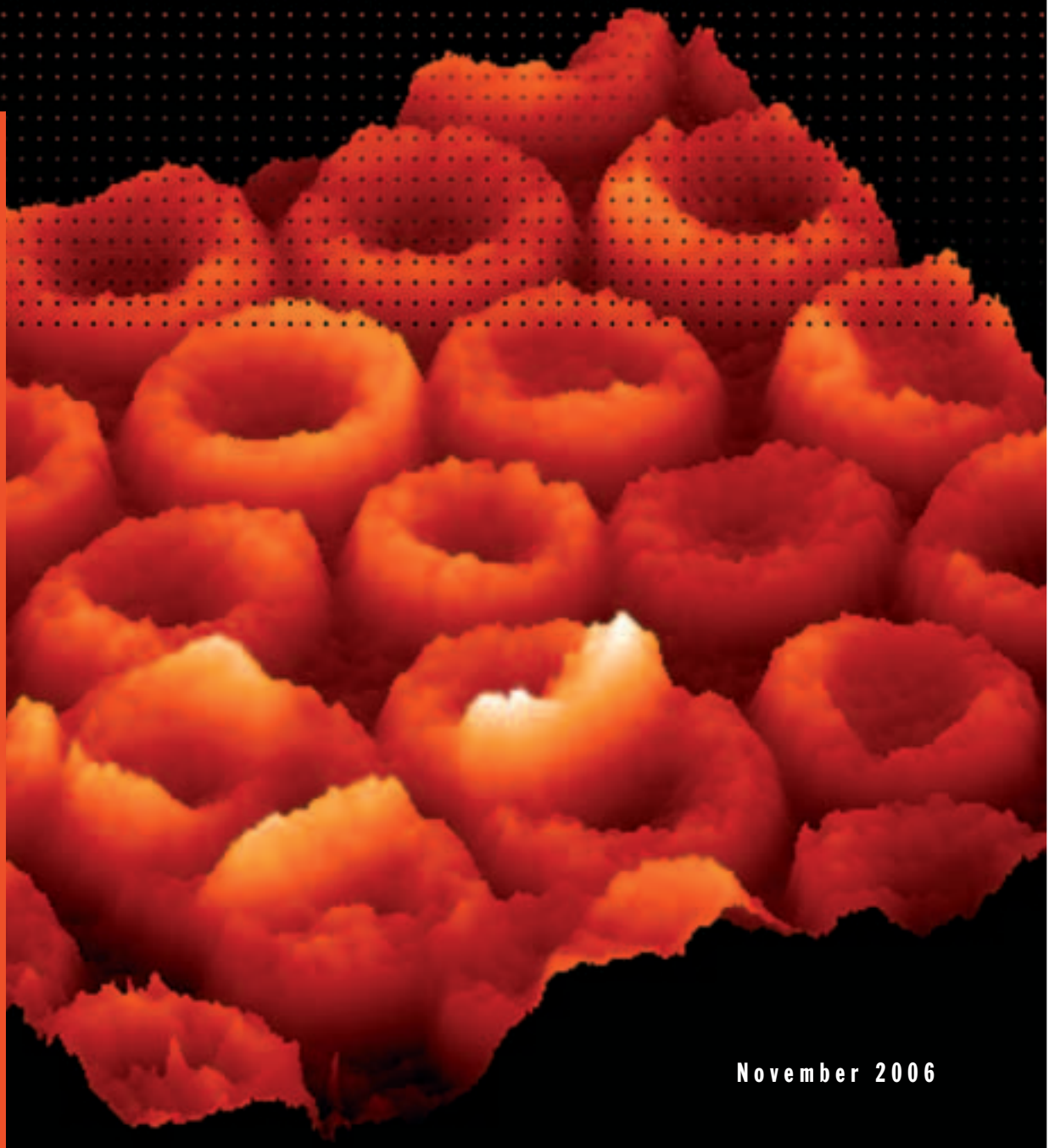
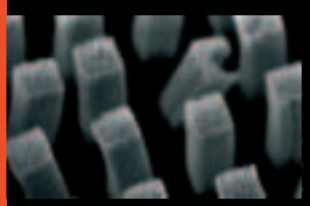
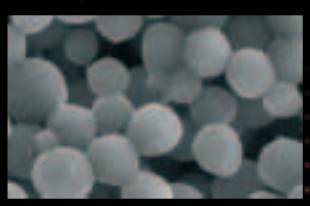
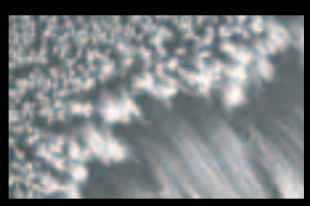
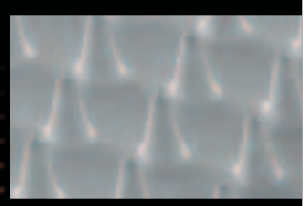
Nanomedicine
Nanotechnology for Health

European Technology Platform

Strategic Research Agenda for Nanomedicine



November 2006

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Executive Summary

Nanomedicine, the application of nanotechnology in healthcare, offers numerous very promising possibilities to significantly improve medical diagnosis and therapy, leading to an affordable higher quality of life for everyone. At the same time nanomedicine is a strategic issue for the sustainable competitiveness of Europe.

In order to avoid that this young and very fast growing discipline suffers from fragmentation and a lack of coordination, industry and academia – together with the European Commission – have identified the need for a European initiative to intermesh the several strands of nanomedicine into a firm strategy for advancement.

The resulting "European Technology Platform on NanoMedicine" is an industry-led consortium, bringing together the key European stakeholders in the sector. In September 2005 it delivered a common vision of this technologically and structurally multi-faceted area[1], and defines the most important objectives in this Strategic Research Agenda (SRA).

The SRA addresses the Member States of the European Union, its Candidate Countries and Associated States to the EU Framework Programmes for research and technological development, as well as the European Commission itself. Its main aim is to put forward a sound basis for decision making processes for policy makers and funding agencies, providing an overview of needs and challenges, existing technologies and future opportunities in nanomedicine. The SRA also takes into consideration education and training, ethical requirements, benefit/risk assessment, public acceptance, regulatory framework and intellectual property issues, thus representing a possible reference document for regulatory bodies.

The proposed disease oriented priority setting of this SRA is based on several parameters such as mortality rate, the level of suffering that an illness imposes on a patient, the burden put on society, the prevalence of the disease and the impact that nanotechnology might have to diagnose and overcome certain illnesses.

The scientific and technical approach is horizontal and exploits the benefits of interdisciplinarity and convergence of relevant technologies via breakthrough developments in the areas of diagnosis, targeted delivery systems, and regenerative medicine.

The effective implementation of the SRA is expected to provide a major step forward in patient oriented affordable healthcare.

1. European Technology Platform on NanoMedicine "Nanotechnology for Health: Vision Paper and Basis for a Strategic Research Agenda for NanoMedicine", September 2005 Available online at: http://cordis.europa.eu/nanotechnology/nanomedicine.htm

1. Introduction

1.1. Nanomedicine: Answering Clinical Needs

Over the coming decades, the populations of many countries around the world will age due to a declining birth rate and an increasing life expectancy. At the same time life-styles in developed countries have become increasingly sedentary. These developments will dramatically impact the healthcare system: certain diseases related to life-style will become more prevalent earlier in life, and the older generation wants to spend their additional years with a higher quality of life. Nevertheless, healthcare costs should be kept affordable. Nanomedicine, the application of nanotechnology to healthcare, will be an essential tool to address many unmet clinical needs of today and in the future.

This document describes the potential of nanomedicine to address clinical needs in significant diseases. It identifies those diseases that cause the most suffering for patients and the highest burden on society, and for which nanomedicine is expected to have a major impact. It describes where in the care-process and by which technology nanomedicine could have an impact. Finally it develops a Strategic Research Agenda, prioritising the most important technologies, which Europe has to develop in the near future, to realise the potential of nanomedicine for health care.

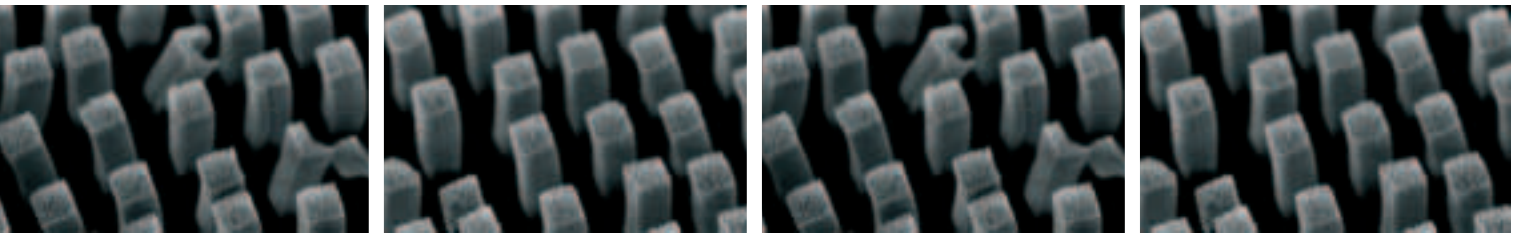
Nanomedical research should be initiated and supported in those areas of the care process, where the benefit for the patient is highest and should focus on diseases that have the highest socio-economical impact. The major diseases that impose the highest burden on society should be addressed first such as: cardiovascular diseases, cancer, musculoskeletal and inflammatory conditions, neurodegenerative and psychiatric diseases, diabetes, and infectious diseases. Cardiovascular disease remains the most frequent cause of death in the European Union, myocardial infarction and stroke accounting for about half of all deaths in Europe. Cancer is currently the number two cause of death behind cardiovascular diseases in the western world. Due to an aging population and improvements in the therapy of cardiovascular diseases, cancer will become the number one cause of death in the coming decades. Musculoskeletal and inflammatory diseases such as arthritis have a devastating impact on the quality of life and require constant medication. Neurodegenerative diseases such as Alzheimer's or Parkinson's are other age related diseases, reducing the quality of life and furthermore put a tremendous burden on society. Diabetes is another example of a disease that requires constant monitoring and medication, and is expected to increase in occurrence dramatically. Globally, bacterial and viral infections claim many lives with inadequate therapeutic options in some cases.

As soon as the onset of a disease is suspected, the patient enters into a care process comprising diagnosis, therapy, and follow-up monitoring. In the future, healthcare will start before the onset of symptoms. New sensitive diagnostics devices will permit very early personal risk assessment by monitoring disease indicative biomarkers. Due to its much larger analytical capacity, nanomedicine will allow an earlier and more personalised treatment for many diseases, exploiting the in-depth understanding of diseases at a molecular level. Nanomedicine holds the promise to greatly improve the efficacy of pharmaceutical therapy, reduce side-effects and make drug-administration more convenient. Nano-assisted regenerative medicine has the potential to create a paradigm shift in the healthcare systems of tomorrow, aiming to trigger endogenous self-repair mechanisms rather than just managing or palliating the symptoms.

Therefore, nanomedicine has the potential, by enabling earlier diagnosis, better therapy and improved follow-up care, to make the care process more effective in terms of clinical outcome for the patient, and more affordable for society.

Nanomedicine

Definition: Nanomedicine, for the purpose of this document is defined as the application of nanotechnology to achieve breakthroughs in healthcare. It exploits the improved and often novel physical, chemical and biological properties of materials at the nanometer scale. Nanomedicine has the potential to enable early detection and prevention, and to essentially improve diagnosis, treatment and follow-up of diseases.



1.2. The Impact of Nanomedicine on the Care Process

Nanotechnology allows the manufacturing and manipulation of matter at basically any scale, ranging from single atoms and molecules to micrometer-sized objects. This already enables the miniaturisation of many current devices, resulting in faster operation or the integration of several operations. Furthermore, at this scale, man-made structures match typical sizes of natural functional units in living organisms. This allows them to interact with the biology of living organisms. Finally, nanometer sized materials and devices often show novel properties. These three aspects hold the promise to provide breakthroughs in nanomedicine, leading to clinical solutions within preventive medicine, diagnosis, therapy and follow-up care.

1.2.1. Preventive Medicine

New diagnostic tests making use of nanotechnology to quantify disease-related biomarkers could offer an earlier and more personalised risk assessment before symptoms show up. In general, these analyses must be cost-effective, sensitive, and reliable. The test itself should inflict only minimal discomfort on the patient. Supported by such an analysis and bioinformatics, health professionals could advise patients with an increased risk to take up a personalised prevention program. People with an increased risk for a certain disease could benefit from regular personalised check-ups to monitor changes in the pattern of their biomarkers.

Nanotechnology could improve in vitro diagnostic tests by providing more sensitive detection technologies or by providing better nano-labels that can be detected with high sensitivity once they bind to disease-specific molecules present in the sample. Nanotechnology could also improve the ease-of-use of in vitro diagnostic tests done by untrained users or even by patients at home. For example a relatively painless minimally invasive sampling technique would greatly improve patient comfort. Diseases with no secretion of biomarkers into blood or urine will require imaging procedures of high specificity for their early detection. One well-known example used already is x-ray mammography for the early detection of breast cancer. Novel targeted imaging agents, precisely homing in on diseased cells, promise a much higher sensitivity than today's imaging procedures making possible the detecting of cancer at an even earlier stage.

Biomarkers

A biomarker is an indicator of a biological process or state, for example a disease, or the response to a therapeutic intervention. Biomarkers are diverse in nature, ranging from an altered gene, to a change in protein-production, to a change in a regulated metabolic pathway, or even physical features of cells. Biomarkers can be analysed using in vitro diagnostics of samples, or they can be visualised and quantified in vivo.

1.2.2. Diagnosis

If a medical check-up had found an indication or a hint of symptoms for a disease, it is important that “false positives” are excluded by applying more specific diagnostic procedures. These can be more laborious and expensive as they are applied to a smaller number of patients. In this case, molecular imaging, which makes use of specific targeted agents, plays a crucial role for localisation and staging of a disease, or – equally important – for ascertaining the health of a patient. Here, nanotechnology could help to design a plethora of very specific imaging agents over the next ten years. Miniaturised imaging systems will make it possible to perform image-based diagnostics everywhere and not only in research centres. Automatic methods will give diagnostic results without an on site expert. Conceptually novel methods, combining biochemical techniques with advanced imaging and spectroscopy provide insight to the behaviour of single diseased cells and their micro-environment for the individual patient. This could lead to personalised treatment and medication tailored to the specific needs of a patient.

The main advantage of nanomedicine on quality of life and on costs for healthcare is earlier detection of a disease, leading to less severe and costly therapeutic demands, and an improved clinical result. However, once a disease is diagnosed, therapeutic action is required. A decision needs to be taken as to which cure offers the best therapeutic ratio (risk/benefit) for the patient. Here, diagnostic imaging procedures provide crucial input for clinical decision taking and therapy planning.

1.2.3. Therapy

In many cases, therapy will not be restricted to medication only but requires more severe therapeutic action such as surgery or radiation treatment. Planning of therapeutic interventions will be based on imaging, or may be performed under image guidance. Here, nanotechnology will lead to a miniaturisation of devices that enable minimally invasive procedures and new ways of treatment. The possibilities range from minimally invasive catheter-based interventions to implantable devices. Targeted delivery systems and nanotechnology-assisted regenerative

medicine will play the central role in future therapy. Targeted delivery agents will allow a localised therapy which targets only the diseased cells, thereby increasing efficacy while reducing unwanted side effects. Thanks to nanotechnology, pluripotent stem cells and bioactive signalling factors will be essential components of smart, multi-functional implants which can react to the surrounding micro-environment and facilitate site-specific, endogenous tissue regeneration (making lifelong immune-suppressing medication obsolete). Imaging and biochemical assay techniques will be used to monitor drug release or to follow the therapy progress. This therapeutic logic will lead to the development of novel, disease modifying treatments that will not only significantly increase quality of life of European citizens but also dramatically reduce societal and economic costs related to the management of permanent disabilities.

1.2.4. Follow-Up Monitoring

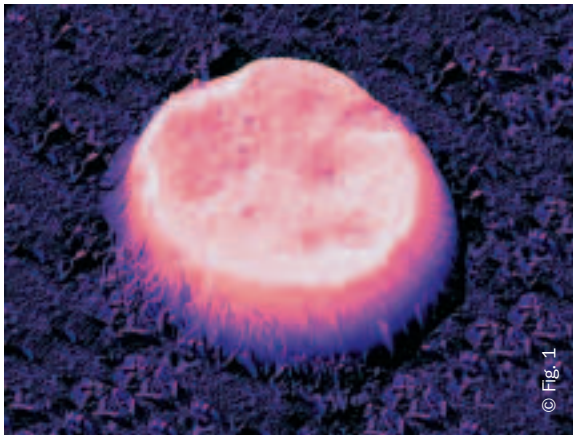
Medical reasons may call for an ongoing monitoring of the patient after completing the acute therapy. This might be a regular check for reoccurrence, or, in the case of chronic diseases, a frequent assessment of the actual disease status and medication planning. Continuous medication could be made more convenient by implants, which release drugs in a controlled way over an extended length of time. In vitro diagnostic techniques and molecular imaging play an important role in this part of the care-process, as well. Biomarkers could be systematically monitored to pick up early signs of reoccurrence, complemented by molecular imaging where necessary. Oncology is one of the areas where these techniques are already being evaluated today. Some types of tumours can be controlled by continuous medication extending life expectancy. However, in the case of drug resistance, signs of disease progression can be immediately picked up and alternative treatments can be prescribed.

1.3. Selected Disease Areas

Nanomedicine should focus on the patient; it should aim for meaningful improvements in areas that contain the most severe challenges in future healthcare appropriate to the technology. Therefore, six disease areas were selected based on the following criteria: all chosen diseases strongly reduce the patient's quality of life and have a very high prevalence, they impose a high socio-economical burden on society, and nanotechnology is expected to have a high impact on the care process for these diseases.

1.3.1. Cardiovascular Diseases

Cardiovascular diseases remain the most frequent cause of death in the European Union and in the world, according to the World Health Organisation, with myocardial infarction and stroke accounting for about half of all deaths in Europe. The underlying cause of cardiovascular disease is in most cases the formation of a plaque in the blood vessels. The formation of plaque can lead to a stenosis of the blood vessels, accompanied by a decreased tissue perfusion and a lack of oxygen. In acute cases, such as an infarct or a stroke, the plaque becomes unstable and ruptured leading to an acute clogging of the blood vessel with death or disability as the consequence. Many aspects of cardiovascular diseases at present, for example the biochemistry of unstable plaques, are not completely understood. Cardiovascular diseases are often associated with risk factors such as little exercise, high cholesterol that are typical for western life-style; however, recent research also indicates inherited causes.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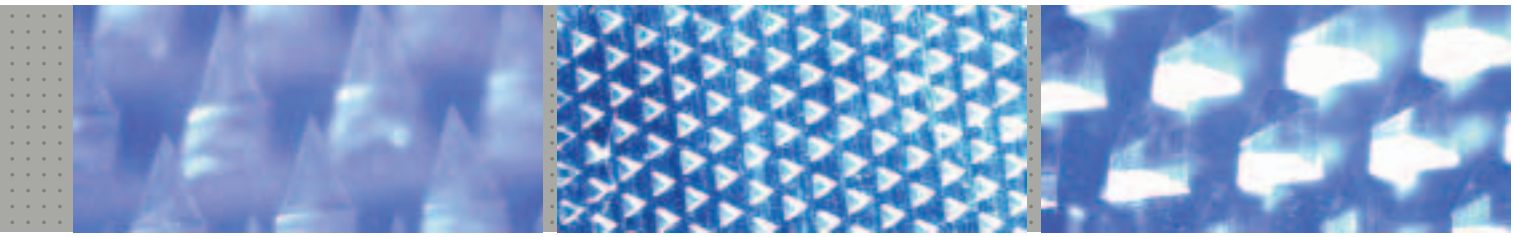
Nanomedicine is anticipated to aim for improvements in early diagnosis, acute intervention and follow-up-therapy. For early diagnosis, nanotechnology could be used to realise new in vitro diagnostic tests for atherosclerosis or even for the presence of highly unstable plaque. While today's imaging procedures only indicate the presence of a stenosis, research should try to develop imaging methods that visualise plaques that are at the brink of rupturing.

Targeted agents could deliver a therapeutic payload, for example a drug that stabilises the plaque and prevents rupturing. Already, nanometer-sized agents are being preclinically tested that render an unstable plaque visible in magnetic resonance imaging and at the same time release a drug to stabilise the plaque. In the case of an acute stenosis and aneurysms in the vascular system, ballooning and drug eluting stents are interventional,



minimally invasive therapeutic options that are used today. They should be further optimised using intravascular micro-navigation and image guided technologies as well as smart materials.

In case of an infarct of the heart muscle itself, some of the heart tissue usually gets seriously damaged. The regeneration potential of the heart and its ability for tissue repair after ischemic injury has been considered limited or nonexistent. However, recent scientific results in regenerative medicine have radically changed this view and thus opened the possibility of cell therapy as well as new pharmacological concepts for the treatment of cardiac insufficiency. New treatments will include intelligent nanobiomaterials with the ability to attract local adult stem cells or cultured cells to the site of injury, providing cell therapy that should improve heart function and decrease mortality for patients with severe heart insufficiency. Early treatment in myocardial infarction with cells/stem cell modifying drugs could improve early rescue of injured myocardium and thus reduce the number of patients with severe cardiac insufficiency.

1.3.2. Cancer

Cancer is currently the second leading cause of death in Europe, while it shows probably the highest clinical complexity. Nanomedicine bears the potential to provide an effective answer to the complexity of the disease as it offers more therapeutic options compared to present conventional therapy.

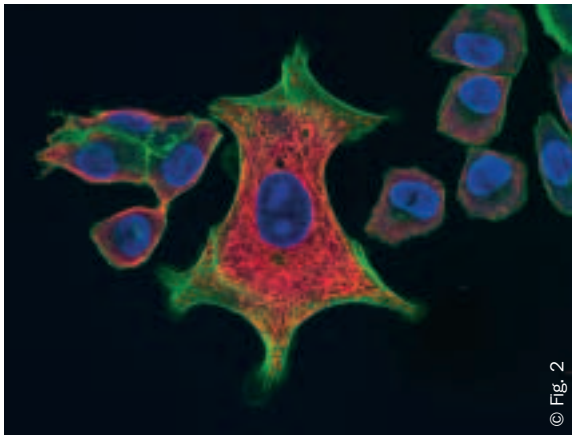
Especially in cancer, early diagnosis is of utmost importance. Late-stage metastatic cancer is difficult to cure and treatment leaves severe side-effects, suffering for the patient, and high costs. Diagnostic tests that allow measurement of a biomarker panel are necessary to catch the disease at on-set. Nanotechnology could enable the parallel in vitro measurements of many biomarkers at the same time, while keeping the test itself simple, sensitive, reliable, and inexpensive. In addition nanotechnology provides the tools to discover novel biomarkers, enhancing reliability and accuracy of diagnosis.

In over 50% of all cancer cases, radiation therapy is the standard form of therapy. Today, dose planning for radiation therapy is based on computer tomography, and prescribes a constant dose within the tumour outline. This ignores the tumour's inner structure consisting of sections being more or less sensitive to radiation. Molecular imaging procedures, using dedicated agents together with imaging systems and software, may soon be able to reveal these inner sections. The imaging procedure will serve as an input to a better radiotherapy planning that puts higher doses on the radiation-resistant sections and lower doses on the radiation-sensitive sections, thereby reducing damage in the healthy neighbourhood. Chemotherapy is today the other standard form of therapy. Chemotherapy is usually applied systemically which leads to damage of healthy tissue causing severe side effects for the patients. Targeted delivery schemes can be used to accumulate the therapeutic agent specifically on the diseased cells. An example, already in clinical use, is an antibody that is either labelled with a radioactive isotope for single photon emission computed tomography imaging or with a beta-radiation emitting isotope, which efficiently kills metastases throughout the body. Targeted nano-carriers, both loaded with pharmaceutical and acting as imaging agent, are promising concepts under development. The drug release can be purely passive over time or can be induced actively from outside, i.e. by highly focused ultrasound pulses or heating with radio frequency waves. The combination of imaging with drug release allows a higher control over dosing and an improved quantification of the treatment. Today, shrinking of the tumour is monitored by computer tomography, which occurs usually weeks after the treatment. Molecular imaging would allow faster assessment of the response of a patient to a therapy; making possible an earlier modification of the oncological treatment regime, reducing stress and pain for the patient.

Regenerative medicine offers unique therapeutic options to deal with side effects of standard chemotherapy like secondary immunodeficiency. Regenerative medicine may be applied to create a new lymphocyte factory that re-establishes a normal immune response in a patient. One option is to make haemopoietic stem cells that proliferate without differentiating, in order to correct the bone marrow condition and to have a large number of haemopoietic cells available in immunodeficient patients. Secondly, the thymic structure and function has to be reproduced so as to stimulate haemopoietic stem cells to differentiate and become lymphocytes. The critical issue and challenge is to construct an environment able to trigger proliferation and differentiation. Possible avenues for development include the use of microporous scaffolds, paved with stromal cells, which may be coupled with attached/eluted signalling molecules and growth factors.

1.3.3. Musculoskeletal Disorders

Musculoskeletal disorders are the most common causes of severe long-term pain and physical disability, affecting hundreds of millions of people across the world and having a negative influence on the quality of life and industrial output, inflicting an enormous cost on health systems. The extent of the problem and its burden on patients and society can be illustrated by considering that joint diseases account for half of all chronic conditions in persons aged 65 and over. Back pain is the second leading cause of sick leave, and fractures related to osteoporosis have almost doubled in number in the last decade. It is estimated that 40% of all women over 50 years in age will suffer from an osteoporotic fracture. The clinical symptoms are pain and functional impairment that induce joint stiffness and dysfunction with subsequent impaired performances in daily living and at work. About 25% of patients cannot cope with daily activities, often resulting in depression and social isolation. In the European Union and the USA combined, over one million joint replacements are performed each year.



© Fig. 2

A focus area here is osteoarthritis. The main risk factors for osteoarthritis are age, obesity and joint traumata where the limited repair capacity of articular cartilage is a confounding factor. The diagnosis of osteoarthritis in the late stage by symptoms is obvious but the challenge for the future is to provide early, pre-symptomatic diagnosis by the use of biomarkers or by novel imaging techniques. Molecular imaging should focus on methods to visualise disease progression and monitor therapy in vivo.

Osteoarthritis and osteochondrosis induce a severe process of inflammation, which results in a dramatic increase in the degenerative processes. Nano-assisted regenerative medicine treatments of osteoarthritis could include disease modifying therapies with bioactive molecules coupled to biomaterials based on nanostructures locally implanted in the area of injury or a systemic targeted approach, both aiming at recruiting, attracting and stimulating local stem cells for local repair or anabolic actions. Cell-based therapies could involve the delivery of a universal donor stem cell line alone or in combination with a biomaterial to modulate the immune system and inhibit inflammation. Other treatments could be the delivery of nanoparticles that selectively attach to stem cell niches and release local stimulating factors. Together with anti-inflammatory drugs this treatment might allow repair of articular cartilage and regain homeostasis within the joint.

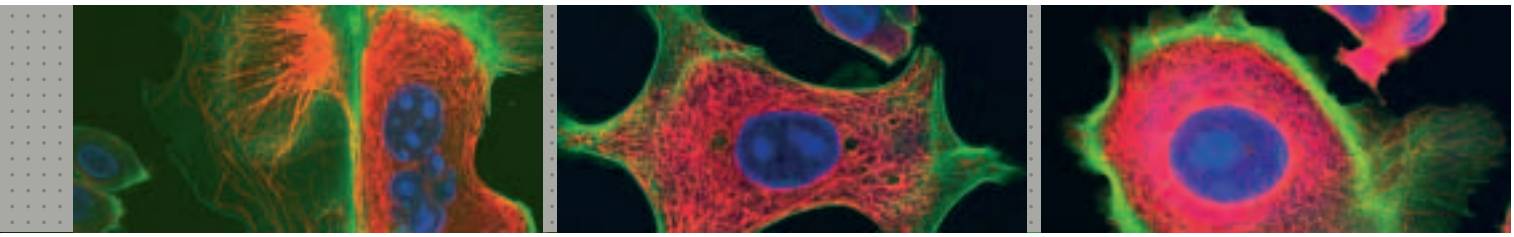
Both arthritis and diabetic nephropathy are thought to be ultimately a consequence of modern European life-style. It is expected that treatments for these diseases may well impact other inflammatory diseases such as Crohn's disease and psoriasis. At present, nanomedicines for these diseases are under research, but there is significant scope for improvement in the quality of life for patients and to improve the availability of these drugs.

1.3.4. Neurodegenerative Diseases and Psychiatric Conditions

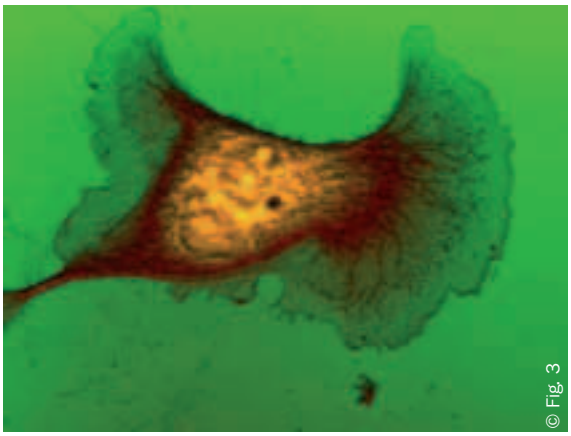
Age-associated neurodegenerative conditions like Alzheimer's and Parkinson's disease will strongly increase in prevalence over the next decade due to changing demographics. Neurodegenerative diseases come with a diminution in quality of life, while necessary patient care puts a financial and social burden on society. Three aspects make this disease area particularly challenging for healthcare: the diseases are slowly progressing and difficult to detect, responsiveness to therapy strongly depends on the individual patient and often needs to be personalised, and all present and future medication will have to cross the blood brain barrier. The latter imposes in a literal sense a barrier to early diagnostic and new medication.

Nanomedical research in this area should tackle the above ambitious challenges. In particular, new types of nanoagents may be transported through the blood brain barrier. Regenerative medicine holds the remarkable promise to not only treat symptoms but also restore neural functionality. The challenge is to convert this to a reality.

Also here, in vitro detection of disease specific biomarkers may hold the answer to early diagnosis of degenerative conditions, preventing irreversible damage of neural tissue. Imaging tracers that pass the blood brain barrier could indicate the status of the brain tissue and the



expression level of neuro-receptors in the brain. The distribution and metabolism of relevant body-immanent neurotransmitters could be monitored in vivo for this purpose. Secondly finding the correct drug and its dosing to treat a psychiatric condition often relies a good deal on trial-and-error today. This is well illustrated by the example of depression where there is a growing assortment of anti-depressives. However, it often needs many trials of several weeks each until the symptoms of an individual patient can be assessed; and about 25% of the patients show no benefit. Improved positron emission tomography of the brain could allow an earlier recognition of patients, who don't respond to a certain medication. Getting more information about the patient's individual response by imaging in connection with genomic and proteomic analysis, opens the long-term opportunity to a treatment tuned to the individual patient's needs. Furthermore, the very same methods could clarify the underlying specific defect mechanisms of several neurodegenerative and psychiatric conditions, which manifest with the same symptoms.



© Fig. 3

The blood brain barrier usually prohibits brain uptake of larger molecules, which excludes many potential drugs for neurodegenerative or psychiatric conditions. Nanocarriers with special surface properties may offer new and efficient options to carry a therapeutic payload through the blood brain barrier. For severe cases, brain implantable devices are conceivable which release the drug over extended periods of time, or stimulate specific regions of the brain electrically. Here, miniaturisation and biocompatibility of the device are crucial challenges that may be effectively addressed by nanotechnology.

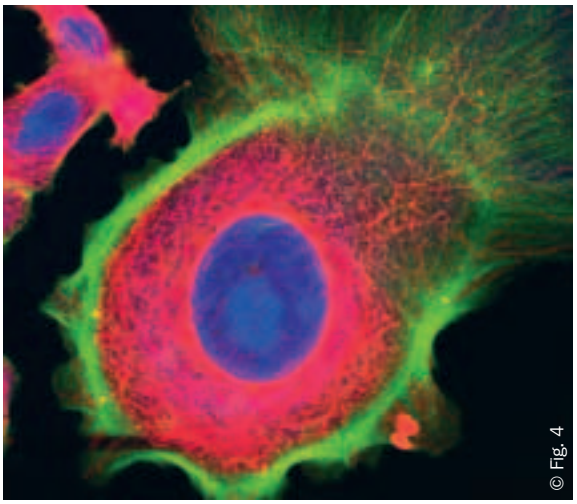
Regenerative medicine has enormous potential for neuro-degenerative conditions, an area where there is no therapy available that reverses or cures the disease. Treating the symptoms and slowing down further degeneration is often all that can be achieved today. Recent findings have shown that adult stem cells can be retrieved from many kinds of human tissue and in various differentiation stages, and that they can be controlled in vitro to de-differentiate or differentiate into many types of cells, including neuronal cells, precursor cells, and sensory cells. There are several disorders related to the central nervous system, which would benefit tremendously from safe and affordable therapeutic strategies to regenerate tissue. Some major disorders of the central nervous system are characterised by the malfunctioning of specific types of cells, and subsequent reduction of inter alia the level of neurotransmitters being secreted. A therapy for advanced stages of these diseases would consist of regenerating cells secreting certain proteins or metabolites in order to keep surrounding tissue functional. In addition, it would require inhibition of those factors that had killed the cells prior to treatment – factors, which today are unknown in most cases – or protective measures for the regenerated cells, including absorbing matrices, or matrices, including enzymes to degrade those factors, or modified cells expressing protective factors. The ultimate goal would be to carry out the integration of the cells inside the human body to ensure that full integration, even in nerve tissue, takes place. However, earlier development steps would probably require partial expansion in vitro.

1.3.5. Diabetes

Diabetes presents an increasingly severe problem, with 48 million patients in Europe, with often serious side effects which require costly long-term medical care. It is the major cause of blindness in adults aged 20-74 years, and of renal dysfunction, where diabetes type 2 induces renal inflammation. Diabetes can result in heart infarcts and stroke, doubling the risk of myocardial infarction in men, and raising the risk fourfold in women. It is the leading cause of non-traumatic lower-extremity amputation (with more than 85% of diabetic foot amputations preceded by a chronic wound). Type 2 diabetes, from which approximately 90% of all diabetics suffer, is expected to increase in prevalence by 46% during 2000-2010, following the approximately five-fold increase since 1960. It is becoming increasingly common, partly because people are living longer, but the current epidemic of obesity and the prevalence of sedentary life-styles are driving a rapid increase in both children and adolescents worldwide. In early disease stages, many patients are asymptomatic. Therefore, diagnosis often occurs late or by chance. The typical patient had

diabetes type 2 for at least 4-7 years before diagnosis. The pathophysiological processes leading to complications are already active in 50% of all patients who are not yet diagnosed.

Early diagnosis of pre-diabetes type 2 offers both individual health and economic benefits, because many people with inadequate glucose tolerance can reduce their relative risk of progressing to diabetes by 58% by lifestyle changes, if diagnosed early enough. The disease has a polygenetic background, obesity promoting its occurrence in those genetically disposed. Nanomedicine has significant contributions to make here, providing rapid and effective in vitro diagnostic tests capable of detecting genes associated with diabetes type 2, and of assaying peptides, permitting differential diagnoses between various diabetes types. Since some genes responsible for type 2 diabetes can be detected already, using commercially available assays, progress here could be quite rapid.



© Fig. 4

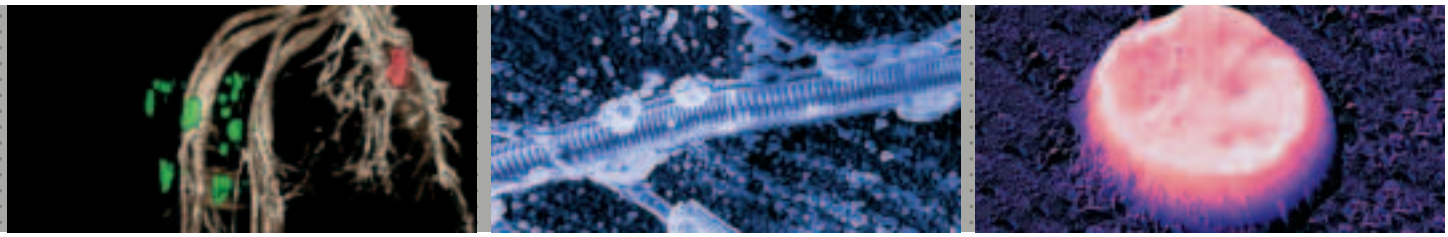
The need for daily injections and blood measurements worsens compliance in millions of patients, promoting earlier appearance of the devastating and costly complications. The development of a glucose sensor that allows non-invasive monitoring of the blood glucose level is one of the important clinical needs to improve patient compliance. The development and clinical introduction of better application forms, both for insulin and also for the newly-developed incretin agents, is therefore urgent. Non-parenteral formulations of nanoparticles containing insulin, designed to cross physiological barriers and to release the insulin in the bloodstream are becoming possible, and should be extended to the newly available therapeutic agents as soon as possible. Nanotechnology should also improve on this by developing non-injectable forms of drug-bearing nanoparticles capable of feedback-modulated release of therapeutic agents to control glucose homeostasis according to the current physiological needs of the patient.

Regenerative medicine will be crucial in achieving the ultimate goal in diabetes treatment- i.e. to free diabetic patients from the need to inject insulin. While conventional medication serves purely a disease management, regenerative medicine may actually allow restoring endogenous insulin production by providing stem-cell-based therapeutic modalities capable of conserving and rebuilding pancreatic islets. A breakthrough in this technology may finally provide curative therapies for both type 1 and type 2 diabetes. In addition, regenerative medicine therapeutic strategies could also play a significant role in the management of the most serious and complex complication of diabetes by providing therapies with intelligent nanostructured biomaterials releasing bioactive molecules with the purpose of efficient healing of diabetic foot ulcers.

1.3.6. Bacterial and Viral Infectious Diseases

Worldwide, various bacterial and viral infections add up to being one of the most common causes of death. In general, infectious diseases are more prevalent in the poor and less developed countries. The most threatening diseases are HIV, tuberculosis, malaria and influenza. In 2001, HIV, tuberculosis and malaria claimed together 5.7 million lives, with 90% and more in less developed countries. The recent threat of the avian influenza virus to become a highly infectious human disease demonstrated that infectious diseases still impose a severe global health risk. In western countries, the extensive use of antibiotics has generated a problem as many bacteria develop resistance. Not diagnosed or treated with alternative antibiotics in time, the patient can enter into septic shock. Currently, an increasing number of deaths due to infection by antibiotic resistant bacteria-strains can be observed in many western countries.

Nanotechnology research should focus on new diagnostic tools that allow a rapid identification of the underlying cause of infection. These diagnostic tests need to be affordable for third world countries and should be easy to use. One example here is a rapid and reliable sputum smear test to diagnose tuberculosis. Another example is the need for a rapid diagnosis of the bacterial strain responsible for an infection. Subsequently, dedicated antibiotics can be prescribed for a more effective treatment.



Nanotechnology may in the first instance not come up with novel, more effective drugs; however, it may certainly help to administer vaccines or current drugs in a more effective way.

1.4. Outlook

Nanomedicine will be important to improve healthcare in all phases of the care process. New in vitro diagnostic tests will shift diagnosis to an earlier stage, hopefully before symptoms really develop and allow pre-emptive therapeutic measures. in vivo diagnosis will become more sensitive and precise thanks to new imaging techniques and nano-sized targeted agents. Therapy as well could be greatly improved in efficacy by new systems that allow targeted delivery of therapeutic agents to the diseased site, ideally avoiding conventional parenteral delivery. Regenerative medicine may provide a therapeutic solution to revitalise tissue or organs, which may make life-long medication unnecessary.

While the diseases vary in their pathways, and often demand very different levels of maturity from the proposed technologies, they also share some common clinical needs. Those activities which could be applied broadly should have top priority. For example, in all diseases new in vitro diagnostic tests are generally required that allow rapid, sensitive and reliable detection of a broad set of disease indicative biomarkers. The discovery of disease-specific biomarkers itself is beyond the scope of nanomedicine and should be the focus of medical research. Following the same line of thought, research on multi-tasking agents for in vivo use and aspects of regenerative medicine that could offer broad applications in different diseases should be supported. Additionally, research is needed on clinical needs, which are specific to one disease. For example, the clinical need for non-invasive measurement of blood glucose levels or the need for agents that cross the blood brain barrier are unique aspects to diabetes and neurodegenerative diseases respectively.

Seamlessly connecting Diagnostics, Targeted Delivery and Regenerative Medicine

Diagnostics, targeted delivery and regenerative medicine constitute the core disciplines of nanomedicine. The European Technology Platform on NanoMedicine acknowledges and wishes to actively support research at the interface between its three science areas. It is committed to supporting such activities as theranostics, where nanotechnology will enable diagnostic devices and therapeutics to be combined for a real benefit to patients.

2. Technology Development driven by Healthcare Needs

Technologies for Therapeutic Benefits

This Strategic Research Agenda addresses a choice of diseases, selected by their impact on patients, their prevalence and burden to society, and by the expected beneficial impact nanomedicine is likely to have on them in the near future.

Consideration has been given to the prospects from more conventional approaches as well as the industrial progress made to date with nanomedicines. All three research areas – diagnostics, targeted delivery and regenerative medicine – have different priorities on different diseases but they can significantly impact virtually all of the chosen disease areas.

2.1. Nanotechnology based Diagnostics and Imaging

2.1.1. Introduction

The application of micro- and nanobiotechnology in medical diagnostics can be subdivided into three areas: in vitro diagnostics, in vivo diagnostics and medical devices. The development of these applications relies on a common ground of enabling technologies.

The basis of modern medicine was laid already in the middle of the 19th century by the recognition that the cell is the source of health and disease. It followed that basic research to provide a better understanding of the highly complex working of cells is mandatory for medicine. Therefore, the improvement and combination of methods to characterise cells or cell compartments in vitro (like novel optical and luminescence microscopy, scanning probe microscopy, electron microscopy and imaging mass-spectrometry) will be of importance for nanomedicine.

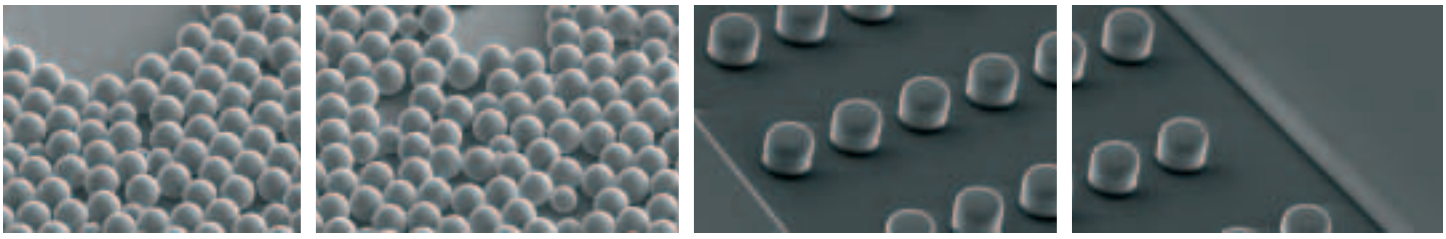
In vitro diagnosis for medical applications has traditionally been a laborious task. Blood and other body fluids or tissue samples are sent to a laboratory for analysis, which could take hours, days or weeks, and could be highly labour intensive. Steadily, miniaturisation, parallelisation and integration of different functions on a single device, based on techniques derived from the electronics industry, have led to the development of a new generation of devices that are smaller, faster and cheaper, do not require special skills, and provide accurate readings. These analytical devices require much smaller samples and will deliver more complete and more accurate biological data from a single measurement.

The requirement for smaller samples also means less invasive and traumatic methods of sample extraction. Nanotechnology enables further refinement of diagnostic techniques, leading to high throughput screening (to test one sample for numerous diseases, or screen large numbers of samples for one disease) and ultimately point-of-care diagnostics. These technological advancements pave the way towards major changes in the way drugs can be prescribed in future, by enabling “personalised” medicine tailored to individual needs.

Many new in vitro techniques initially developed for medical testing often find diverse applications in other important areas later, such as in environmental monitoring and security.

Medical imaging has advanced from a marginal role in healthcare to become an essential tool of diagnostics over the last 25 years. Molecular imaging and image-guided therapy are now basic tools for monitoring disease and in developing almost all the applications of in vivo nanomedicine. Originally, imaging techniques could only detect changes in the appearance of tissues when the symptoms were relatively advanced. Later, contrast agents were introduced to more easily identify and map the locus of disease. Today, through improved positron emission tomography, the advanced applications of magnetic resonance techniques and the application of nanotechnology both imaging tools and marker/contrast-agents are being refined towards the goals of detecting disease as early as possible. Ultimately this will occur at the level of a single cell, combined with monitoring the effectiveness of therapy.

Molecular imaging has had a late start in Europe. One of the challenges has been to define research partnerships



between the imaging industry and the contrast agent industry, which bring complementing competencies to the table.

The convergence of nanotechnology and medical imaging opens the doors to a revolution in molecular imaging (also called nano-imaging) in the foreseeable future, leading to the detection of a single molecule or a single cell in a complex biological environment.

2.1.2. In Vitro Applications

An in vitro diagnostic tool can be a single chemo- or biosensor, or an integrated device containing many sensors. A sensor contains an element, capable of recognising and 'signalling' through some biochemical change, the presence, activity or concentration of a specific molecule of biological importance in solution. A transducer is used to convert the biochemical signal into a quantifiable signal. Key attributes of theses types of sensors are their specificity, sensitivity, and robustness.

Techniques derived from the electronics industry have made possible the miniaturisation of sensors, allowing for smaller samples and highly integrated sensor arrays, which take different measurements in parallel from a single sample. Higher sensitivity and specificity reduce the invasiveness of the diagnostic tools and simultaneously increase their effectiveness significantly in terms of providing biological information such as phenotypes, genotypes or proteomes. Several complex preparation and analytical steps can be incorporated into “lab-on-a-chip” devices, which can mix, process and separate fluids before carrying out sample identification and quantification. Integrated devices can measure tens to thousands of signals from one sample, thus providing the general practitioner or the surgeon with much more extensive data from the patient's sample. Some nanobio-devices for diagnostics have been developed to measure parts of the genome or proteome using DNA fragments or antibodies as sensing elements and are thus called gene or protein chips. “Cells-on-chips” use cells as their sensing elements, employed in many cases for pathogen or toxicology screening.

A range of microscopic and spectroscopic methods is used for analysing ex vivo the biological samples. Optical, near field or electron microscopies are the most usual ones. Nanoanalytical tools like scanning probe microscopy, imaging mass spectrometry, and advanced ultrasound technologies offer new opportunities for in vitro diagnostics, like molecular pathology or reading highly integrated ultra-sensitive biochips.

2.1.3. In Vivo Imaging

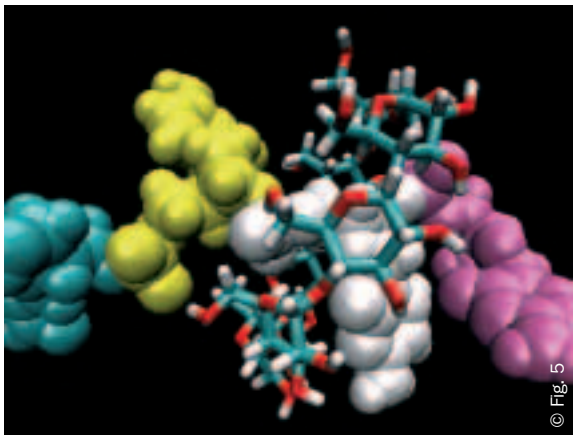
In vivo diagnostics refers in general to imaging techniques, but also covers implantable devices. Nano-imaging or molecular imaging includes techniques for the study of molecular events in vivo and for molecule manipulation. The main benefits of molecular imaging for in vivo diagnostics are the early detection of diseases and the monitoring of disease stages (e.g. in cancer metastasis), leading to individualised medicine and real-time assessment of therapeutic and surgical efficacy.

Imaging techniques cover advanced optical and luminescence imaging and spectroscopy, nuclear imaging with radioactive tracers, magnetic resonance imaging and spectroscopy, ultrasound, and X-ray imaging, most of which depend on targeting agents or contrast agents that have been introduced into the body to mark the disease site. In vivo molecular diagnostics performed by improved positron emission tomography (quantitative-PET) and by advanced applications of magnetic resonance techniques such as magnetic resonance spectroscopy (MRS), magnetic resonance spectroscopic imaging (MRSI), diffusion spectroscopy (d-MRI) and functional magnetic resonance (f-MRI) have made it possible to study human biochemical processes in different organs in vivo, opening up new horizons in instrumental diagnostic medicine.

However, in order to avoid potential problems regarding toxicity and patient safety, label-free techniques like optical nano-imaging methods offer interesting alternatives. This holds true especially when exploiting their capabilities for quantitative measurement in functional (imaging) analysis and quality assessment of tissue engineered implants or self-repaired tissue in regenerative medicine.

Targeted molecular imaging is important for a wide range of diagnostic purposes, such as the identification of the locus of inflammation, the visualisation of vascular structures or specific disease states and the examination of anatomy. It is also important for research on controlled drug release, in assessing the distribution of a drug, and for the early detection of unexpected and potentially dangerous drug accumulations. The ability to trace the distribution of a drug leads to the possibility of activating it only where needed, thus reducing the potential for toxicity (see chapter on targeted delivery). Nano-imaging is also expected to bring a real improvement in the monitoring of therapy thus providing direct feedback to the physician.

A wide range of particles or molecules is currently used for medical imaging. Some recent developments in optical imaging focus on using nanoparticles as tracers or contrast agents. Fluorescent nanoparticles such as quantum dots and dye-doped silica nanoparticles are systems that, depending on their coating and their physical and chemical properties, can target a specific tissue or cell. Their fluorescence can easily be tuned for specific imaging purposes. They offer a more intense fluorescent light emission, longer fluorescence lifetimes and a much broader spectrum of colours than conventional fluorophores. They are expected to be particularly useful for imaging in living tissues, where scattering can obscure signals. Toxicological studies are underway to precisely study their impact on humans, animals and the environment. New developments are focusing on the nanoparticle coating, to improve its efficiency of targeting and biocompatibility. Other agents are based on liposomes, emulsions, dendrimers or other macromolecular constructs.


© Fig. 5

Besides the use of nano-agents for in vivo imaging of molecules or cells, the use of nanoscale agents for diagnosis and manipulation may lead to an improvement of surgical techniques in the clinic. This may be achieved, for example, through a better mapping of cancer distribution using near-infrared imaging and applying photothermal therapy or heat treatment, the characterisation and non-destructive removal of cells or tissue in a specific area, the tracking of specific cell types used in therapy, as well as the visualisation of bio-therapeutic agents.

2.1.4. Medical Devices

Integrated systems will deliver new functionalities that provide assistance during therapy. They will open up additional possibilities of treatment and on the monitoring and optimisation of medical treatment. These aids can be grouped into four blocks concerning innovative and minimally invasive surgery, heart assisting devices, drugs on demand and finally pain therapy and management.

Medical devices can be used in vitro or in vivo. In the latter case their development is aimed at minimising their invasiveness.

Nanotechnology has application in transfection devices for therapeutic uses. An example of a future application would be the development of devices that can cross biological barriers, like the blood-brain barrier, to deliver multiple therapeutic agents at high local concentrations directly to cancer cells and to their neighbouring tissues that play a critical role in the spread of the disease.

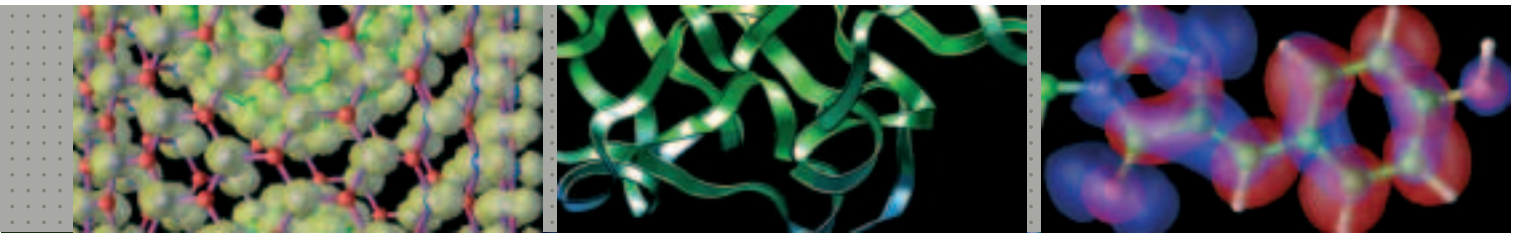
Nanotechnology also has many implications for in vivo diagnostic devices such as the swallowable imaging, diagnostic and therapeutic 'pill' and new endoscopic instruments. Monitoring of circulating molecules is also of great interest for some chronic diseases such as diabetes or HIV. Continuous, smart measurement of glucose or blood markers of infection constitutes a substantial market for implantable devices. Miniaturisation for lower invasiveness, combined with surface functionalisation and the 'biologicalisation' of instruments will help to increase their acceptance by the body. Minimally invasive image guided therapy using navigation technologies and advanced multi-modal imaging will improve accuracy and outcome of therapy. Autonomous power, self-diagnosis, remote control and external transmission of data are other considerations in the development of these devices.

Nanosensors, for example those used in catheters, will also provide data to surgeons making it possible to guide an interventional procedure with increased safety, less radiation and improved patient outcome. In addition, in vivo sensors can follow up important parameters as pressure or biological structures, which are essential for further follow up of the patient. Nanoscale entities could identify pathology/defects, and the subsequent removal or correction of lesions by nanomanipulation could also set a future vision.

2.1.5. Strategic Research Priorities

In Vitro Diagnostics

Within the next five years, the priority for improving in vitro diagnostics is designing integrated multifunctional devices with a broad range of applications. Nanotechnology is expected to enable fast, reliable, and user friendly diagnostic devices for a wide range of



pathologies. Nevertheless, centralised analytical laboratories require reliable, cheap, fast and multiplexed highly sensitive detectors providing high content results from a single sample, with fewer constraints in terms of miniaturisation. While the precise specifications will depend on the target users of the diagnostic devices, whether the analysis is centralised or decentralised, operated by the patient or by trained medical staff, the following are examples of envisaged improvements in the new generations of diagnostic devices:

- Pre-test non-destructive, minimally invasive or non-invasive sampling for biopsy material should be possible with painless collection of bio-samples usually from body fluids or tissue.
- Sample preparation should no longer be a bottleneck for routine applications of micro- and nanobio-diagnostic devices, based on integration of sample preparation with analysis devices, enabling secure and user friendly sample preparation by laboratory personnel.
- Improvements in micro- and nanofluidics should help achieve significant reductions in the volumes of biological samples and reagents, gaining speed in reaction times.
- Miniaturisation should deliver faster and more cost effective systems with higher performance in terms of resolution, sensitivity, specificity, reliability, robustness (stability of the analytical process in a single laboratory, independent of the laboratory personnel), reproducibility (from laboratory to laboratory) and integration (all operations in a single device).
- The detection process should enable multiplex analysis of a complete bio-pattern including genes, peptides, and small molecules in a complex, non-amplified and preferably unlabelled sample.
- A broad range of detection sensitivity is needed, such as for analysis of certain proteins that can occur over a wide concentration range.
- Diagnostic systems should be developed with fully integrated hardware and associated software. The hardware should enable remote data collection in a wireless environment and smart data processing needs to be addressed simultaneously in the development of coherent and reliable in vitro diagnostic devices.

E-health, data management, telemedicine, and networking rely on the acquisition, management, analysis and exchange of biotech/life science data and on the integration of this data with information from clinical sources. To determine which procedures and clinical protocols are most effective, it is crucial to understand the underlying relations and patterns in this collected data.

- Data-acquisition and -processing by micro- and nanobiosystems requires specific investment in data mining, data integration and data presentation.
- Tools are required for microarray analysis, both for gene expression levels and genotype analysis, to enable detection of new types of interactions and cell networking.
- Production of accurate, validated and calibrated quantitative results will require new specialised centres for data analysis and interpretation.
- The management of data from in vitro diagnostics should also be integrated with other analytical data of the patient coming from other instruments.

Modelling and computational tools are required to improve the design and manufacturing of devices with molecular constituents such as proteins and nucleic acids. Computer simulation represents a useful tool for technological investigation. Computer models of micro- and nano-biosystems are tuned for the identification of the fundamental characteristics of the processes. More potently, they allow quantitative tests of a given theory and also allow the reconstruction of a process on the basis of a set of responses to stimulations. In-silico tools should simulate the interaction between artificial and biological constituents.

In parallel to technological development, new diagnostic markers specific to diseases have to be identified so that in vitro diagnostic techniques can enable an earlier and personalised diagnosis for patients. Development of nanotechnology-based tools for recognising specific markers, will provide accurate diagnosis not only at an early disease stage, but also before onset of symptoms, where diagnosis is the first step in treating patients with the most appropriate therapeutic protocols.

In the case of diseases like Alzheimer's, where only limited therapy exists at present, a synergistic effort between the development of nanotechnology for diagnosis and research towards finding effective therapy is required. In that sense, adequate instruments are needed to initiate parallel R&D programs for research into successful therapeutic tools that are closely associated with the nanotechnology-based diagnosis research projects.

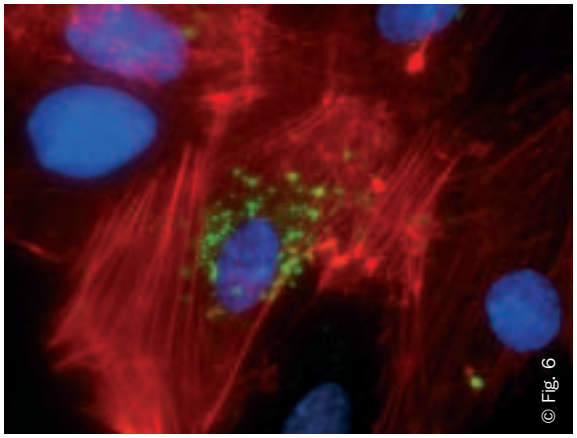
In Vitro Imaging

Better ex vivo imaging of biological samples could be achieved by nanotechnology-based enhancements of a range of techniques including:

- Optical, electron or X-ray microscopies

- Scanning probes/near field methods
- Hybrid microscopies like combinations of scanning probe/optics, scanning probe/force, magnetic manipulation and optical microscopy, vibrational and fluorescence imaging, scanning probe nanography and electrophysiology
- Combinations of the above with spectroscopies like spectrally resolved photo-acoustic imaging.

Investment in enabling basic science such as physics and engineering is needed to support this kind of technological development.



© Fig. 6

In Vivo Imaging

The ultimate objective of in vivo imaging is to get highly sensitive, highly reliable imaging techniques usable for diagnosis in personalised medicine for delivering drugs, following their distribution, and monitoring therapy. This concept is called theranostics (therapy and diagnostics), and is based on the "find, fight and follow" approach.

Research priorities for in vivo imaging should address simultaneously each step of the analytical process:

- The development of improved nanoprobes or of label-free detection
- The improvement of detection systems
- The analysis and the management of the acquired data.

Image guided intervention and therapy as well as metabolic imaging are also applications related to in vivo nanoimaging.

The expected improvements in detection systems focus on developing smaller, more efficient and cheaper cameras for whole body imaging, with multi-isotopes, and ideally multimodal detectors enabling imaging techniques that combine some of the following:

- Positron emission tomography
- Magnetic resonance imaging/spectroscopy
- Ultrasound
- Optics/biophotonics
- Photo-acoustic.

Existing detectors should also be improved with new architectures and materials.

New probes with enhanced capabilities and performance should be developed specific to micro- and nanoimaging techniques including:

- An ability to penetrate into cells
- The ability to crossover biological barriers like the blood-brain barrier
- Compatibility with external activation by magnetic field, radio frequency, ultrasound, X-ray, or optics to trigger the therapeutic activity
- Non-toxic
- Free from any immune or inflammatory response.

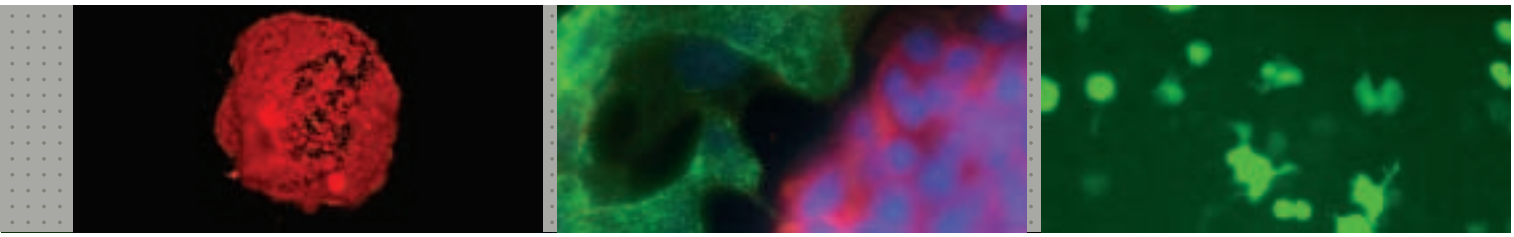
Therefore, ADME-Tox [1] studies of nano-probes will be most probably needed as for any new drug of this type. The development of multi-modal detectors requires specific multi-modal probes, which should be suitable for active drug release on the site of disease, and for reporting on the efficacy of the therapy. The required developments on particle design, on their surface functionalisation, and on adequate labelling techniques are more extensively elaborated in chapter 2.2 on targeted delivery.

Both the use of labels, and label-free imaging strategies based on physical properties are very promising for analysing in vivo target molecules, cells or tissues. In this respect, improvements in the following basic enabling technologies will benefit in vivo imaging:

- Magnetic resonance spectroscopy (MRS)
- Magnetic resonance spectroscopy imaging (MRSI)
- Diffusion spectroscopy (d-MRI)
- Functional magnetic resonance (f-MRI)
- Holography
- Coherent optics
- Auto-fluorescence
- Raman methods
- Coherent anti-Stokes Raman (CARS) methods
- Radio-frequency
- Measurement of small local temperature gradients.

With new detectors and smart probes, the last bottlenecks of in vivo imaging are signal acquisition, image analysis and data management. Thus remote transduction

1. ADME-Tox: Absorption, Distribution, Metabolism, Excretion and Toxicity (aspects of toxicity-testing are addressed in chapter 2.2 on targeted delivery in more detail).



of signals from detectors should be implemented. Efforts in 3D, 4D, and 5D reconstruction (multiple parameters) in 3D space and time, or real time intracellular tomography are needed to get a dynamic analysis of biological events. Of course, this would require computer aided detection and diagnosis for facilitating the extraction of information.

In general, the development of all new in vivo techniques will need better (small) animal models for translational research and adapted imaging techniques to be used on these animal models for a more accurate probe development. This need is valid in general for all new development of drugs as well (see chapter 2.2 on targeted delivery).

Medical Devices

Medical devices can be classified according to their invasiveness. Envisaged improvements from nanotechnology will yield enhanced:

- Catheters
- Endoscopes
- Needles for electro-stimulation
- Smart stents
- Gene or cell transfection systems
- Syringes for less traumatic sampling
- Local delivery of therapeutic agents
- On-line monitoring sensors for detection of circulating molecules with low concentration.

These minimally invasive instruments should get an ability to cross biological barriers like the blood-brain barrier or on the contrary prevent crossing of biological barriers.

By reducing the size of the active components or the components interacting with the biological samples, micro- and nanotechnologies are expected to bring real breakthroughs by revising some existing techniques, and by introducing some novel concepts for challenges such as:

- Improved instrumental biocompatibility (can be achieved with improved surface functionalisation)
- Sustainable power supply (can be achieved with energy provided by external sources)
- Remote control
- Self-diagnosis capacity.

Non-invasive medical devices like sensors for glucose monitoring, swallowable pills or surface electrodes could also benefit from miniaturisation and integration of several functions on a chip or on a device. Data acquisition and processing from these devices should be thought of in an integrated approach.

2.2 Targeted Delivery-Multi-Tasking Medicines

2.2.1 Introduction

This area deals with synthetic nanometre sized delivery systems for therapeutic agents, and biologically active drug products, consisting of at least two components, one of which is the active component. This application of nanotechnology encompasses not only delivery of pharmaceuticals or other therapeutic agents, but offers also utilities for diagnostics and regenerative medicine, areas where research is at an earlier stage.

Therapeutic systems in this class are larger than classical drugs like aspirin – up to a million times larger. Being larger there is more scope for diversity and complexity, which makes their description much more challenging and their delivery more difficult. Their increased complexity, however, gives these systems the unique power to tackle more challenging diseases. This steady increase in the complexity of technology has parallels in many other aspects of our daily life. These systems for diagnosis, targeted delivery, and regenerative medicine are capable of multi-tasking and can even combine roles such as diagnosis and therapy – leading to a new paradigm, theranostics.

It should be noted that, as with more conventional drugs, the timescale for developing new nanomedicines to the point where they are approved and marketed could be up to a decade. For society, patients, medical professionals, and regulatory bodies this timescale allows for changes in the regulatory process and for communication with the public and patients, to facilitate the growing of awareness, acceptance and patient adherence to these new therapeutic regimens. Targeted delivery is one of the most developed areas in nanomedicine with early products starting to reach the market; as such it is expected that this will be a significant growth area in the next decade.

2.2.2 Strategic Research Priorities

Moving Established and Novel Nano-Therapeutic Delivery Systems from the Laboratory to the Clinic

By virtue of their increased size targeted delivery systems are more complex, covering a much wider range of chemistries (and physics) than conventional drugs or biologicals. This drug class has been around for a decade but exploiting relatively simple chemistries. It is expected that more complex approaches will be explored; with the caveat that these will have to provide a real benefit for

the patient for them to get to the market. An early research focus should be moving the most advanced therapeutic modalities into the clinic. These include:

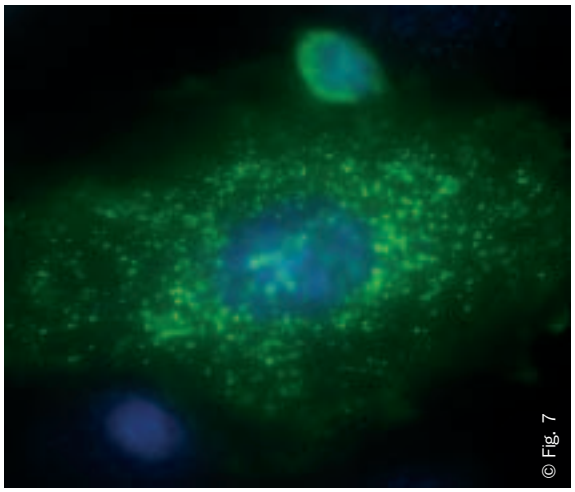
- Liposomes
- Micellular and micro-emulsion Systems
- Liquid crystal based formulations
- Nanocrystals
- Antibodies and conjugates
- Naturally occurring proteins as delivery systems
- Polymer conjugates and bio-conjugates based on the conjugation of polypeptides and polymers, which can be hierarchically self-assembled into well-defined tertiary and quaternary structures
- Biodegradable nanoparticles/nanocapsules. This includes systems, which dissemble in vivo for targeting or clearance
- Virus-like particles for gene delivery. These still present major problems in vivo but offer an alternative and probably longer term approach
- Delivery of small nucleic acids or mimetics
- Delivery of vaccines
- Synthetic biomimetics to induce physiological mechanisms, for example they may activate either immune stimulatory or immune regulatory cascades.

Besides development of approaches with a clear intrinsic therapeutic activity, targeted nano-delivery systems that facilitate other medical interventions should be subject of study, e.g., those that facilitate external radiotherapy planning, monitoring, and radioimmunotherapy that combines diagnostic and therapeutic potential.

Exploring the more novel nanomedicines should focus on measuring critically their efficacy and safety in vitro and in vivo as well as potential scale-up issues. These broadly include:

- Polymersomes based on the self-assembly of linear or highly branched hydrophilic-hydrophobic copolymers
- Prodrug therapy, in situ activation, self and/or covalent assembly of drugs in situ in vivo
- Activation of smart/responsive prodrugs (pH, light, temperature, metabolites/analytes, enzymes, protein interactions). Imaging of in vivo prodrug activation (prodrug-proprobe constructs)
- Systems that localise/image the agent followed by activation by an external source, e.g. targeted boron neutron capture therapy, guided photodynamic therapy, magnetotherapy
- Self-assembling systems, including host – guest systems.

Such systems have to be capable of taking major steps towards clinical application. To do so, such systems have to have appropriate DMPK (Drug Metabolism and Pharmaco-Kinetics) and toxicological properties and any pharmaceutics liabilities should be known. They should also have a realistic prospect of successful therapy in the chosen disease area, based on pre-clinical models including perhaps biomarker studies.



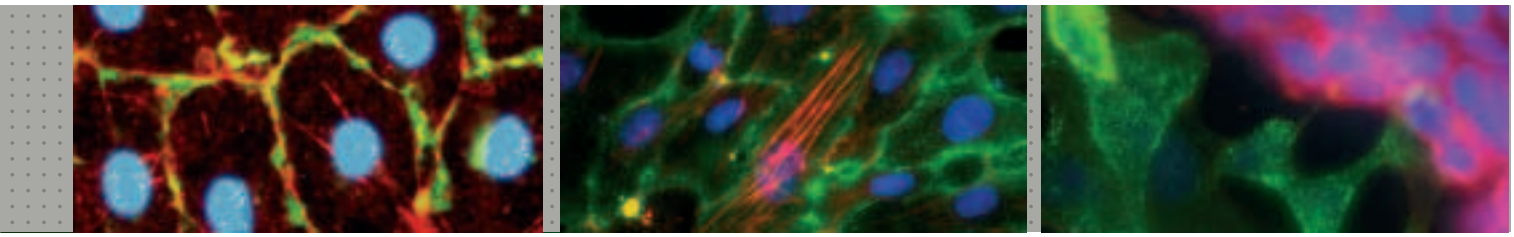
© Fig. 7

Improving Targeting Agents

Targeted delivery systems can have multiple functions, a key one is their ability to recognise specific molecules implicated in disease which can be located either in the membrane of target cells, or in specific compartments within the cell. Research efforts to enhance this function and particularly to reduce production costs are essential, if the benefits of this approach are to be available to all. The identification of such molecules can be rational design or by high throughput screening or even by a combination of the two.

Key research areas are:

- New types of targeting agents by rational design that uses structural knowledge of a docking interaction between two (bio)molecules
- New targeting agents arising from random, but high throughput methods, using active selection. Suitable approaches could be from chemistry or biology or hybrids
- Targeting to specific intracellular compartments
- Multi-target approaches, to deal with target cell heterogeneity and pharmacological target heterogeneity, aiming to increase efficacy
- New methodologies for the activation of prodrugs and smart agents in situ, in vivo drug assembly, pre-targeting, and in vivo chemistry.



Interactions between Biological Systems and Artificial Nanostructures

The potential of targeted delivery will only be realised with a much better understanding of how such structures interact with the body and its components – in vitro, ex vivo and in vivo. Very few studies are in the public domain on how potential nanomedicines are transported and eliminated in vivo, and what the possible serious consequences such as immunogenicity will mean for body homeostasis. Areas of priority are:

- Design of nanostructures with stealth properties that prevent them from being opsonised or cleared before reaching the target cells
- Fundamental studies on the interaction of nanostructures with plasma proteins and the relation between protein adsorption and removal of nanostructures from the circulation by the reticulo-endothelial system
- Absorption of nanostructures to cells (with emphasis on relation to the surface chemical characteristics, size and shape of the nanostructures)
- Uptake and recycling of nanostructures
- Trans-endocytosis of nanostructures
- Endosomal escape of nanostructures
- Safety evaluation. In vitro/in vivo cytotoxicity, haemocompatibility, immunogenicity and genotoxicity testing. Immunogenicity is an expensive function to evaluate in the clinic and other non-in vivo methodologies should be evaluated and validated, it is recognised that this is a challenging objective
- In vivo carrier biodistribution and degradation.

Pharmaceutics – Formulation and Stability

There are many basic problems associated with nanoparticles, before they can become therapeutic agents – such as removing their tendency to aggregate either during storage or under physiological conditions. Understanding and preventing aggregation of nano-scale therapeutic agents must be a top research priority before any development. Many diseases of the central nervous system are the result of protein-protein interactions (aggregation) and there may be useful spin-offs from this research. Complex delivery systems must be chemically analysable and stable over extended times to both covalent and non-covalent changes to be manufacturable. The importance of this area cannot be over emphasised as it is a major hurdle with many technical challenges.

Easier Routes of Administration – Crossing Biological Barriers

Most nanomedicines are currently administered parenterally, but both the market and patients would prefer other routes such as oral, pulmonary or transdermal. Getting such large molecules to cross biological barriers is challenging and requires an understanding of macromolecular transport. This is difficult, but perhaps less so than a decade ago and should be an objective of future research. Success would fundamentally change the way nanotechnology-based drugs were administered and perceived.

The oral route continues to be the most intensively studied one for drug administration. Priorities will be placed on the ability on nano-formulations to cross the gastrointestinal tract epithelium overcoming enzymatic and permeability barriers. Pulmonary delivery is another non-invasive method of delivery where priority should be focused on aerodynamic characterisation of delivery systems and their ability to deliver drugs with excellent bioavailability. There are several advantages in delivering drugs to the lungs. These include a non-invasive method of delivery, a large surface area for drug absorption and thin alveolar epithelium, permitting rapid absorption, and absence of first-pass metabolism.

The ability of delivery systems to cross the blood-brain barrier should also be assessed especially for some diseases of the central nervous system. Rational and high throughput screening methods for technologies to transport through biological barriers and target an entity to a specific location is perceived as an important issue. There is early data suggesting this could be a fruitful area.

The use of Nano-Devices for Targeted Delivery

Cutting across many therapeutic areas is the use of nano-devices for targeted delivery. Examples are nanoneedles with programmable injection regimes. Such alternative devices are important, as traditional methods of injection by a needle are much less popular with patients. Knowledge of microfluidics is also to be supported for such devices, which are described below.

To miniaturise pumps, including nanosensors to measure the actual concentration of the therapeutic agent in body fluids, combined with a delivery unit is an interesting concept. Delivery systems can also be a part of biomedical devices for implantation or tools for surgical use, e.g. endoscopy, cannulas, etc, are some examples which could provide a real benefit for the patient. Areas of priority are:

- Controlled release mechanisms – sustained or pulsatile

- Microelectromechanical systems (MEMS) in or more likely on the skin
- Temporal/sequential release of multiple drugs
- Gels, patches, sensor-pump systems, e.g. integrated glucose sensor and insulin release for diabetics
- Implantable biochips/microfluidics
- Nanosized devices or components on devices e.g. pill on a chip type technology
- Carriers for therapeutic agents, in particular advanced polymeric carriers. These have to contain sufficient amounts of the agent for a therapeutically useful effect; biocompatibility and solubility must be good.
- Smart carriers, such as polymersomes or liposomes that release drugs, induced by pH, temperature, light, local metabolite/analytes, enzyme action
- Physical stimuli, e.g. electric or ultrasonic, by external or implantable nanodevices to specific sites in organs to increase transiently the penetration of the released drugs into the intracellular compartment
- Nanodevices possessing a sensor for a specific metabolite/entity with a feedback action for drug release, e.g. glucose sensor and insulin release.

© Fig. 8

Manufacturing Improvements

The scale up and nanofabrication of nanomedicines, especially with respect to reducing healthcare costs for patients in Europe and the rest of the world is of central importance. Increased complexity often leads to increased costs and it is hoped that researchers will address this from the outset. Whilst extra complexity will add to overall cost of goods, it is hoped that higher potencies and targeting will counter-balance this increase. Reducing the cost of targeting entities is also important as discussed earlier.

The feasibility of manufacturing should be considered and explored from the outset in parallel with consideration of the specification, characterisation of the product and control of the process.

2.3. Regenerative Medicine

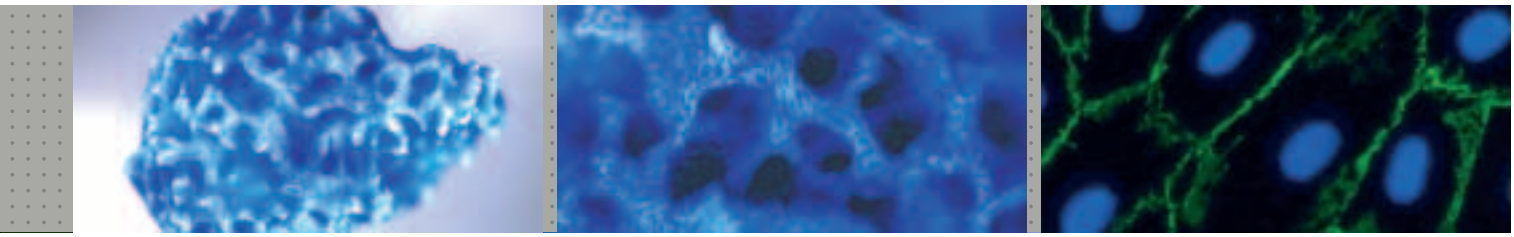
2.3.1. Introduction

Perhaps uniquely this area has the capability to radically change the way some diseases are managed in the future, as this is a new therapeutic modality in its infancy. The last decade has seen the rise of biological drugs and the start of nanomedicines coming onto the market. Regenerative medicine is a far reaching technology, and for the area to be commercialised, real and steady progress has to be seen. This section prioritises what is a large field with the need to take the technology to the patients as soon as possible.

By leveraging novel cell culture techniques and the design of bio-resorbable polymers, tissue engineering strategies have recently emerged as the most advanced therapeutic option presently available in regenerative medicine.

Tissue engineering encompasses the use of cells and their molecules in artificial constructs that compensate for lost or impaired body functions. It is based upon scaffold-guided tissue regeneration and involves the seeding of porous, biodegradable scaffolds with donor cells, which differentiate and mimic naturally occurring tissues. These tissue-engineered constructs are then implanted into the patient to replace diseased or damaged tissues. With time, the scaffolds are resorbed and replaced by host tissues that include viable blood supplies and nerves. Current clinical applications of tissue-engineered constructs include engineering of skin, cartilage and bone for autologous implantation. Recent advancement in therapeutic strategies involves tissue engineering and includes the use of adult stem cells as a source of regenerative cells, and the use of cell-signalling molecules as a source of molecular regeneration messengers.

The clinical availability of therapies based on tissue engineering represents a tremendous step forward in regenerative medicine. By building on the pioneering achievements of tissue engineering, advanced therapies in regenerative medicine can address even more challenging objectives – to initiate and control the regeneration of pathological tissue, and to treat, modify and prevent disabling chronic disorders such as osteoarthritis, diseases of the cardiovascular and central nervous system. Given the dynamics of Europe's societal growth and the need to provide advanced and cost-effective therapies for an ageing population, it is a further challenge for regenerative medicine to deliver the disease



modifying benefits of tissue-engineered products to a wide patient population. Thus, the vision for nano-assisted regenerative medicine is the development of cost-effective disease-modifying therapies for in situ tissue regeneration. The implementation of this approach involves not only a deeper understanding of the basic biology of tissue regeneration – wound healing, in its widest sense – but also the development of effective strategies and tools to initiate and control the regenerative process.

In the field of biomaterials and biotechnology, the term "biomimesis" has been established to describe the process of simulating what occurs in nature. The biomimetic philosophy can be condensed into three basic elements: intelligent biomaterials, bioactive signalling molecules and cells.

2.3.2. Intelligent Biomaterials and Smart Implants

Artificial biomaterial scaffolds designed to support cell and tissue growth have traditionally aimed, at a macroscopic level, to match the properties of the organs they are to replace without recreating the intricate and essential nanoscale detail observed in real organs. In the body, the nanoscale structure of the extra-cellular matrix provides a natural web of intricate nanofibers to support cells and present an instructive background to guide their behaviour. Unwinding the fibers of the extra-cellular matrix reveals a level of detail unmatched outside the biological world. Each hides clues that pave the way for cells to form tissue as complex as bone, liver, heart, and kidney. The ability to engineer materials to a similar level of complexity is fast becoming a reality.

Engineering extra-cellular matrix ligands, such as the RGD-sequence, into artificial surfaces enhances functionality in terms of cell behaviour.

Thus, intricate nanoscale engineering will enable the creation of more biomimetic cellular environments. Nanoscale alterations in topography elicit diverse cell behaviour, ranging from changes in cell adhesion, cell orientation, cell motility, surface antigen display, cytoskeletal condensation, activation of tyrosine kinases, and modulation of intracellular signalling pathways that regulate transcriptional activity and gene expression. Third-generation biomaterials that involve tailoring of resorbable polymers at the molecular level to elicit specific cellular responses show great promise as scaffolds or matrices in tissue regeneration. These "intelligent" biomaterials are designed to react to changes in the immediate environment and to stimulate specific cellular responses at the molecular level. Molecular modifications of resorbable polymer systems elicit specific interactions with cells and direct cell proliferation, differentiation and extracellular matrix production and organisation. For example, new generations of synthetic polymers are being developed which can change their molecular conformation in response to changes in temperature, pH, electrical, physical stimuli or energetic status.

Access to nanotechnology has offered a completely new perspective to the material scientist to mimic the different types of extra-cellular matrices present in tissues. Techniques are now available which can produce macromolecular structures of nanometer size, with finely controlled composition and architecture. Conventional polymer chemistry, combined with novel methodologies such as electrospinning, phase separation, direct patterning and self-assembly, have been used to manufacture a range of structures, such as nanofibers of different and well defined diameters and surface morphologies, nanofibrous and porous scaffolds, nanowires and nanocues, nanospheres, nano-"trees" (e.g. dendrimers), nano-composites and other macromolecular structures. Nanofibrous scaffolds can be developed allowing for integrated manufacturing of 3D nanofibre-matrices with high porosity, high special interconnectivity, and controlled alignment of fibres to direct cell orientation and migration.

Given the diversity of tissue-specific orientation of fibrils (parallel and aligned in tendon, concentric weaves in bone, orthogonal lattices in cornea, and mesh-like in skin), this latter feature is yet to be fully exploited. In addition, it is also possible to build mimics of cell membranes, which can imitate certain features of cell surfaces. The "biological" fine-tuning of these scaffolds toward particular cell types is of growing interest. Once challenges in materials design and solvent compatibility have been overcome, bioactive composite and core-shell fibres may be engineered to deliver growth factors, peptides, enzymes, drugs, and even DNA.

Nanotechnology also allows for improvement of non-resorbable biomaterials and effective manipulation of biological interactions at the nanometer level, which will dramatically increase the functionality and longevity of implanted materials. By applying bioactive nanoparticle coatings on the surface of implants, it will be possible to bond the implant more naturally to the adjoining tissue and significantly prolong the implant lifetime. Similarly,

it may be possible to surround implanted tissue with a nanofabricated barrier that would prevent activation of the rejection mechanisms of the host, allowing a wider utilisation of donated organs. Nanomaterials and/or nanocomposites with enhanced mechanical properties could replace the materials that undergo fatigue failure due to crack initiation and propagation during physiological loading conditions. Nanomaterials with enhanced electrical properties that remain functional for the duration of implantation could replace the conventional materials utilised for neural prostheses, whose performance deteriorates over time. Third-generation bioactive glasses and macroporous foams can be designed to activate genes that stimulate regeneration of living tissues. Nano and micro engineered biocompatible membranes may be used e.g. for cell seeding, cell growth or cell encapsulation. By understanding the fundamental contractile and propulsive properties of tissues, biomaterials can be fabricated that will have nanometer-scale patterns representing the imprinted features of specific proteins. Biomimetic membranes can provide cell specific adhesion sites (integrins) for cells and incorporation of membrane-bound, cell signalling molecules can potentially be stimuli for specific proliferation of adhered cells. Finally, nanotechnology has enabled the development of a new generation of so-called nanowire sensors functionalised with specific receptor layers, capable of monitoring the presence of e.g. small organic molecules, proteins, cancer cells, viruses, etc. - the advantage of these sensors is that they offer direct, real time measurement of captured ligands and are therefore well suited for use as a sensor device inside a small implant.

© Fig. 9

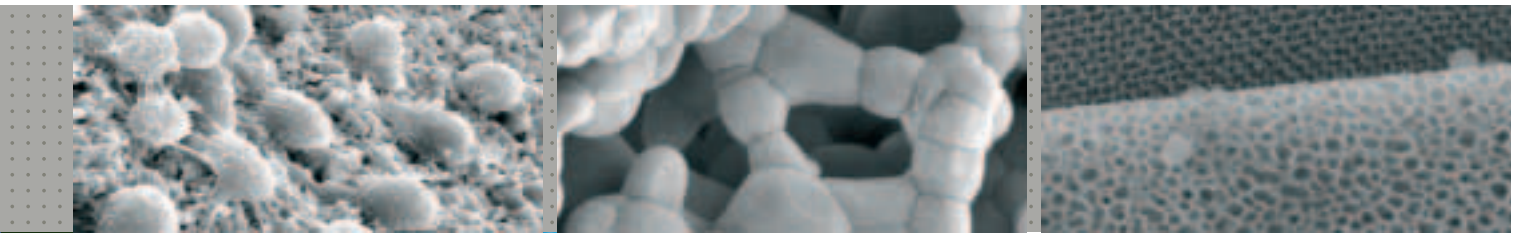
In conclusion, nanotechnology can assist in the development of biomimetic, intelligent biomaterials, which are designed to positively react to changes in their immediate environment and stimulate specific regenerative events at the molecular level. Advances in the areas of fundamental matrix biology, nanofabrication, synthetic molecular self-assembly, recombinant DNA technologies, and printing technologies will enable the generation of materials that can provide enhanced 3D tissue context maps of molecular and structural information.

2.3.3. Bioactive Signalling Molecules

Bioactive signalling molecules are defined as those molecules, which are naturally present in cells (cytokines, growth factors, receptors, second messengers) and trigger regenerative events at the cellular level. Recently available therapies based on signalling molecules involve the uncontrolled delivery of a single growth factor. This is an obvious oversimplification, in light of the complexities associated with the healing cascades of living tissues, especially in chronic pathologies. Sequential signalling is obligatory in the fabrication and repair of tissues. Therefore, the development of technologies for the sequential delivery of proteins, peptides and genes is crucial.

The provision of the correct bioactive signalling molecules to initiate and direct the regenerative process is being pursued, by designing bioactive materials containing biological signals able to trigger biological events. The primary goal is to develop extracellular, matrix-like materials, by either combining natural polymers or developing structures starting from synthetic molecules combined with matricellular cues. By immobilising specific proteins, peptides and other biomolecules onto a material, it is possible to mimic the extracellular matrix environment and provide a multifunctional cell-adhesive surface. Cell-specific recognition factors can be incorporated into the resorbable polymer surface, including the adhesive proteins, fibronectin or functional domains of extra-cellular matrix components. Polymer surfaces can be tailored with proteins that influence interactions with endothelium, synaptic development and neurite stimulation. These surfaces would also create reservoirs absorbing and releasing cytokines produced by cells in the neighbourhood, mimicking one of the roles of various glycostructures within the extra-cellular matrix.

To achieve any advance it is essential to understand those molecular interactions that lead to regenerative pathways and the development of technologies for the sequential delivery of proteins, peptides and genes to mimic the signalling cascade. The use of nanotechnologies is advocated in assisting in the development of therapies involving the activation and spatio-temporal control of in vivo tissue regeneration.



Bioactive molecules as therapeutic agents could be incorporated in the degradable tailored scaffolds to be delivered in a controlled manner. In addition, bioactive signalling may also be effected by biomimetics capable of modulating body systems through the interaction with specific cells and receptors. Such biomimetics are designed to induce physiological mechanisms, for example they may activate either immune stimulatory or immune regulatory cascades.

Finally, drug and gene delivery methodologies could be coupled to provide in a temporal and spatial manner the physiological concentrations of signalling molecules required for tissue regeneration. Incorporation of such systems into the biomaterial scaffold, whether permanent or biodegradable, will be essential for clinical success.

In conclusion, nano-assisted technologies will enable the development of bioactive materials which release signalling molecules at controlled rates by diffusion or network breakdown that in turn activate the cells in contact with the stimuli. The cells then produce additional growth factors that will stimulate multiple generations of growing cells to self-assemble into the required tissues in situ.

2.3.4. Cell Based Therapies

Cellular differentiation occurs in mammals as part of the embryological development and continues in adult life as part of the normal cell turnover or repair following injury. Growth, from the cellular aspect, means a continuous process of cellular turnover that is dependent on the presence of self-renewing tissue stem cells that give rise to progenitor and mature cells. Cellular turnover is known to be fast in certain tissues, such as intestinal epithelium, blood and epidermis, and slow in others, such as bone and cartilage, while it has been considered limited or non-existent in tissues such as the brain and the heart. However, scientific results in recent years have radically changed the view of the ability of even these tissues to regenerate after ischemic injury. This paradigm shift has refocused research into the understanding of mechanisms for stem cell recruitment, activation, control and homing.

The major goal of ongoing and future efforts in regenerative medicine will be to effectively exploit the enormous newly discovered self-repair potential that has been observed in adult stem cells. Given the logistical complexities and the costs associated with today's tissue engineering therapies, which are based on the autologous reimplantation of culture-expanded differentiated cells, next generation therapies will need to build on the progress made with tissue engineering in understanding the huge potential for cell-based therapies which involve undifferentiated cells. Nanotechnology will aid in pursuing two main objectives: 1. identifying signalling systems in order to leverage the self-healing potential of endogenous adult stem cells, and 2. developing efficient targeting systems for adult stem cell therapies.

One possible application for future regenerative medicine strategies is to avoid having to pre-seed a nanostructured biomaterial scaffold or matrix with the patient's own cells, but rather to have the biomaterials loaded with essential signalling molecules targeting adult progenitor cells in the implant site. Thus, how adult human stem cells react to such nanostructures depending on the site of tissue regeneration will be a conditio sine qua non for specific applications.

The fulfilment of these visions will require better knowledge of the localisation and identity of adult stem cell niches for each specific tissue. This includes knowledge of cell isolation and culture techniques, the identification of critical signalling mechanisms suitable for drug targets as well as the identification of critical surface markers that could be potential targets for loaded nanoparticles or particles aimed for local stem cell niche imaging.

In conclusion, cell-based therapies should be aimed at the efficient harvesting of adult stem cells, to allow for a brief pre-implantation, cultivation stage, or, preferably, for immediate intra-operative administration using an intelligent biomaterial as a bio-interactive delivery vehicle. Of huge impact would also be the ability to implant cell-free, intelligent, bioactive materials that would effectively provide signalling to leverage the self-healing potential of the patient's own stem cells.

2.3.5. Strategic Research Priorities

The available scientific knowledge and technological platform offer a unique opportunity to create regenerative medicine products and procedures capable of dramatically improving patients' mortality and morbidity caused by major diseases.

Careful analysis of regenerative medicine leads to the conclusion that much basic and applied research must be undertaken, not only in developmental biology and stem cell research, but also in the field of biomaterials. As numerous European groups are amongst the world leaders in biomaterials and cell therapies, there are great

opportunities here for European small and middle-sized enterprises, in particular. This is an emerging market sector where the European Research Area can gain prestige and an early share of the world market in the development, production and marketing of such "intelligent" biomaterials.

Thanks to nanotechnology, a cellular and molecular basis has been established for the development of third-generation biomaterials that will provide the scientific foundation for the design of scaffolds for tissue engineering, and for in situ tissue regeneration and repair, needing only minimally-invasive surgery. It is strongly recommended that future planning policy, attention and resources should be focused on developing these biomaterials.

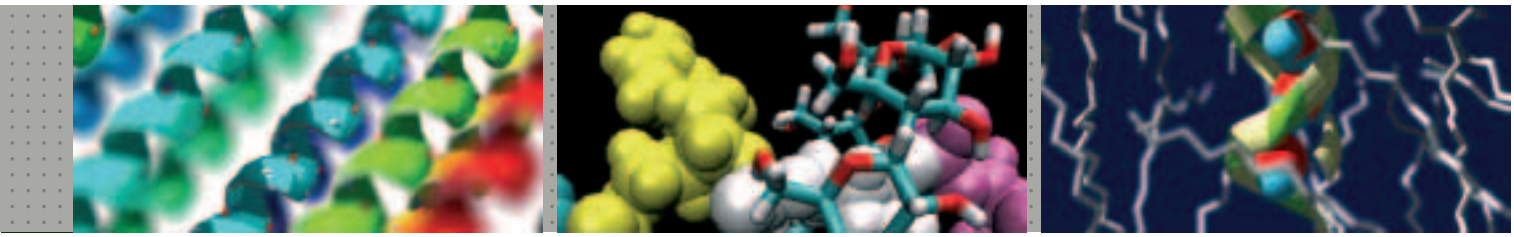
Projects will also need to be highly focused towards clearly identified clinical applications, not being confined to basic research on the optimisation of generic cell/artificial matrix constructs. They must be rooted in the specific characteristics of the tissue to be regenerated, and in the economic advantage of one approach over another.

Emphasis should be given to projects designed with the objective of developing disease-modifying, cost-effective treatments for chronic disabilities that mostly affect the elderly, such as osteoarthritis, cardiovascular and central nervous system degenerative disorders.

The following is a list of recommended research topics in nano-assisted regenerative medicine:

Intelligent Biomaterials and Smart Implants

- Design, production and characterisation of intelligent biomaterials with topographically and chemically patterned bioactive surfaces which are biodegradable with adjustable degradation rates
- Design, production and characterisation of a new generation of gene-activating biomaterials tailored for specific patients and disease states
- Design, production and characterisation of intelligent, multi-functional, and time-programmed biomaterials. These smart biomaterials should guide cellular and tissue growth, deliver morphogenic factors or cells and provide the temporary or permanent mechanical support of a damaged tissue or organ
- Control of the topographic and chemical structure of materials at the micro – and nanoscale – mandatory in the design of intelligent scaffolds for ex vivo and in situ tissue engineering. This will also require research in the fields of micro- and nanofabrication for the creation of structures that differentially control cell adhesion, and orientation, proliferation and function. Research on modalities to promote and control angiogenesis will also be relevant
- Design and production of intelligent biomaterials that have the ability to attract stem cells in situ, followed by their differentiation to the desired tissue type
- Biomimetic membranes with built-in functionality, which can mimic real cell membranes for (stem) cell attachment and/or stimulation (proliferation, differentiation)
- Technologies for the development of new generations of synthetic polymers that can change their molecular conformation in response to changes in external stimuli (mechanical, temperature, pH, electric field or energetic status)
- Technologies for the development of bioactive nano-structured coatings
- Projects which include electronic and/or communication components in forms of nanowires and nanopores (or their equivalents) for the stimulation and biosensing of cells within an artificial matrix
- Sensor technology for the assessment of the interface activity and the progress of implant integration and functional state
- Sensors for precise gene activation and control during cell and tissue growth
- Development of appropriate sensor technologies to be developed for in vitro and in vivo use
- Development of regenerative medicine strategies to target the central nervous system and cardiac tissues under conditions of transient or chronic, emerging or lasting oxygen deficiency
- Control of donor-receptor-incompatibilities and implant rejection-development of immunomodulatory technologies
- Control of implant associated infection
- Nano-assembling biomaterials capable of forming in situ a micro-architecture and biochemistry similar to the extracellular matrix of several tissues
- Induction of dedifferentiation and differentiation processes in situ by biomaterial, "helper cells", and intelligent implants.



Bioactive Signalling Molecules

- Design, synthesis and characterisation of extracellular-matrix analogues
- Identification, design, synthesis and characterisation of bioactive signalling factors
- Identification, design, synthesis and characterisation of small molecules triggering stem cell recruitment and activation
- Novel technologies that enable the development of biomaterials for the sequential delivery of actives and/or chemo-attractants for the triggering of endogenous self-repair mechanisms
- Technologies for controlled release of stem cell signalling factors
- In vitro and in vivo toxicity testing of engineered nanoparticles
- Application of nanotechnologies to promote rapid vascularisation in targeted tissues
- Incorporation of drug and gene delivery systems into biomaterial scaffolds
- Biodegradable biomaterials where the by-products are bioactive agents
- Alternative bioactive molecules (e.g. plant bioactive principles) which can replace the use of expensive growth factors and drugs in tissue engineering constructs
- Matrices for integrating cells in tissue and developing macroscopic functionality
- Combination of drugs and delivery technologies, using e.g. vesicles or micelles, with cell therapies
- Matrices resorbing and releasing cytokines passively or actively.

Cell-Based Therapies

- Stem cell research, aimed at understanding the potential and plasticity of adult stem cells
- The development of technologies for minimally-invasive, site-specific cell therapy

© Fig. 10

- Research aiming to generate knowledge and products centred on the nanoscale interactions between different types of cells and their immediate environment
- Monitoring tissue regeneration
- Study and construction of biological niches for stem and/or precursor cells to be propagated and later on differentiated
- Study of the life cycle of newly designed bioengineered specimen with their short-term and long-term effects in the biological environment (in vitro and in vivo)
- Human adult progenitor cells and their gene control on nanostructured biomaterials
- Identification and characterisation of stem cell niches in different tissues
- Stem cell homing and migration
- Stem cell phenotype i.e. surface markers, to allow specific gene expression
- Methods for isolation and enrichment of stem cell populations
- Methods for culturing stem cells while maintaining the pluripotent state
- Induction and control of differentiation processes (time and space resolved)
- Methods of stem cell delivery in biomaterial scaffolds overcoming the problems of cell survival. Rationalised database providing information to the scientific community about cell adhesion, proliferation and differentiation pathways as well as on cell and tissue biochemistry
- Minimally invasive methods for identification and isolation of progenitor cells
- Environment for storing and maintaining few or even single cells
- Cell reactors for dedifferentiation and differentiation of cells, including matrices, cytokine releasing structures and contact induction/inhibition of cells
- Cell reactors for dedifferentiation and differentiation of cells, including mechanical, electrical and physical stimuli
- Analytical tools for controlling status of cell development, evolution of gene, protein and metabolite network (link to systems biology)
- Genetic engineering of individual cells
- In vivo animal models of neurodegenerative diseases and ex vivo manipulation aimed at understanding potential and functionality of stem cells
- Stem cells as in vitro systems for drug testing and toxicity assays.

3. Providing the Environment to Facilitate Nanomedicine

3.1. Ethical and Social Aspects of Nanomedicine

The potential impact that nanotechnology will have on diagnostics, regenerative medicine, and targeted delivery raises the question, which ethical, legal, and social aspects have to be addressed to create an environment for the socially acceptable and economically successful development of nanomedical applications. The enabling character of nanotechnology generates familiar biomedical ethics like the gap between diagnostics and therapy or sensitivity of genetic information. This means we build on a familiar pool of ethical and social discussions, from principles of human dignity to generic questions of science ethics.

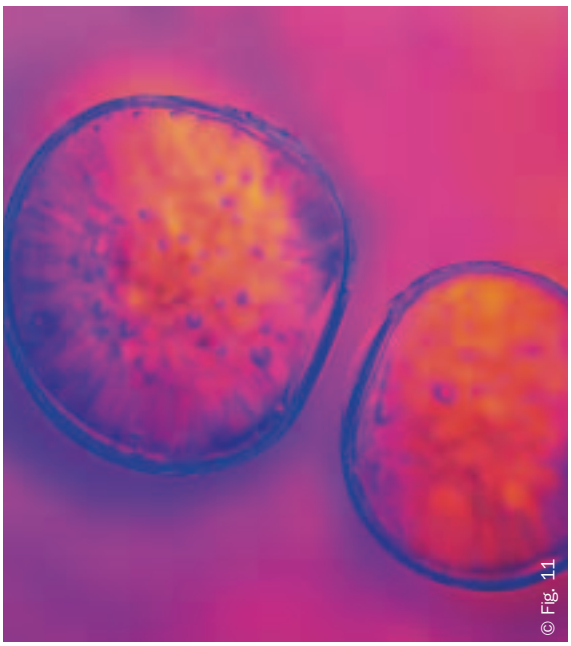
Nanotechnology may also add a new dimension to the bio (human) and non-bio (machine) interface such as retina implants due to improved biocompatibility, or nanoelectronics. This latter example shows that new inventions might add new horizons to ethical, legal, and social considerations. For example “where do we draw the line between medical treatment and enhancement” or “when do we call a person ill” (genetic disposition to get a disease, detection of a single cancer cell vs. tumour, etc.)?

Regardless of the question, whether new normative issues arise or known aspects have to be adapted, an ethical analysis of new nanomedical applications is necessary. Of special interest are:

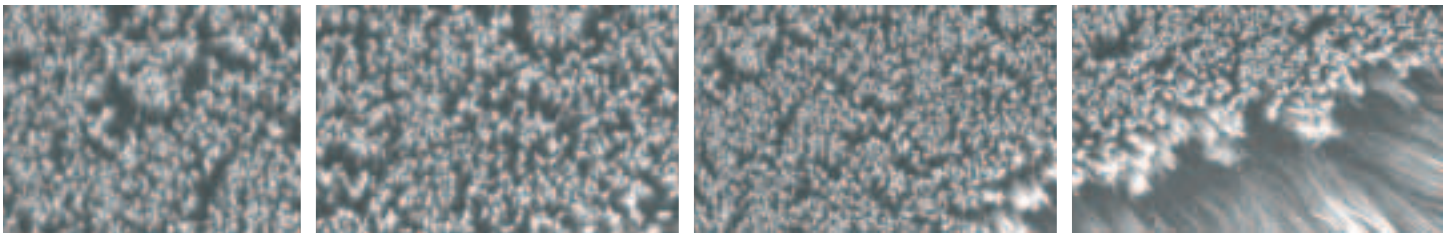
- Privacy: The ethical principal of not invading a person's right to privacy
- Non-discrimination: People deserve equal treatment, unless there are reasons that justify any differences in treatment
- Informed consent: The ethical principal that patients are not exposed to treatment or research without their free and informed consent
- Autonomy (for instance regarding brain implants)
- Right not to know: Patients have to be able to decide, which information they want to get when, for example in case of diagnosis of predisposition for a disease without an existing therapy
- Non-instrumentalisation: The ethical requirement of never defining individuals merely as a means but always as an end of their own
- Enhancement: The improvement of body functions without a medical indication
- Human dignity and integrity: Nanomedicine should respect human dignity and integrity
- Precautionary principle: The moral duty of continuous risk assessment with regard to the non-foreseeable impact of new technologies, as for example in the case of novel implants in the human body.

Besides the effect on ethical issues, nanomedicine will also have a large impact on social issues such as:

- Reduced healthcare expenses due to earlier and more sensitive diagnostics together with improved therapy
- Increased costs of social security systems due to ageing of population
- Unequal access to nanomedicine (nationally and internationally)
- Shift of responsibility for example from physician to patient due to point of care diagnostics
- Impact on health care systems with an expected shift from current acute therapies in central hospitals to future earlier diagnosis by general practitioners.



© Fig. 11



These issues call for a proactive round table approach involving scientists, experts in ethical, legal, and social aspects, patient groups, regulatory agencies, health insurances, national healthcare systems representatives, policy makers and company representatives to forecast the impact on healthcare and social security systems. This round table will help that new nanomedical innovations will meet the requirements of the health insurance systems and regulatory frameworks, which will be essential for introducing new nanomedical innovations into the market.

The broad scope and the speed of nanotechnological innovations in the medical sector make it extremely difficult for experts in ethical, legal, and social aspects to understand the technological background and impact of these innovations. To overcome this problem it is suggested:

- To involve experts in ethical, legal, and social aspects in prospective studies and technology assessments
- To involve experts in ethical, legal, and social aspects in research projects where it is appropriate, to get advice on possible emerging issues
- To develop tutorials for experts in ethical, legal, and social aspects on nanotechnologies in medical applications to build up expertise for informed monitoring of research projects and for basic academic discussions and evaluation of the ethical, legal, and social aspects of nanomedicine.

A close collaboration between technology developers and ethics and social specialists will support the socially and ethically acceptable development of innovative tools and devices in nanomedicine.

3.2. Public Acceptance of Nanomedicine

Another important building block for an environment in favour of nanomedicine is the public acceptance of this novel technology. So far European public opinion as expressed by the media and focus groups is largely positive because nanotechnology promises great benefits for the health and everyday life of people in addition to economic success. However, one has to be cautious not to fuel the hype about the technology, which in this regulated sector will have to mature over a prolonged period of time.

The fascination about nanotechnology is largely based on technical achievements like self-cleaning windows, scratch resistant paintings or coffee repellent cloths, which are not directly related to the human body, food or the environment. The importance of the latter three areas for the public acceptance of nanotechnology is demonstrated by the emerging debate on the possible risks related to certain nanoparticles, although in reality some nanoparticles have been in many products for a decade. To prevent an overflow of this partly over-negative opinion to nanomedicine, an open and transparent dialogue with the public, based on facts and supported by communication experts is necessary. Special needs are:

- Media training of scientists, to teach them to work with the public and especially with journalists
- Workshops with journalists, scientists and company representatives to discuss nanomedical topics and developments
- To speak from the perspective of nanomedicine (instead of nanotechnology in general), as it seems to be important for this field to have a specific profile of its own in the public opinion
- To use experts in ethical, legal, and social aspects as neutral mediators
- Tutorials for groups like patient organisations, who are well trusted by the public and can act as multiplicators or mediators
- Public engagement such as public consultations, consensus conferences, citizen's juries to get feedback about public opinion and degree of information
- Lectures on ethical, legal, and social aspects at scientific conferences
- Material for teaching, both at schools and universities
- Other creative forms of outreach, such as exhibitions, science centres, TV programmes, etc.
- To encourage industry to answer questions about societal and environmental impacts whilst products are still under development.
- To facilitate communication between the industrial and academic sectors.

The goal of all these activities has to be a public, which is well informed about the benefits of nanomedicine and is willing to accept the normal risks associated with medical advances. Furthermore to foster a scientific community which cares for the general public's expectations and concerns. The regulatory system should reduce the inherent risk associated with any new medical product and should allow any side effects to be further quantified.

3.3. Risk Assessment

In the three areas of nanomedicine (nanotechnology-based diagnostics, including imaging, targeted delivery and release, and regenerative medicine) possible side effects have to be considered. Although there is no reason from our present perspective to think that a nano-structured surface on say an implant should represent any increase in risk compared with a non-nanostructured surface, the unknown properties of certain nanostructures call for careful attention regarding their reliability and potential side effects.

For medical applications based on free nanostructures as with any new medicine the following safety issues are important:

1. Systemic distribution: kinetics, variation depending on route of administration
2. Accumulation phenomena: dose-response, tissue/organs involved
3. Ability to disturb cellular metabolism
4. Ability to cause protein conformational change
5. Ability to promote tumour formation.

Coupled with these questions there are various basic scientific questions which arise:

1. How do cells interact with nanoparticles and is this similar to or different from the reaction to micro-particles?
   - Mechanisms of cellular uptake
   - Is there sub-cellular compartmentalisation?
   - What determines intracellular accumulation?
   - Relative importance of size, shape and chemistry of nanoparticles.

© Fig. 12

2. What are the mechanisms for transcellular transportation? This is an essential question, as in imaging and targeted delivery it is of great significance whether the nanoparticles stay within a biological barrier or are able to cross it (e.g. blood-brain barrier, air-blood barrier in the lung, skin, etc.).

Such scientific considerations lead on to specific research:

1. Development of suitable in vitro models to study nanobiology, e.g. how nanoparticles interact with cells, especially of human origin.
2. Search for suitable cell and molecular biological parameters, which could indicate deleterious effects of nanoparticles in different cell and tissue systems.
3. Which animal models are suitable to study nano-biology and how can they be reduced to a minimum?
4. Comparison of in vivo and in vitro models.

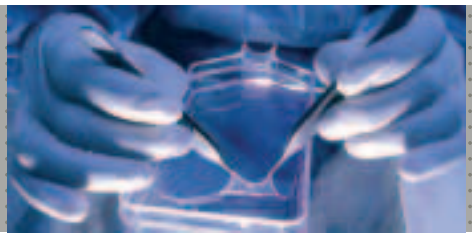
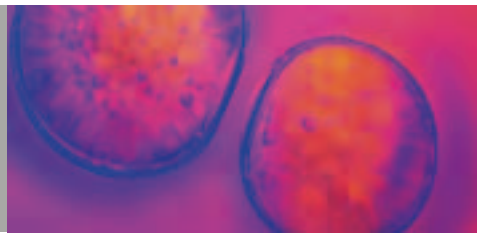
3.4. Regulatory Framework

The possibility to work at the nano level is not totally new and nanotechnology has already found several applications in medicine both in the medicinal products and medical devices area.

For some time there has been a debate on the appropriateness and adequacy of the current legislative framework to cope with the challenges that the possible presence of nanoparticles in the body or the use of technology at nano level may bring about.

First of all it is important to underline that nanomedicine is not a new category of healthcare products, but rather a new enabling technology used in the design and production of medical devices and pharmaceuticals. For this reason, the first check to be made is whether a medical device that is CE marked in conformity to directive 93/42/EEC is safe when it has been designed using or incorporating nanotechnology or whether a medicinal product, approved in conformity with Directive 2001/83/EC is safe when it has been designed using or incorporating nanotechnology.

Medical Devices: Directive 93/42/EEC does not give prescriptive requirements, but requires that the manufacturer of a medical device takes responsibility for the performance and related safety of its products on the basis of an appropriately conducted and systematic risk

management procedure. In conducting the analysis of the risks related to the product, the manufacturer has to take into account all relevant information he can gather on the technology and on the product at stake. This task is facilitated by the reference to harmonised standards for current and well-established technologies. For innovative technologies, the manufacturer has to be aware of the latest scientific data. Further products classified in class III, IIb or IIa shall be examined by an independent third party (Notified Body), which, under the control of the authorities of the Member State in which it is located, will confirm or challenge the conclusions of the manufacturer. The structure of the system seems to be appropriate to cope with any new emerging technologies incorporated into or applied to medical devices. This assessment has recently been recognised by an ad-hoc Working Group hosted by the European Commission, which has clearly indicated that the medical devices regulatory system is an appropriate framework to deal with nanotech-based medical devices. Nevertheless, the Commission is analysing if there is a need for specific guidance or supporting instruments, particularly concerning the classification of medical devices, for new technologies including products based on nanotechnology.

Medicinal Products: The legislative framework for medicinal products can be prescriptive both in terms of technical requirements and in terms of manufacturing, but flexibility is embedded provided that the applicant has scientifically sound justifications. The system is based on evaluation of the quality, safety and efficacy of the product, leading to a risk/benefit assessment and related risks minimization and management. Risk management may also be required in the post authorisation phase. Whenever a new technology is applied, the regulatory framework follows science by making new guidelines and where necessary, legal amendments to lay down appropriate requirements. In the absence of guidelines, applicants can seek scientific advice from the European Medicines Agency (EMEA) for issues relating to the development of their individual products that are not yet fully covered by existing guidance.
While the overall framework could be quickly complemented by new guidelines specific to nanotechnology (developed by EMEA or the Commission), the process for developing specific legal requirements for new technologies takes more time.

Conclusion: The assessment procedures for medical devices and medicinal products both appear suitable for coping with the challenges of this new technology. While the medical devices system is likely to be able to cope with it effectively with relatively few amendments in a short time, the system for pharmaceutical products might require more extensive work. However, this should not delay patients' access to innovative medicines since there are procedures in place for guiding the applicants from the early stages of the development of their products even in absence of specific guidelines. A need for improved collaboration between regulators responsible for Medical Devices and Medicinal Products is strongly perceived, as integration of competences might be required for complex nanotechnology based products.

Imaging Agents: Imaging agents for system use are pharmaceuticals under the MPD (Medicinal Products Directives and Regulations), whereas scanners are treated under the MDD (Medical Device Directive). Due to the potential risks associated with pharmaceuticals, which are administered and used systemically in humans, the necessary series of laboratory, animal and clinical tests with different phases take longer time for market approval than the tests of medical devices. However, material that is “intended for research and development trials” (MPD Article 3.3) is not covered by the rules of the MPD.

In the USA, where the responsibility for approval and oversight of clinical trials is centralised at the Food and Drug Administration (FDA), change has been introduced to speed up the development of diagnostic imaging agents. Recently the FDA has taken action to speed first-in-man assessments of imaging agents under the exploratory Investigational New Drug program. The FDA also developed new Guidance for Industry on Developing Medical Imaging Drug and Biological Products, which is intended to modernise the agency's approach for the approval of these types of agents recognising their relative safety as compared to therapeutic drug products.

In view of this, and in the light of the benefits of molecular imaging it is the intention to form a working group, which will gain more insight on the risk level of imaging agents. As an accompanying action it is suggested to analyse the large amount of data that is available about the application of radiotracers in nuclear medicine and of magnetic resonance imaging-contrast agents in radiology over decades with hundreds of thousands of patients.

3.5. Intellectual Property Rights

Within the general rules on intellectual property for the Seventh Framework Programme, an intellectual property model will be developed by the European Technology Platform on NanoMedicine.

This model aims to achieve a large participation in the initiative and a fair allocation of rights on generated intellectual property. The basic principle of the ownership and exploitation of intellectual property will include:

- The foreground will be owned by the party that is the employer of the inventor(s). The employer will ensure, that it claims all rights to the invention. In case of remuneration obligations, the employer will be responsible for remuneration. Where several participants have jointly carried out work generating foreground and where their respective share of the work cannot be ascertained, they shall agree among themselves on the allocation and the terms of exercising the ownership of the joint foreground in accordance with the provisions of the Seventh Framework Programme regulations. Parties will try to reach a common agreement on ideally "one applicant per patent" case to reduce administrative burden. In case joint owners do not come to agreement on territorial scope, each owner will be allowed to file in all countries the other owners are not interested in. He shall then be the sole owner in such country and shall bear all costs. The other co-owners of an invention retain a royalty free right to use the same also in such country for their own purposes.
- Use of foreground rights for research purposes, including clinical trials will be royalty free for at least the project members of the related specific project of the European Technology Platform on NanoMedicine. Further access rights for other parties and conditions of these access rights are under discussion.
- Use of foreground rights for commercial purposes:
  - Free or favourable conditions for anybody who has participated in the specific project in which the respective rights have been generated. The final intellectual property policy will contain further details regarding sublicensing and use by affiliates.
  - Participation is defined by financial investment of a certain level or provision of certain data and/or tools/materials or undertakings determined/defined by the funding organisations.
- The access rights to background IP are still under discussion.

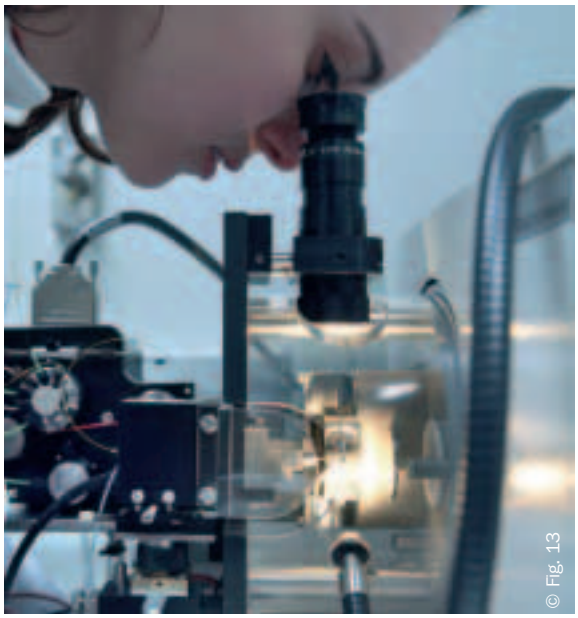
A working group composed of representatives from industry, academia, and public administration has been established to further elaborate the principles of the intellectual property policy of the European Technology Platform on NanoMedicine.

3.6. Required Research Infrastructure

Nanomedicine is a very special area of nanotechnology, because:

- It is an extremely large field ranging from in vivo and in vitro diagnostics to therapy including targeted delivery and regenerative medicine.
- It has to interface nanomaterials (surfaces, particles, etc.) or analytical instruments with "living" human material (cells, tissue, body fluids).
- It creates new tools and methods that impact significantly existing conservative practices.

In the near future, the second and the third points represent the biggest challenge for developing nanomedical tools and devices, because due to the novelty of the field no infrastructures of European scale have evolved yet, which create the necessary close proximity between experts and facilities of different areas. This is essential for innovations in this field, and to create the condition of the fast translation of research results to the clinic for patients. To overcome this problem a distributed infrastructure of specialised



© Fig. 13



European poles of excellence of complementary expertise is a necessary first step like “nanotechnologies in cancer”. Each centre or node should already have: excellence in one area of nano-technology (surfaces, particles, analytics, integrated systems, etc.), a biological and/or medical research centre and hospital, and (most importantly) companies, which have access to and knowledge of the relevant markets. The missing expertise should be quickly and very easily accessible within this network of distributed infrastructures and experts pools. Dedicated clinics or hospital units developing and testing nanotechnology based tools, devices and protocols should be supported in the key places across Europe. In fact, a few technological/clinical centres will have to specialise on the transfer of nanomedical systems from the bench to the patient's bed – the “clinicalisation” of the nanomedical devices – to take into account its specificities. Testing patient's bio-samples on nanobio-analytical systems, implanting an in vivo nanobio device or injecting a nanotech based drug carrier require a specific environment in dedicated clinics as close as possible to nanotechnology centres, which is not currently found in the usual university hospitals. These places will also be key support facilities for joint training of medical doctors and technology developers.

A European infrastructure based on such places with complementary nanotechnological and biomedical excellences will have the capacity to build up scientific and technical expertise at the interface between “nano” and “bio” to speed up the development of tools and devices for the market. Upgrading and combining these places therefore is crucial for effective market oriented developments in nanobiotechnology, because speed is the most critical key factor of success for bringing nanomedical devices or methods to the market in a competitive situation.

3.7. Education and Training Needs

Due to its novelty, no dedicated education programme in nanomedicine exists in Europe at present, with the exception of a few regional initiatives. There is a growing need for qualified personnel with training in at least two or three major disciplines related to nanomedicine. Therefore, it is necessary to synchronise and further develop regional education schemes in order to establish comprehensive education programmes so that a student can get credits in the most competent universities over Europe in the framework of a coherent and comprehensive curriculum. The education programmes should first concentrate on graduate students, who have a degree in one of the basic disciplines like biology, chemistry, physics, material or medical science. In the long run programmes at all levels should be developed, e.g. by exchange of experience and agreements on common standards for European certificates. In terms of dissemination and distant learning, especially towards the new Member States of the European Union one important tool at the European level could be an E-learning programme, jointly created by the members of European nanomedicine clusters.

Besides education of students, training of industry and clinical personnel is needed at all levels from the nurse to the physicians or the surgeons. Tutorial courses and practical training are essential to enable penetration of nanotechnology into medical applications. For these purpose physicians, pharmacists, and biologists have to be trained in nanomedicine related technological research whereas physicists, nanotechnologists, and engineers have to be trained in biological/clinical methods. Training of medical personnel in technological units is a good way to facilitate the adoption of technology in routine operation in hospitals and clinics.

The education and training efforts have to be supported by a mobility programme, because the expertise in the different areas of nanomedicine is spread across many centres in Europe. The access of personnel to expertise in the best centres in Europe will be essential to ensure the fast and sustainable development of nanomedicine in Europe. A special emphasis has to be given to the mobility of PhD and postdocs who are much more mobile than senior scientists and who represent the European networks of tomorrow.

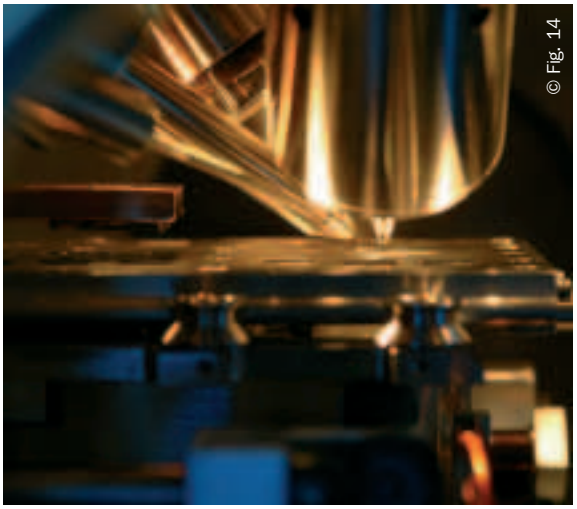
4. Making it Happen

The European Technology Platform on NanoMedicine addresses ambitious, responsible research, development and innovation in nanotechnology for health to strengthen the competitive scientific and industrial position of Europe in the area of nanomedicine and improve the quality of life and healthcare of its citizens.

The European Technology Platform on NanoMedicine identifies the most important socio-economic challenges facing Europe in this area, focusing on some major diseases with main economic impact. It aims to improve the standard of healthcare across the population, enhancing quality of life, and focusing on breakthrough therapies, in a cost effective framework.

As well as dissemination of knowledge, regulatory and intellectual property issues, the European Technology Platform in general addresses ethical, environmental and toxicological aspects as well as public perception.

Research on nanomedicine is unusually spread across industrial, clinical and academic sectors. For real clinical progress improved communication is required between all three parties; as ultimately only those teams able to manage clinical studies through phases 1-3, regulatory submissions and marketing will be able to provide benefits for patients. Depending on the stage of the research, it will be advisable for proposals to show that collaborators are really capable of transitioning their work through the clinic. Researchers should note that ultimately this is a regulated sector and that the quality of scientific evidence required and proof of viability will be higher than that required for academic publication.



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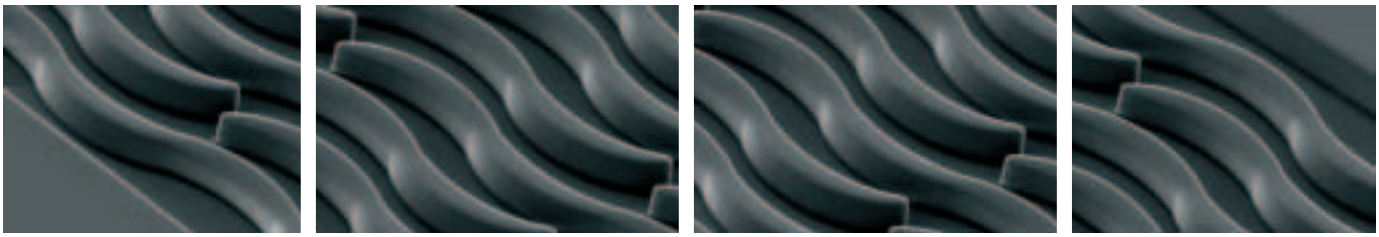
Due to the major importance of future healthcare, this issue is covered by various other European Technology Platforms. Besides the European Technology Platform on NanoMedicine, three other European Technology Platforms are addressing different facets of medical applications:
The scope of most European Technology Platforms is to identify and describe core trends in the healthcare sector that benefit the citizen in the light of emerging challenges such as an ageing population and personalised health care as well as to focus upon technology trends that impact industry.

European Technology Platform on Innovative Medicines

The overall policy objective of the Technology Platform on Innovative Medicines is to enhance and accelerate the development process of medicines so as to ensure the most rapid application of scientific breakthroughs into approved new medicines. This will be achieved by stimulating integrated forms of cooperation in research and development, in particular through reinforced public-private partnerships, with a view to providing the European population with early access to new, more targeted medicines, while at the same time, strengthening the European science base and fostering economic growth in the pharma/biotechnology industry.
http://europa.eu.int/comm/research/fp6/index_en.cfm?p=1_innomed

European Technology Platform on Smart System Integration (EpoSS)

The recommended research priorities of EPoSS address requirements and R&D needs related to smart systems contributing to emerging challenges like the ageing population and personalised health care as well as related to the integration of these smart systems into medical technology products. The long term market developments and technology requirements are taken into account



with a time horizon on developments beyond existing product roadmaps. *http://www.smart-systems-integration.org/public*

European Technology Platform on Photonics (Photonics 21)

This European Technology Platform is paving the way for Europe's scientific, technological and economic leadership in photonics. Life science and healthcare are areas where photonic technologies are expected to bring benefits. *www.photonics21.org*

The European Technology Platform on NanoMedicine will be connected with its three "sister" European Technology Platforms to prevent duplication, double funding of projects and ensure better use of knowledge. For instance, generic development in photonics under Photonics 21 can be then exploited by the European Technology Platform for NanoMedicine for a specific device or application. The same principle can be envisaged with the two other European Technology Platforms.

The European Technology Platform on NanoMedicine has developed the following Strategic Research Priorities. They are addressed to the Member States of the European Union, its Candidate Countries and Associated States to the EU Framework Programmes for research and technological development, as well as the European Commission. They should serve as a basis for and encourage the launching of innovative nanomedical research programmes at European, national and regional level, and should strengthen the cooperation of multisectorial consortia.

Strategic Research Priorities

DIAGNOSTICS

Activities should start in:	1-2 years	3-5 years	more than 5 years
Cardiovascular Diseases	Non- and minimal invasive dynamic functional 3D imaging techniques (i.e. tissue elasticity, blood flow) in the cardiovascular system Surface nanostructured bioelectrical sensors for continuous monitoring 3-in-1 smart in vivo nanodiagnostics system for combined diagnostics, therapy and therapy monitoring	Intracorporal robotics for heart diagnostic and therapy	Telemedicine for heart monitoring using smart maintenance-free implantable devices
Cancer	Smart probes with reduced toxicity for drug targeting, contrast carrier for imaging, local activation and controlled activity Integrated nanotechnology devices for cancer related proteomic, metabolomic and epigenomic molecular serum pattern detection Identification of biomarkers or patterns for predisposition and early screening in body fluids	Nanostructured surfaces as specific in vivo and in vitro biosensors for cancer related molecular markers Minimal invasive endoscope/catheder for diagnostics and therapy	Implantable mobile systems for detection of cancer cells and localised delivery of optimal therapeutic agents. These systems should also enable communication with other implanted devices and external systems
Musculoskeletal & Inflammatory Diseases	Intelligent blood filtration devices detecting/removing inflammation related molecules (e.g. interleukines) Identification of biomarkers or patterns for predisposition and early screening	Imaging of labelled white cells	
Neurodegenerative Diseases	Probes than can cross blood-brain barrier for imaging (like amyloid plaque in vivo), and delivering therapy Imaging/spectroscopy strategies for rapid identification of protein aggregates relevant for neurodegenerative disease Dynamic optical imaging tools for 3D neurotissue engineering	In vivo drug delivery probes coupled to sensors in autonomous systems Image guided implatantation of advanced neurostimulators	Biosensors for faster and earlier differential diagnosis at the point of care
Diabetes	Non- and minimal-invasive diagnostic tools to measure glycemia In vivo characterisation of glucose metabolism Whole-body imaging of fat distribution and fat characterisation	Minimally invasive, combined glucose sensor/insulin delivery systems for daily home-care Monitoring of labelled islet transplantation	
Infectious Diseases	Integrated diagnostic test (incl. sample preparation) for rapid and early diagnosis of viral or bacterial infection Identification of diagnostics markers and early screening of changes in RNA expression in infected cells		
Enabling Technologies	Integrated systems for detection by cell, protein, transcript and/or genetic analysis Identification of early diagnostic/prognostic marker biomolecules Probes that can cross cytosol-nucleus barrier for imaging and delivering therapy	Image guided therapy with multimodal molecular and functional as well as intraoperative imaging Biocompatible dynamic surfaces for coating of implantable devices to enable controlled drug release and provide optimal cell adhesion Therapy response prediction by appropriate markers	Management of heterogeneous data from various analytical sources and devices Diagnostics devices for telemedecine

TARGETED DELIVERY

Activities should start in:	1-2 years	3-5 years	more than 5 years
Cardiovascular Diseases	Identification of markers on plaque or infarcted area Theranostic programme for cardiovascular diseases, especially ischaemic heart disease	Research into theranostics for CVD especially cerebrovascular disease	Clinical trials for theranostics
Cancer	Critically evaluating existing nanomedicines in a pre-clinical context prior to validation in the clinic. Of particular importance is understanding the science behind the pharmaceutics of these complex and multi-tasking entities Researching new and low cost targeting agents. Multi-target approaches Research into novel Nanomedicines to critically explore their potential in a non-clinical context. The interaction of nanoparticles with biological systems requires much more critical and in depth studies	Clinical trials for Cancer nanomedicines Exploring easier routes of administration, e.g. not with a conventional needle	Expansion of disease foci into other less common cancer indications
Musculoskeletal & Inflammatory Diseases	Research into new types of lower cost targeting agents to reduce the cost of goods for such nanomedicines Rheumatoid Arthritis and Crohn's disease should be a therapeutic focus	Nanomedicines to facilitate bone regeneration or the treatment of Osteoporosis. Perhaps including aspects of regenerative medicine.	Programme aimed at prostate hypertrophy and inflammatory processes
Neurodegenerative Diseases	Design and synthesis of nanomedicines capable of crossing the blood brain barrier with Alzheimer's Disease/Parkinson's as the longer term targets	Semi-invasive programmable nano-devices to deliver drugs with Parkinson's as the target disease	
Diabetes	Treatment of vascular inflammatory processes in diabetes types 1 and 2, diet related nephropathy and auto-immune disease induced vascular inflammation Development of inhalable forms of insulin or other drugs capable of modifying blood glucose levels. High bioavailability is a priority	Treatment of diabetes by insulin delivery by a responsive nano-enabled device (e.g. capable of detecting glucose levels)	
Infectious Diseases		Nano-vaccines	
Enabling Technologies	Understanding aggregation phenomena including that involving proteins Understanding how nanomedicines interact with the body and its components. Transport through membranes and tissues. In Vitro models Understanding the drug metabolism and pharmaco-kinetics of nanomedicines in order to achieve appropriate therapeutic cover Easier routes of administration such as transdermal, oral and pulmonary delivery. Nano-delivery devices. Enhancing bio-availability Novel types of targeting entities	Crossing the blood-brain barrier Manufacturing and lowering the cost of goods Predicting immunogenicity. Synthetic immune systems (real or virtual)	

REGENERATIVE MEDICINE

Activities should start in:	1-2 years	3-5 years	more than 5 years
Cardiovascular Diseases	Cell based therapies for treatment of cardiovascular diseases Advanced biomaterials for site specific cell therapy Biomimetic biomaterials for vascular replacement	Bioactive signalling factors triggering regenerative events in the heart Advanced biomaterials for site specific delivery of bioactive signalling factors Advanced – biomaterials as targets for stem cell therapies	Intelligent bioactive materials promoting and controlling regenerative events in the heart Strategies for stem cell mobilization and homing at the site of injury
Cancer	Cell based therapies for management of cancer related immunodeficiencies	Technologies for mass production of immune cells Advanced biomaterials for site specific delivery of bioactive signalling factor	Advanced biomaterials for in vivo activation of hematopoieitic stem cell production
Musculoskeletal & Inflammatory Diseases	Cell based therapies for treatment of osteoarthritis Bioactive coatings of orthopaedic implants for cell attraction, Nanostructures stimulating bone deposition Advanced biomaterials for treatment of spinal disorders	Identification of bioactive signalling factors stimulating bone remodelling Advanced bioactive biomaterials designed for disease-modifying treatments of osteoarthritis	Intelligent biomaterials promoting and controlling regenerative events in bone and cartilage Strategies for stem cell mobilization and homing at the site of injury
Neurodegenerative Diseases	Advanced nanomaterials as neural prostheses Methodologies for cell therapies in tissues of the adult central nervous system	Cell based therapies for disorders of the central nervous system Bioactive signalling factors triggering regenerative events in the central nervous system Biomimetic biomaterials for site-specific cell therapy	Intelligent biomaterials, responsive to changes in the microenvironment of the central nervous system, promoting and controlling regenerative events in the central nervous system Technologies for site-specific delivery of neuro-active molecules
Diabetes	Bioengineered pancreatic cells in the management of diabetes	Development of glucose sensitive devices for controlled delivery of insulin/insulin analogues Advanced biomaterials for delivery bioengineered pancreatic cells Advanced biomaterials for site specific delivery of bioactive signalling factors in healing of diabetic wounds	Strategies for development of artificial pancreas
Enabling Technologies	Identification of mechanisms for activation and control of tissue-specific progenitor cells Identification and synthesis of bio-active signalling molecules and extra-cellular matrix analogues Design and control of biomaterial structure at nano-level	Identification of signalling systems for leveraging regenerative potential of progenitor cells Associations of biomaterial and bio-active signalling molecules for biomi-metic therapies Biomimetic biomaterials which can react with the microenvironment	Strategies for progenitor cell mobiliza-tion and homing, Biomaterials able to trigger and control progenitor cell recruitment at site of injury Technologies for targeted, sequential delivery of bioactive signalling molecules

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