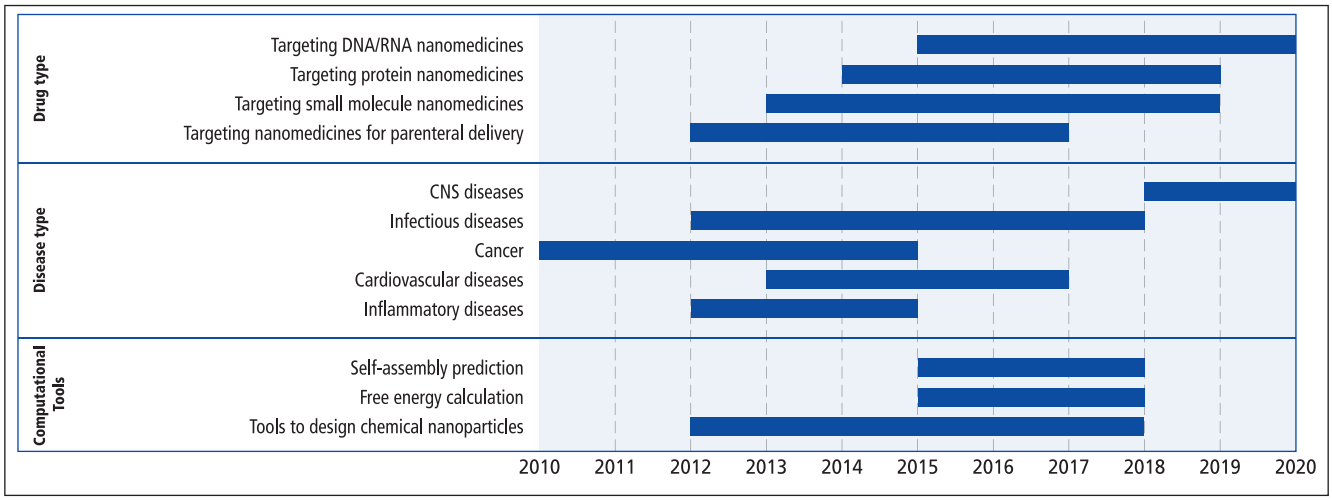
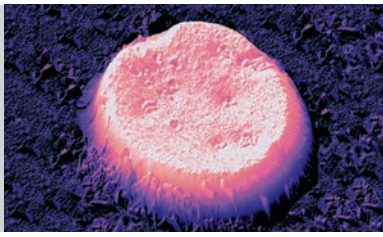


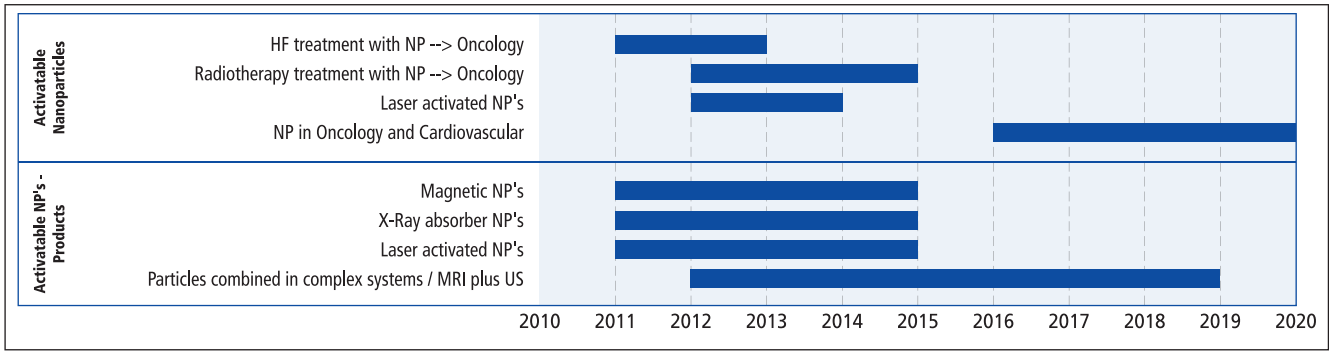

**Figure 7: Nanopharmaceuticals - Products & Applications**





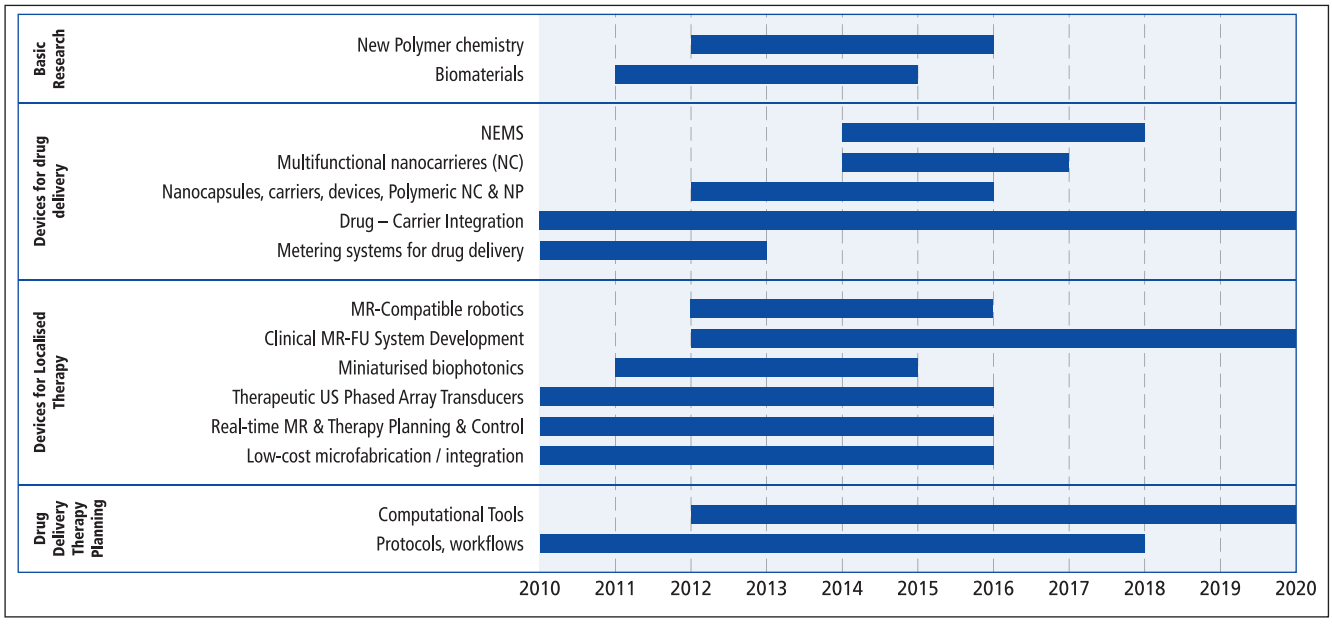
### 6.2.2 Timelines – Radical Innovation based Nanomedicines

**Figure 8: RI based - Products & Applications**




### 6.2.3 Timelines Nanodevices

**Figure 9: Nanodevices – Technology**



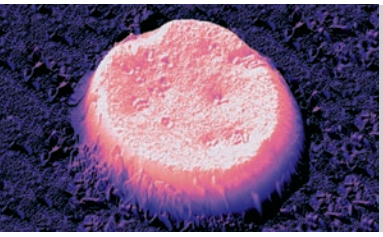
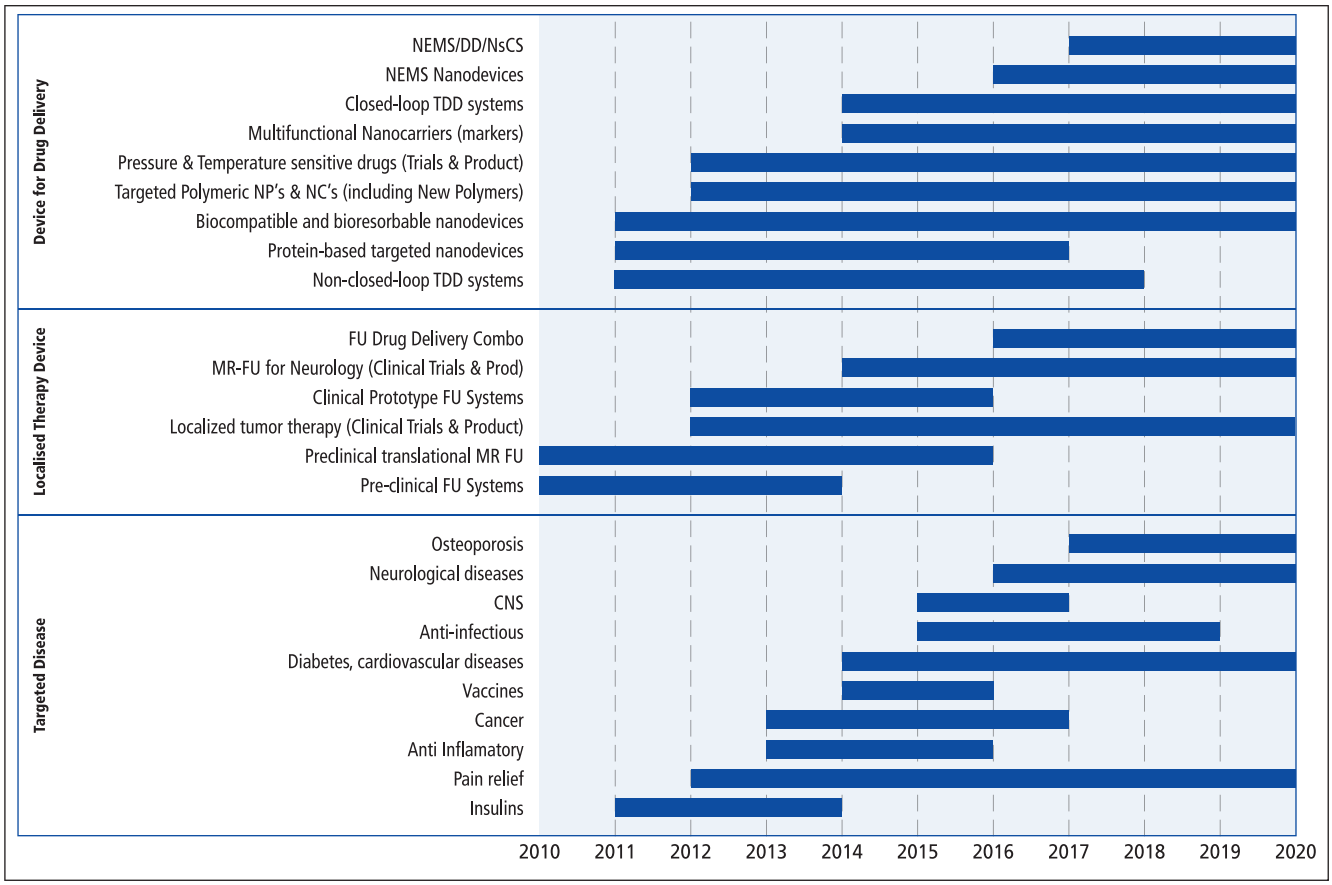
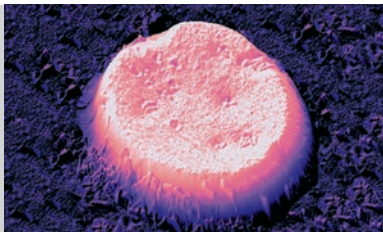


**Figure 10: Nanodevices - Products & Applications**



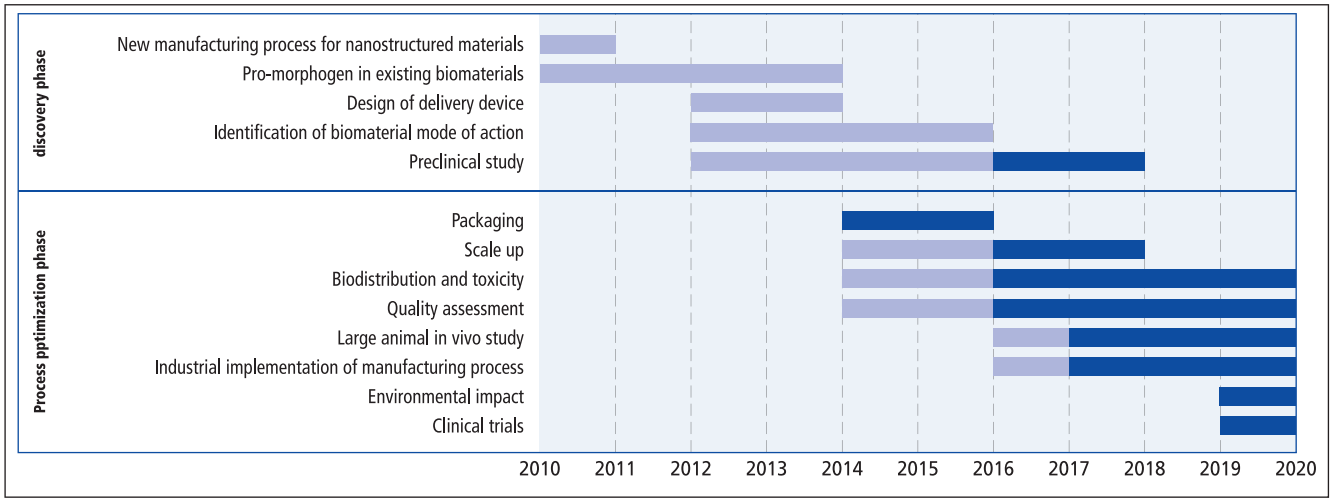


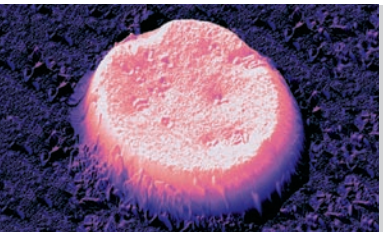
## 6.3 Regenerative Medicine

### 6.3.1 Timeline – Smart Biomaterials

In the timeline in the figure below the discovery process is indicated by light blue bars, the process optimization phase by dark blue bars.

**Figure 11: Smart Biomaterials – ST Challenges**

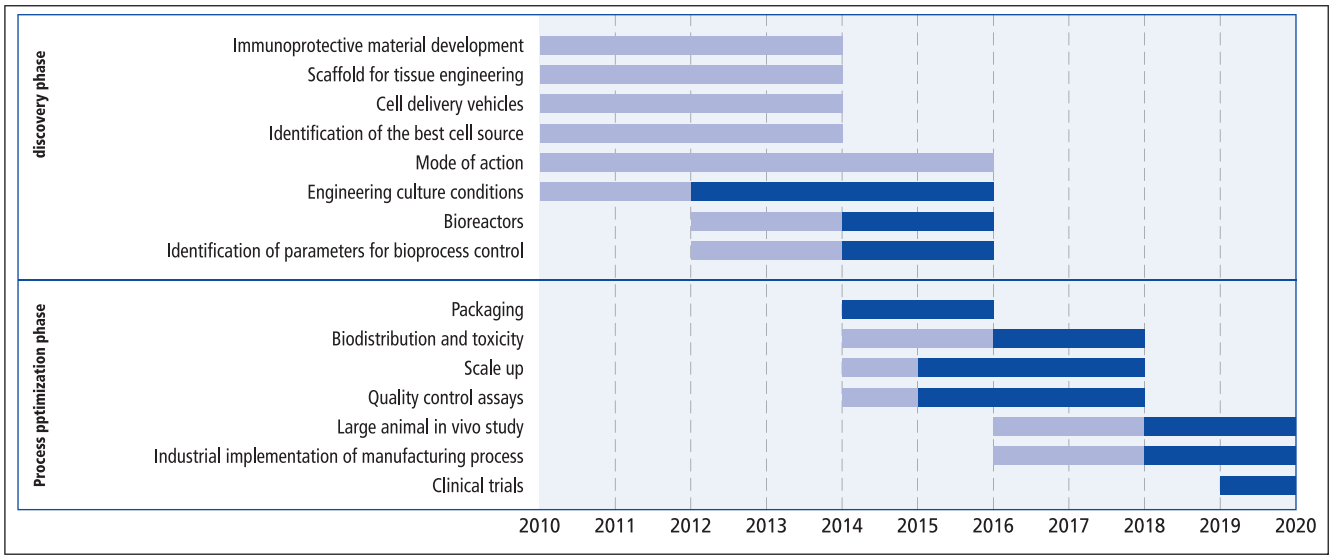


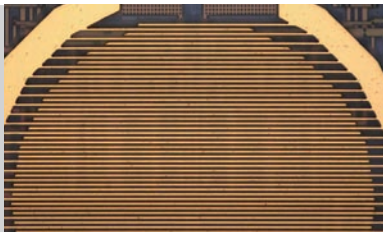


### 6.3.2 Timeline – Cell Therapies

In the timeline in the figure below the discovery process is indicated by light blue bars, the process optimization phase by dark blue bars.

**Figure 12: Cell Therapies – ST Challenges**





# 7. Acknowledgments & Contributors

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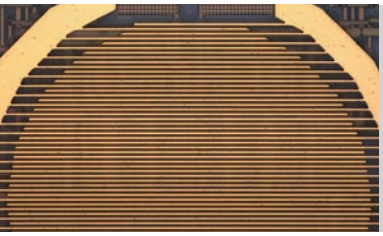

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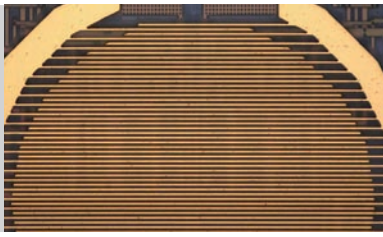

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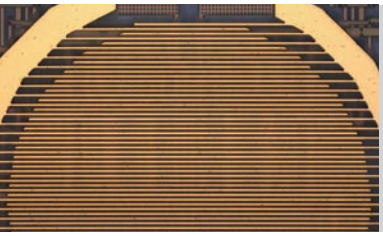

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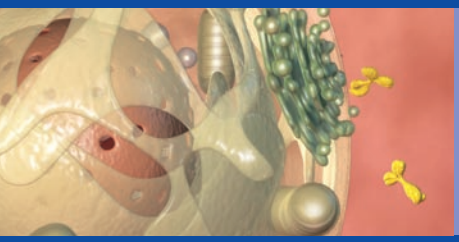

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