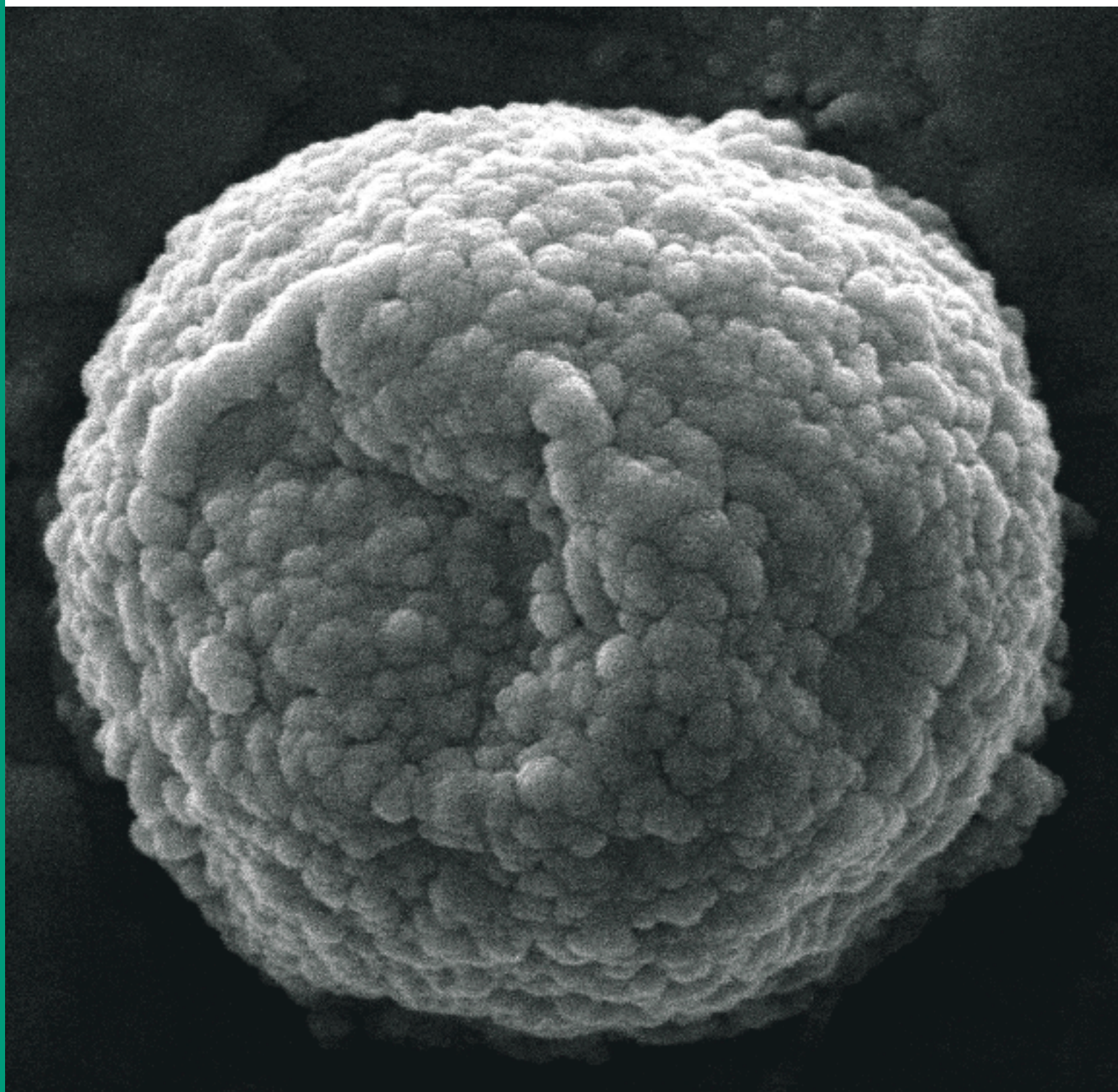
EUROPEAN
SCIENCE
FOUNDATION

Nanomedicine

An ESF–European Medical Research Councils (EMRC) Forward Look report



ESF focuses on science driven collaboration between the best European researchers in all disciplines. We promote the identification and advancement of leading edge science in Europe in close co-operation with our Member Organisations. We bring together leading scientists, scholars and funding agencies to explore new directions in research and to plan and implement European level research collaboration in a global context. Our main instruments include conferences, scientific foresights, collaboration programmes and support to outstanding young researchers. ESF also manages COST, an intergovernmental framework for European co-operation in the field of Scientific and Technical Research.

Integrative Biology is currently a hot topic in the Life Sciences. The potential applications of Integrative Biology will contribute significantly to maximizing the value of knowledge generated in the biomedical field and the outcome expected for the public health care system. In this context, the strategy developed by the European Medical Research Councils (EMRC), one of the five Standing Committees at ESF, aims to:

- foster an interdisciplinary approach towards the Functional Genomics domain embracing all the *–omics* disciplines (including the DNA, RNA, protein and other macromolecules world) and their integration into Systems Biology;
- focus on biomedical applications emerging from these and related domains, such as Nanomedicine and Structural Medicine; Molecular Imaging, Genetic Epidemiology and Pharmacogenetics in order to advance the promising field of Personalized Medicine also qualified as Individualized pharmacotherapy;
- develop translational research to overcome boundaries between basic research/science and clinical applications (e.g., application of cell and gene therapies in Tissue Engineering and Regenerative Medicine, identification and validation of biomarkers and therapeutic/diagnostic tools that will allow the transfer of innovation through a collaborative public-private process of research and development, etc.). In this respect, special attention will be paid to therapeutic domains identified as a burden for European citizens[1]:
  – cardiovascular and respiratory diseases
  – cancer
  – allergic, immunological and infectious diseases
  – neurodegenerative diseases including neurosciences and mental health
  – diabetes, digestive and renal diseases
  – rheumatic diseases, musculoskeletal disorders and skin diseases
  – rare diseases for instance through its sponsorship of The European Rare Diseases Therapeutic Initiative (ERDITI), and specific patient populations like children, the elderly and women.
- gather expertise and advance the methodology for the evaluation of the socio-economic value of research in the above-mentioned fields.
  In addition, further attention has been paid on the identification of related regulatory and ethical issues and to the promotion of biomedical research to the European general public and political stakeholders. In this respect EMRC is a permanent observer of the Comité directeur pour la Bioéthique at the European Council and is being involved in further developments brought by the WHO and EMEA to its recommendation to build an open international registry for clinical trials.
- develop new partnering to support and leverage these activities, i.e. with European Agencies, intergovernmental organizations (EMBO), charities, pharmaceutical and biotechnological industries, etc.
  Due to the progressive character of these scientific fields, the EMRC portfolio will provide flexibility to cover newly emerging trends in science in a timely manner.

1. WHO Report on "Priority Medicines for Europe and the World" (The Hague, NL, 18 November 2004) commissioned by the Government of the Netherlands.

Cover picture: An image of one selected gas-filled polymer-stabilized microcapsule obtained by electron microscopy. The "magic bullet" is spherical with a diameter of about 1.7µm and the substructure made of polymer nanoparticles is clearly visible. In order to indicate that the particles are in fact gas-filled, an imperfect capsule with a bump has been carefully selected.
These kinds of particles are the basis for Ultrasound Theranostics: Antibody based microbubble conjugates as targeted *in vivo* ultrasound contrast agents and advanced drug delivery systems.
A. Briel, M. Reinhardt, M. Mäurer, P. Hauff; Modern Biopharmaceuticals, 2005 Wiley-VCH, p. 1301

ESF Forward Look on *Nanomedicine* 2005

Participants at the European Science Foundation's Forward Look on Nanomedicine Consensus Conference, Le Bischenberg, 8-10 November 2004

Sponsored by the
European Science Foundation
and organised by its Standing Committee, the
European Medical Research Councils (EMRC)

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Hui Wang, Science Officer

The Steering Committee would particularly like to thank the following persons for their valuable contributions:
Alberto Gabizon, Israel
Mauro Giacca, Italy
Rogerio Gaspar, Portugal
Thomas Kissel, Germany
Bert Meijer, The Netherlands

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Foreword

Recent years have witnessed an unprecedented growth in research in the area of nanoscience. There is increasing optimism that nanotechnology applied to medicine will bring significant advances in the diagnosis and treatment of disease. However, many challenges must be overcome if the application of Nanomedicine is to realise the improved understanding of the patho-physiological basis of disease, bring more sophisticated diagnostic opportunities and yield more effective therapies. Both the optimism and the challenges have prompted governmental science and funding organisations to undertake strategic reviews of the current status of the field[1], their primary objectives being to assess potential opportunities for better healthcare as well as the risk-benefit of these new technologies, and to determine priorities for future funding.

In early 2003, the European Science Foundation launched its Scientific Forward Look on Nanomedicine. I am pleased to see the successful conclusion of this foresight study, which has been the first such exercise focused on medical applications of nanoscience and nanotechnology. The Forward Look involved leading European experts and led to a definition of the current status of the field and debates on strategic policy issues. The recently published Policy Briefing summarised the recommendations made[2].

Here the discussions and recommendations are presented in full. Implementation of these recommendations should ensure continuing European leading-edge research and development in the field of Nanomedicine, resulting in reduced healthcare costs and the rapid realisation of medical benefits for all European citizens. ESF will commit itself to taking the initiative and facilitating the relevant bodies, including ESF Member Organisations and the European Commission, for actions based on these recommendations.

Bertil Andersson
ESF Chief Executive

1. **Commission of the European Communities Communication: (2004)** Towards a European Strategy for Nanotechnology, EU, DG Research, Brussels, (www.cordis.lu/nanotechnology). ftp://ftp.cordis.lu/pub/era/docs/3_nanomedicinetp_en.pdf
NIH Roadmap: Nanomedicine (2004), NIH, USA (http://nihroadmap.nih.gov) (http://www.capconcorp.com/roadmap04)
UK Royal Society and Royal Academy of Engineering (2004) Report on Nanoscience and nanotechnologies: Opportunities and uncertainties, (www.nanotec.org.uk)
National Institutes of Health - National Cancer Institute (2004) Cancer Nanotechnology Plan: A strategic initiative to transform clinical oncology and basic research through the directed application of nanotechnology, NCI, NIH, USA (http://nano.cancer.gov/alliance_cancer_nanotechnology_plan.pdf)
2. **ESF Scientific Forward Look on Nanomedicine: Policy Briefing 23** February 2005 (www.esf.org)

Executive summary

Background

Recent years have witnessed an unprecedented growth in research in the area of nanoscience. There is increasing optimism that nanotechnology applied to medicine will bring significant advances in the diagnosis treatment and prevention of disease. However, many challenges must be overcome if the application of Nanomedicine is to realise the improved understanding of the pathophysiological basis of disease, bring more sophisticated diagnostic opportunities, and yield more effective therapies and preventive measures.

Both the optimism and the challenges have prompted governmental, science and funding organisations to undertake strategic reviews of the current status of the field, their primary objectives being to assess potential opportunities for better healthcare as well as to assess the risk-benefit of these new technologies, and determine priorities for future funding. The outcome of the European Science Foundation's Forward Look on Nanomedicine is presented here.

Objectives

In 2003 the Medical Standing Committee of ESF (EMRC) initiated the European Science Foundation's Forward Look on Nanomedicine. The aims of this study were to gather European experts from academia and industry to:

- Define the field
- Discuss the future impact of Nanomedicine on healthcare practice and society
- Review the current state-of-the-art of Nanomedicines research
- Identify Europe's strengths and weaknesses
- Deliver recommendations on:

– future research trends and priorities for funding

– organisational and research infrastructures needed at the national and European levels to support coordinated scientific activities

– the mechanisms needed to facilitate effective dissemination of information to the general public and policy makers.

Procedure

The ESF Forward Look on Nanomedicine was conducted through a Steering Committee which initially organised a series of five specialised workshops held from 1 to 5 March 2004. These workshops involved small groups of experts from academia and industry representing the different subdisciplines of the Nanomedicine field. Each group was invited to review the issues listed above, and to prepare draft recommendations in their area of specific expertise (participants are listed in Appendix I).

A final Consensus Conference was held at Le Bischenberg, France from 8 to 10 November 2004. The meeting was attended by more than 70 representatives coming from academia, industry, private foundations, and governmental agencies supporting scientific research. Collectively they were able to review and revise the outputs from the earlier discipline-specific workshops, paying special attention to the boundaries within this multidisciplinary scientific field. Moreover the Consensus Conference was able to review the underpinning topics of Science Funding and Policy Making, Commercial Exploitation, Education, and Communication. Participants are listed in Appendix II.

Definitions

The field of 'Nanomedicine' is the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. It was perceived as embracing five main sub-disciplines that in many ways are overlapping and underpinned by the following common technical issues

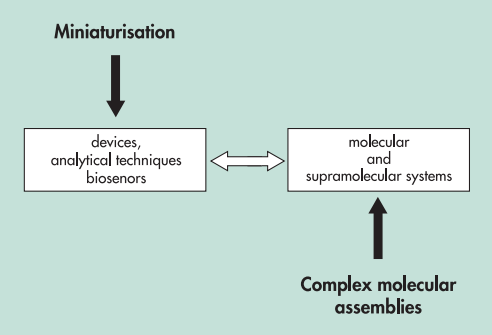
- Analytical Tools
- Nanoimaging
- Nanomaterials and Nanodevices
- Novel Therapeutics and Drug Delivery Systems
- Clinical, Regulatory and Toxicological Issues

The aim of 'Nanomedicine' may be broadly defined as the comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures, ultimately to achieve medical benefit. In this context, nanoscale should be taken to include active components or objects in the size range from one nanometre to hundreds of nanometres. They may be included in a micro-device (that might have a macro-interface) or a biological environment. The focus, however, is always on nanointeractions within a framework of a larger device or biologically, within a sub-cellular (or cellular) system.

Forward Look on Nanomedicine

Miniaturisation of devices, chip-based technologies and, on the other hand, ever more sophisticated novel nanosized materials and chemical assemblies are already providing novel tools that are contributing to improved healthcare in the 21st century. Opportunities include superior diagnostics and biosensors, improved imaging techniques – from molecules to man – and not least, innovative therapeutics and technologies to enable tissue regeneration and repair.

However, to realise Nanomedicine's full potential, important challenges must be addressed. New regulatory authority guidelines must be developed quickly to ensure safe and reliable transfer of new advances in Nanomedicine from laboratory to bedside.



Recommendations

The sub-fields indicated above significantly overlapped in terms of the underpinning science (materials science, analytical techniques, and safety issues), and the perception of the core European strengths and weaknesses in each sub-field were very similar.

• *Nanomaterials and Nanodevices*

Advances should begin with the optimisation of existing technologies towards specific Nanomedicine challenges. The development of new multifunctional, spatially ordered, architecturally varied systems for targeted drug delivery was seen as a priority. There is a pressing need to enhance expertise in scale-up manufacture and material characterisation, and to ensure material reproducibility, effective quality control and cost-effectiveness. These issues should be addressed urgently to enable rapid realisation of clinical benefit (within five years).

For realisation to application within the next decade new materials are needed for sensing multiple, complicated analytes in vitro, for applications in tissue engineering, regenerative medicine and 3D display of multiple biomolecular signals. Telemetrically controlled, functional, mobile in vivo sensors and devices are required, including construction of multifunctional, spatially ordered, architecturally varied systems for diagnosis and combined drug delivery (theranostics). The advancement of bioanalytical methods for single-molecule analysis was seen as a priority.

• *Analytical Tools and Nanoimaging*

These aspects were viewed as complementary even though many of the technologies required are very different in being designed for ex vivo, cellular or in vivo/patient use.

Once again the opportunity was identified to refine existing nanotechniques allowing analysis of normal and pathological tissues to quickly bring a better understanding of initiation and progression of disease. Identification of new biological targets for imaging, analytical tools and therapy is viewed as a research priority. There is a need to develop novel nanotechniques for monitoring in real time cellular and molecular processes in vivo, bringing improved sensitivity and resolution. Mechanisms to allow early translation of research based on molecular imaging using nanoscale tools from animal models to clinical applications should be estab-

lished. This would close the gap between molecular and cellular technologies understudy, and allow rapidly commercialisation of clinical diagnostic nanotechnologies.

In the longer term, research should develop a multimodal approach for nanoimaging technologies, and assist the design of non-invasive, in vivo analytical nanotools with high reproducibility, sensitivity and reliability. Such tools would allow a paradigm shift in pre-symptom disease monitoring, and enable the use of preventative medicines at an early stage. The simultaneous detection of several molecules, analysis of all sub-cellular components at the molecular level, and replacement of antibodies as detection reagents are seen as particularly important challenges for basic research.

Novel Therapeutics and Drug Delivery Systems

Nanosized drug delivery systems have already entered routine clinical use and Europe has been pioneering in this field. The most pressing challenge is application of nanotechnology to design of multifunctional, structured materials able to target specific diseases or containing functionalities to allow transport across biological barriers. In addition, nanostructured scaffolds are urgently needed for tissue engineering, stimuli-sensitive devices for drug delivery and tissue engineering, and physically targeted treatments for local administration of therapeutics (e.g. via the lung, eye or skin).

To realise the desired clinical benefits rapidly, the importance of focusing the design of technologies on specific target diseases was stressed: cancer, neurodegenerative and cardiovascular diseases were identified as the first priority areas.

Longer term priorities include the design of synthetic, bioresponsive systems for intracellular delivery of macromolecular therapeutics (synthetic vectors for gene therapy), and bioresponsive or self-regulated delivery systems including smart nanostructures such as biosensors that are coupled to the therapeutic delivery systems.

Toxicology

There is an urgent need to improve the understanding of toxicological implications of Nanomedicines in relation to the specific nanoscale properties currently being studied, in particular in relation to their proposed clinical use by susceptible patients. In addition, due consideration should be given to the potential environmental impact and there should be a safety assessment of of all manufacturing processes.

Risk-benefit assessment is needed in respect of both acute and chronic effects of nanomedicines in potentially pre-disposed patients – especially in relation to target disease. A shift from risk-assessment to proactive risk-management is considered essential at the earliest stage of the discovery, and then the development of new nanomedicines.

Clinical Applications and Regulatory Issues

As the technologies are designed based on a clear understanding of a particular disease, disease-specific oriented focus is required for the development of novel pharmaceuticals. In addition, it will be important to establish a case-by-case approach to clinical and regulatory evaluation of each nanopharmaceutical. High priority should be given to enhancing communication and exchange of information among academia, industry and regulatory agencies encompassing all facets of this multidisciplinary approach.

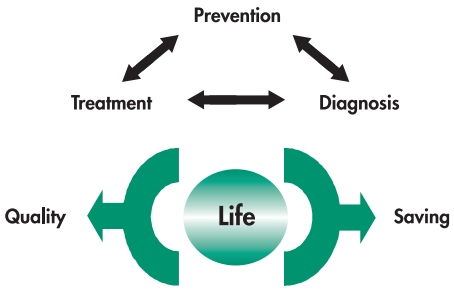
Research Strategy, Policy Organisation, Funding and Communication

In terms of education, a need for more formal interdisciplinary training courses in the area of Nanomedicine was foreseen. At the undergraduate level these would cover the basic scientific disciplines including molecular biology, colloidal chemistry, cell physiology, surface chemistry, and membrane biophysics. In addition, new programmes at master's or early postgraduate level (preferably with combined medical and scientific training) are needed to support the rapidly developing field of Nanomedicine. Encouragement of more interdisciplinary MD/PhD degree programmes with some provision for nanoscience would provide core scientific training for both scientists and physicians. This will be essential to ensure a trained workforce to oversee clinical development of new nanomedicines.

Timely exploitation of newly emerging Nanomedicine technologies was seen as a key issue. This is an area of general weakness. There is a need to establish specific Nanomedicine-related schemes to promote academic-commercial partnerships. The growth of clusters or highly selected teams, chosen for personal excellence or track record would ensure most rapid progress. To facilitate industrial development the establishment of more manufacturing sites with a Good Manufacturing Practice designation able to support small and medium enterprises would help in transferring projects more rapidly into clinical development.

Establishment of good communication is a universal challenge for research and development at the interface of scientific disciplines and at the leading edge. There is a continuing need to promote more truly trans-disciplinary conferences. Encouragement of goal-oriented research partnerships between large medical centres and university research groups is essential to progress the field.

It was noted that scientifically qualified politicians are not common, and the regional, national and European programmes seldom show alignment, suggesting less than optimal communication. Serious effort needs to be made by scientific opinion leaders in Nanomedicine to ensure that politicians are well briefed. Not only will better diagnostics, treatments and prevention for life-threatening and debilitating disease bring healthcare benefits to an ageing population, research and development in Nanomedicine also offers the potential of employment and economic benefits with a reduction of healthcare budgets.



There is an urgent need to more clearly articulate and better communicate the potential benefits of Nanomedicine to the general public as a whole.

Engagement of the scientific community in early dialogue with the general public is crucial in order to discover any public concerns regarding Nanomedicine. Continuing regular dialogue is essential to address and alleviate any public concerns.

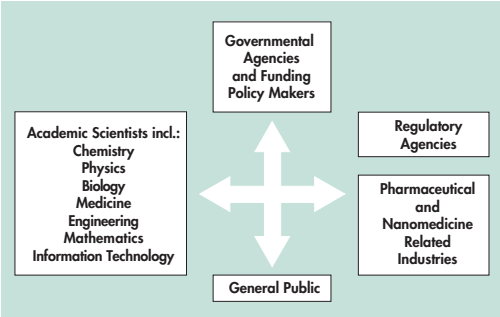
Conclusions

This Forward Look on Nanomedicine has defined the remit of this emerging and important field. Nanomedicine is clearly multidisciplinary and builds on the existing expertise in a large number of different scientific fields.

European strengths have been identified, as have the short- and long-term opportunities, and priorities for the development of Nanomedicine-related technologies have been recognised.

When applying nanotechnology to medical uses, it is particularly important to ensure thorough safety evaluation of any new technologies and also to review the likely environmental impact. In each specific case, careful risk-benefit evaluation is required.

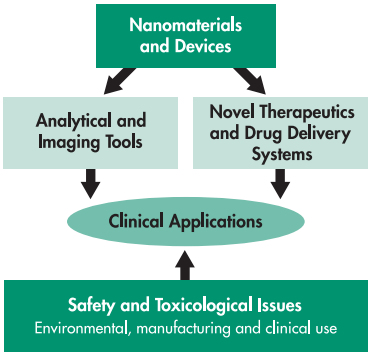
Most importantly, an open and continuing dialogue is required to ensure all interested parties, including the general public, are well informed as to the ongoing technology developments in the field of Nanomedicine. As much has been written in the popular press, quality information is required to assist policy makers and scientists to distinguish "science fact" from "science fiction".



1. Nanomedicine: A New Opportunity for Improved Diagnosis, Prevention and Treatment for Disease

1.1. Definition of Nanomedicine

The field of Nanomedicine is the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. It embraces five main sub-disciplines which are in many ways overlapping and are underpinned by common technical issues.



The aim of Nanomedicine may be broadly defined as the comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures, ultimately to achieve medical benefit. In this context, nanoscale should be taken to include active components or objects in the size range from one nanometre to hundreds of nanometres. They may be included in a micro-device (that might have a macro-interface) or a biological environment. The focus, however, is always on nanointeractions within a framework of a larger device or biologically a sub-cellular (or cellular) system.

It was noted that Nanomedicine is built on the science and technology of complex systems of nanometre-scale size, consisting of at least two components, one of which is an active principle, and the whole system leading to a special function related to the diagnosis, treatment or prevention of disease.

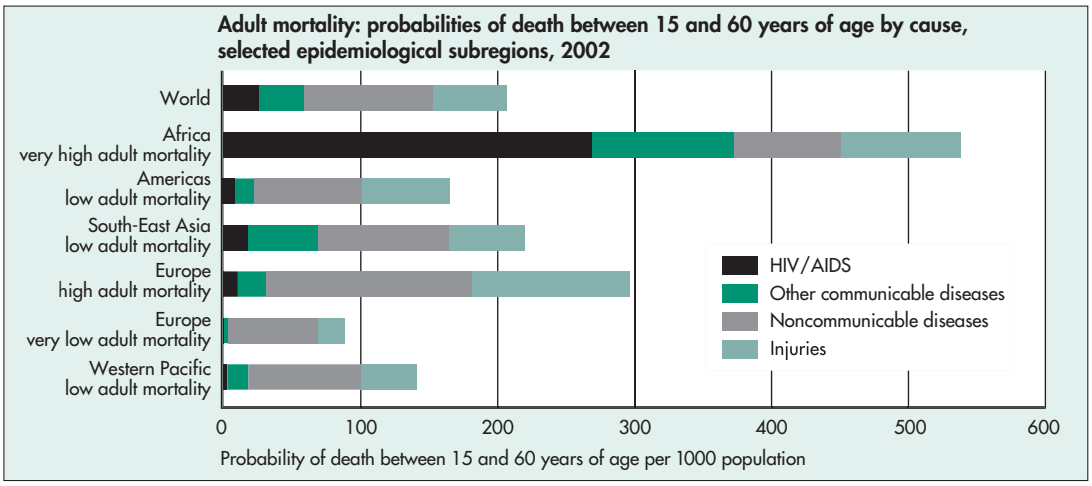
1.2. Position of Nanomedicines within the Healthcare Portfolio

The highest causes of mortality in Europe are cardiovascular disease and cancer. In addition demographic changes are producing an ageing population. This in itself is leading to new healthcare challenges. There is rising prevalence in diseases of the central nervous system, such as senile dementia, Alzheimer's disease, Parkinson's disease, and diseases associated with ageing, for example arthritis and ocular diseases. Whilst much progress was made in the 20th century in respect of the therapies for infectious diseases, emergence of resistance, HIV/AIDS and other new infectious diseases, for example SARS, present new challenges.

Nevertheless, as the 21st century begins, we are witnessing a paradigm shift in medical practice. Nanomedicine is expected to contribute significantly to the overall healthcare portfolio.

Genomics and proteomics research is already rapidly elucidating the molecular basis of many diseases. This has brought new opportunities to develop powerful diagnostic tools able to identify genetic predisposition to diseases. In the future, point-of-care diagnostics will be routinely used to identify those patients requiring preventative medication, to select the most appropriate medication for individual patients, and to monitor response to treatment. Nanotechnology has a vital role to play in realising cost-effective diagnostic tools.

There are increasing challenges within the pharmaceutical industry to locate drugs more efficiently to their disease targets. As the search for improved medicines for life-threatening and debilitating diseases continues, two distinct approaches are being taken to achieve this aim. The first is within drug discovery and builds on identification of new molecular targets which are being used to design 'perfect fit' drug molecules with more specific therapeutic activity. These efforts continue via:
screening of natural product molecules to identify candidates with pharmacological activity;



preparation of carefully tailored synthetic low molecular weight drugs via traditional medicinal or combinatorial chemistry;

- nanofluidics for targeted synthesis;
- nanodetection for target identification; and
- discovery of natural macromolecules, including antibodies, proteins and genes that have inherent biological activity.

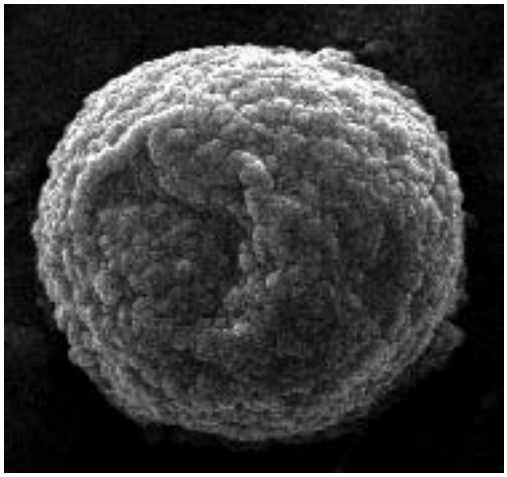
The second, and a complementary approach, is the creation of drug delivery systems that can act as a vehicle to carry and guide more precisely the abovementioned agents to their desired site of action. In 2002 and 2003, more biotechnology products (proteins and antibodies) and drug delivery systems were approved by the US Food and Drug Administration as marketed products than new low molecular weight drugs.

Nanosized hybrid therapeutics (e.g. polymer-protein conjugates) and drug delivery systems (liposomes and nanoparticles) have already been approved for routine use as medicines. The drug delivery systems entering the market have been designed to achieve disease-specific targeting, to control the release of the drug so that a therapeutic concentration is maintained over a prolonged period of time, or to provide more convenient routes of administration (e.g. oral, transdermal and pulmonary) and reach locations in the body that are traditionally difficult to access, such as the brain. Via the use of coatings, ever more sophisticated devices are emerging that allow localised controlled release of biologically active agents.

Complex supramolecular assemblies, nanoparticles and polymeric materials in many different forms are already playing an important role in the construction of nanopharmaceuticals. It is clear that the contribution of nanotechnology will continue to grow in the future, and it is widely believed that effective delivery gene therapy and other macromolecular therapeutics will be realised only with the aid of multicomponent, nanosized delivery vectors.

Non-invasive patient imaging using techniques such as gamma camera imaging, magnetic resonance imaging, X rays and ultrasound are important established tools used to assist diagnosis and monitor response to treatment. Molecular level imaging using techniques such as positron emission tomography (PET) can also provide information on drug targeting, drug metabolism and disease response to therapy. Several nanoparticle-based magnetic resonance imaging (MRI) agents have already been approved for routine clinical use, and it is recognised that future application of nanotechnology has an enormous potential in this field. Complex supramolecular assemblies are already being explored in research and development to yield agents for molecular imaging in the context of MRI, ultrasound, optical imaging, and X-ray imaging.

Moreover, in the longer term, the combination of imaging technologies and drug delivery systems has the potential to yield theranostics devices.



2. Current Status of Nanomedicine Research and Forward Look

Output of workshops held in Amsterdam March 2004 and the Consensus Conference Le Bischenberg November 2004

2.1. Science and Technology

2.1.1. Workshop on Analytical Techniques and Diagnostic Tools

Workshop participants:
Dr Patrick Boisseau (chair)
Dr François Berger, Prof. A.W. McCaskie,
Dr Françoise Charbit, Dr Rosita Cottone,
Prof. H. Allen O. Hill, Prof. Lars Montelius,
Dr Kristina Riehemann, Dr Ottila Saxl,
Dr Jürgen Schnekenburger, Prof. Yosi Shacham,
Prof. Clemens Sorg, Dr Dimitrios Stamou,
Prof. Csaba Szántay

Introduction

There is considerable anticipation that miniaturisation via the application of nanotechnology and new nanotools will lead to novel surgical and analytical tools and diagnostics for use ex vivo. It is envisaged that such techniques will increase our ability to identify predisposition to disease, monitor disease progression and identify the most relevant patient treatments. Moreover, a new generation of surgical tools is predicted that will be able to assist diagnosis and deliver therapy at a cellular level. In the context of larger ex vivo diagnostic devices, the focus of this research lies on nanointeractions. Europe has a relatively strong position in basic research in this field but failure to exploit its inventions is a continuing problem. DNA and protein chips are already widely used as research tools and are helping to provide a better understanding of the molecular basis of diseases and identify new molecular targets for therapy. It is perceived that many nanotechnology-derived tools will, in the future, be routinely used in diagnosis of many diseases long before they will be approved as treatments.

In the case of these devices, nanoscale objects were defined as molecules or devices within a size-range ofone to hundreds of nanometres that are the active component or object, even within the framework of a larger micro-size device or at a macro-interface.

Scope of this discipline

In the area of nanoanalytical techniques and diagnostic tools that will find application in the sectors of diagnostics, medical devices and pharmaceutical drug discovery, a wide range of technologies are being developed for both in vitro (diagnostics and sensors) and in vivo use (in line sensors, implantables and surgical tools) with a range of biological targets including cells, DNA and proteins. Research and development in this field is extremely multidisciplinary and there is considerable synergy with the 'nanoimaging and manipulation' and the 'nanomaterials and nanodevices'.

Analytical and point-of-care diagnostic product design is already supported by the use of nanoparticles and nanodevices. For example, biosensor technology based on nanotechnology represents a huge opportunity to revolutionise diagnostics in the healthcare environment. Healthcare professionals in primary care and hospital clinics are shortly expecting to be able to use low-cost tests able to aid the diagnosis by simultaneous measurement of

Bioarrays and Biosensors	Nanofabrication	Nano-objects	Detection
DNA chips	lab on chip	nanotubes	electrochemical detection
protein-chips	pill on chip	nanowires	optical detection
glyco-chips	nanofluidics	nanoparticles	mechanical detection
cell-chips		nanostructured surfaces	electrical detection - by scanning probes - by mass spectrometry - by electronmicroscopy
biosensors for single and multiple analytes		nanodevices and nanoelectronics	

multiple parameters using a simple test strip without having to measure each parameter individually. Such test strips must be disposable and cost effective. So far only single analyte strips have been available but multisensor dry enzyme, hand-held systems being developed in Europe are leading the way towards fast and accurate multiparameter analysis.

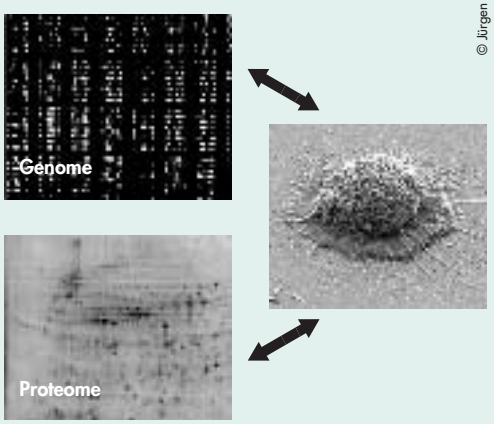
There is an opportunity to focus on technically more mature developments that are more likely to be successful, and also to address niche markets that have better prospects for exploitation. Moreover, techniques and tools developed for analysis and diagnostics in the medical field have the potential for wider application, for example, in the context of environmental monitoring, control of food hygiene etc.

An ideal near-patient diagnostic system	
• **Fast**	Minimise consultation time (<1 minute)
• **Simple**	Lay person (nurse's aid) can use
• **Portable**	Take the test to the patient
• **Storage**	Room temperature for consumables
• **Painless**	Minimally invasive blood sampling
• **Single step**	One sample, one strip, many analytes
• **Platform**	One instrument, many diseases

While there is no lack of innovation in Europe, there was agreement that in many areas Europe is lagging behind. The DNA array market, for example, is dominated by Affimetrix, an American company. While DNA chips are being widely used in research, their difficulties in securing quality assurance and regulatory approval, their production flexibility and speed to result are well known. Although other more technically complex chips are available, so far they are substantially more expensive.

Underlying research was seen as a further European strength, particularly in relation to the identification of medical targets. Current genomics and proteomics techniques give a limited insight into cellular function. In the future, the combination of these techniques with imaging methods such as TOF-SIMS analysis, and raster electron microscopy by atomic force microscopy of living cells will give more information on individual protein function and cell signalling.

Cells as complex 3D systems: the organisation and function of cells can not be described by the simple analysis of their contents



Workshops held under the auspices of the European Federation of Pharmaceutical Industries and Associations (EFPIA) have identified a number of bottlenecks delaying development of new pharmaceuticals. To improve clinical performance and early access to innovative medicine there is a recognised need for improved biomarkers and surrogate markers to allow prediction of efficacy. Improved in silico tools are needed for toxicogenomics, toxicoproteomics, and metabonomics that can be used to improve the predictability of toxicological profile of innovative medicines.

2.1.2. Workshop on Nanoimaging and Manipulation

Imaging at the molecular level, measurement of molecular forces

Workshop Participants:
Prof. Jean-Louis Coatrieux, Dr Mauro Giacca (chairs)
Dr Andreas Briel, Prof. Salvatore Cannistraro, Prof. Martyn Davies, Dr Sjaak Deckers, Dr Nicole Déglon, Dr Franz Dettenwanger, Prof. Paul Dietl, Rainer Erdmann, Prof. Robert Henderson, Dr Arne Hengerer, Dr Peter Hinterdorfer, Dr Corinne Mestais, Prof. Hans Oberleithner, Prof. T.H. Oosterkamp, Dr Andrea Ravasio, Dr Hui Wang

Introduction

Imaging is becoming an ever more important tool in the diagnosis of human diseases. Both the development of imaging agents based on micro- or nanoparticles, organic dyes etc., and the development of

highly sophisticated instruments supported by powerful computation (2D, 3D reconstruction) have already given rise to a significant move from invasive to less invasive clinical imaging. This is allowing an ever more sophisticated imaging-based diagnosis, particularly in cancer, neurological and heart diseases.

Nanotechnology has an important role to play in further developing this field. Earlier diagnosis with a non-invasive tool can allow earlier treatment and this treatment approach can be much less expensive and often more effective. In addition, economists consider living healthier, longer lives to be economically beneficial. There are potential risks and side-effects from new imaging agents based on nanomaterials, but risk-benefit analyses will be/are being conducted at an early stage. One of the greatest problems in the transfer of these approaches into routine clinical use lies in the slow approval process of new materials for human use by regulatory agencies.

Imaging at cellular, and even sub-cellular and molecular level, is still largely a domain of basic research. However, it is anticipated that these techniques will find their way into routine clinical use. Atomic force microscopy (AFM) and AFM-related techniques have become sophisticated tools, not only to image surfaces of molecules or sub-cellular compartments, but also to measure molecular forces between molecules. This is substantially increasing our knowledge of molecular interactions.

Scope of this discipline

Because of its interdisciplinary nature, the field of Nanoimaging and Manipulation is also identified as having a considerable overlap with the other disciplines, particularly in relation to nanomaterials (nanoparticles will play an ever more important role as imaging agents), and clinical, regulatory and toxicological issues.

The field termed here ‘Nanoimaging’ overlaps with the field already called ‘Molecular Imaging’. In this case the target to be imaged will have a spatial resolution in the order of 1-100 nanometres, and preferably a time resolution for imaging in the order of milliseconds. The opportunities for improvements and breakthroughs with the assistance of nanotechnology were seen in terms of both existing and emerging technologies. The imaging techniques discussed are listed:

Techniques	Examples
Optical imaging and Spectroscopy	SNOM, STED, Raman SERS, FRET, FRAP
Surface plasma resonance	TIRF, NIRF, Multiphoton LSM
Magnetic Resonance Imaging	X-CT
Nuclear Imaging	micro-PET, SPECT
Scanning probe microscopy and force microscopy Ultrasound Optical tweezers	AFM
Multimodal nanoimaging is the future and will link structure to function and vice versa	fluorescence probe and SPM, fluorescence and laser tweezers opto-acoustic imaging

Europe has a number of leading academic groups and several leading companies who are pioneers in the development of imaging techniques and innovative contrast agent production (e.g. Bracco SpA, GE formerly Amersham, Philips Medical Systems, Siemens Medical Solutions and Schering AG).

Basic research has already developed the first methods to monitor in vitro the assembly of multi-component biological complexes, protein trafficking and the interactions between single molecules. There is a recognised opportunity to use nanotechnology to improve these molecular imaging techniques, and to construct real-time intracellular tomography. Objective methods for assessment of image quality are also needed in vitro and in vivo. Tools are currently under development that allow in vitro evaluation of basic mechanisms, but it was felt that these could quickly be developed towards real ex vivo and clinical applications.

In the context of in vivo and clinical imaging, the development of novel techniques for macromolecular imaging was seen as a particular priority. Europe has been at the forefront of the development of polymeric gamma camera imaging agents and dendrimer-based MRI imaging agents. Improved image analysis is a particular goal. There is a need to improve 3D reconstruction and quantitative data analysis. Improved visualisation techniques are needed also for stereo-imaging, virtual and augmented reality imaging, and image-guided manipulation.

Opportunities exist for both invasive and non-invasive clinical imaging, e.g. endoscopy for targeted imaging, use of optical catheters and development of nanosized systems allowing manipula-

tion, target selection, local stimulation and potentially local modification.

Development of more sophisticated imaging equipment requires an integrated approach. Underpinning research must involve all aspects of the process.

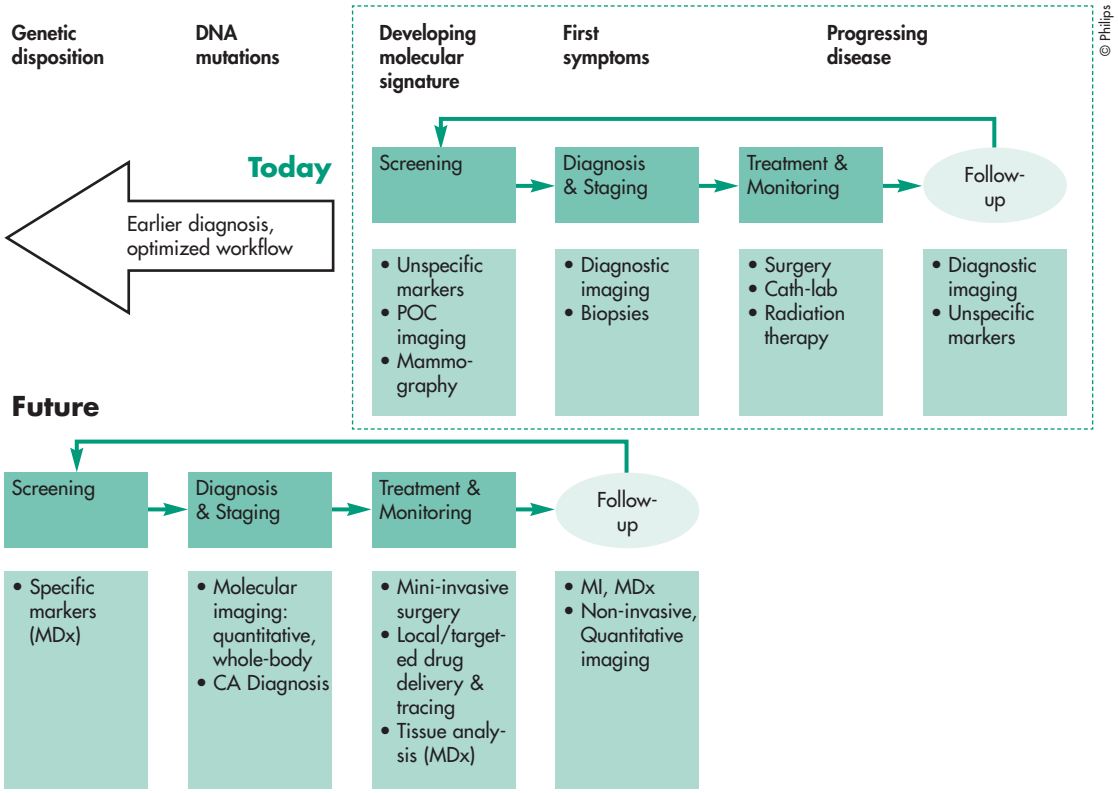
Parallel to the development of the analytical equipment, research and clinical development is ongoing to provide a new generation of nanoimaging agents. These include both synthetic nanoparticles (including dendrimers and polymeric nanoparticles) and biological nanoparticles (nanoorganisms). In the future it is likely that these imaging tools will become ever more complex, multicomponent systems combining contrast agents and tracking probes (e.g. quantum dots, magnetic and superparamagnetic beads, nanoshells and nanocolloids) with new targeting ligands. For targeted systems, carriers can be used which may require additional surface modification, and linkers that bring additional challenges for physicochemical characterisation and safety evaluation. In some cases combination of a range of signal modalities (e.g. organic dyes) is also used. Imaging and contrast agent design has a considerable overlap with nanomaterials and drug delivery system development. Historically, radiolabelled antibodies have already been transferred to market as diagnostic tools in cancer, and in the form of radiolabelled antibodies and antibody conjugates as a therapeutic agent. It can be argued that the radiolabelled therapeutic antibody is the first nanosized theranostic.

Development of molecular imaging diagnostics is expected to have a major impact on healthcare in the future and the opportunities are summarised below.

2.1.3. Workshop on Nanomaterials and Nanodevices

Workshop participants:
Prof. Jeffrey Alan Hubbell, Prof. Ruth Duncan (chairs), Prof. Wim Hennink, Prof. Helmut Ringsdorf (co-chairs), Prof. Hans Börner, Prof. João Pedro Conde, Dr John W Davies, Prof. Harm-Anton Klok, Prof. Helmuth Möhwald, Dr Mihail Pascu, Prof. José Rivas, Dr Christoph Steinbach, Prof. Manuel Vázquez, Dr Peter Venturini, Dr Petra Wolff, Prof. Andrew McCaskie

Molecular Imaging Diagnostics (MDx): Impact on healthcare in the future



Introduction

All aspects of Nanomedicine rely on progress in nanomaterials research, and the nanoengineering needed to create devices to realise their goals. Materials science is being employed to generate probes and techniques that are helping to understand basic biological mechanisms. On the other hand, emergence of more sophisticated nanomaterials and nanodevices is required to develop diagnostic and surgical tools, drug delivery systems and in vivo diagnostics into routine clinical practice. Moreover, nanoscale assemblies for ligand display are already emerging as multicomponent 3D architectures able to assist tissue engineering and promote tissue repair.

Nanopharmaceuticals (drugs and drug delivery systems) are nanoscale assemblies, which can be relatively simple; for example, nanoemulsions, nanoparticles or polymer conjugates (of proteins or drugs), or complex mutlicomponent systems containing drugs, proteins or genes, and an array of targeting ligands and signal systems to enable in vitro or in vivo detection. The nanomaterials and nanodevices that are being developed have scales from molecule-to assembly-to functional device in the nanometre-size range.

This field is rapidly moving from the development of individual building blocks to multifunctional, often biomimetic and bioresponsive systems. The combined knowledge and expertise of synthetic and physical chemistry as well as biological chemistry are required for the development of effective nanomaterials and nanodevices that are efficient and safe in the biological environment.

Most importantly, it was noted that the research in nanomaterials and nanodevices must strive for biological and medical relevance with this in mind. The potential timescale for development of practical-to-use systems could be relatively short. As nanodiagnostics, e.g. a dendrimer-MRI agent, are already in clinical development, it can be predicted that those nanodiagnostics under in vitro development today should be available for clinical evaluation within the next few years. Over the next few decades, considerable growth in the routine clinical use of in vivo nanodiagnostics as well as nanotherapy was predicted.

Scope of this discipline

Europe is particularly strong in physical and multifunctional chemical assembly of nanostructures (supramolecular chemistry), and colloid and polymer science including development of micro-electro-mechanical systems (MEMS), nanoparticles, and polymer therapeutics. There are also considerable strengths in engineering materials (surfaces and nanosized and nanostructured polymers and colloids) to control and direct cellular function for biomedical applications, and the materials science relating to tissue engineering and regenerative medicine, bioactive materials and the related stem cells as sources.

The overall Nanomedicine-related goals for the research and development in nanomaterials and nanodevices were identified as the development of technologies to satisfy the following applications:

Biological Applications:

- **Definition of target and pathway and network identification**
  - Via multiple, co-assembled biomolecules
- **Definition of mechanisms of signalling and signal transduction**
  - Via artificial assemblies in vitro

Medical Applications:

- **Drug targeting**
  - Whole body, cellular, sub-cellular localisation of drugs, proteins and genes
- **Drug discovery**
  - High Throughput Screening technology with biomolecular or cellular read-outs
  - Novel bioactives, obtained through nanotechnology
  - Novel drug delivery systems
- **Diagnostics and sensing**
  - In vitro (multiple analyte detection) and in vivo
- **Regenerative medicine**
  - Materials to regulate cell signalling and differentiation, and also controlling morphogenesis thus helping to bring functional integration

Enabling technologies currently being developed include new systems for physical assembly, new routes to macromolecular synthesis via chemical and biosynthesis. In the latter case, minimisation of nanoparticle or polymer polydispersity and heterogeneity is essential for use in the construction of nanopharmaceuticals.

Further development of combinatorial chemistry and biology is a certainty bringing multiple-functionality into library design to provide high-level functional screening technology. The planar 10-100 nm scale systems for screening and detection that will emerge will have multiple, integrated detection systems. Hierarchical, oriented, multicomponent displays of biological molecules with passivation of

background effects were seen as a particular challenge. Control and feedback technologies are needed to enable biomolecular recognition to be transferred into practical-to-use detector development. For analytical systems, increased sensitivity is needed, and analysis of functional systems.

Development of new materials with complex functionality is already ongoing. This is particularly important in the context of tissue engineering scaffolds and arrays for detection. Spatial control of functionalisation is needed with ordered display of orthogonal functionality, and the ability to design into a system-triggered control of response; that is, new bioresponsive materials. Improved methods for surface functionalisation of colloids and surfaces are needed as well as new and validated analytical techniques to ensure safety and reproducibility. Integration of multiple-functionality (fluidics, with manipulation and detection) will enable translation to implantable configurations with telemetric detection and control.

2.1.4. Workshop on Drug Delivery and Pharmaceutical Development

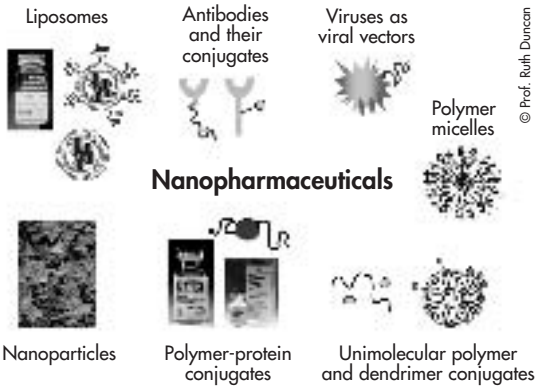
Workshop participants:
Dr María José Alonso, Prof. Ruth Duncan (chairs), Prof. Thomas Kissel (co-chair)
Dr Oliver Bujok, Prof. Patrick Couvreur, Prof. Daan Crommelin, Dr Julie Deacon, Dr Luc Delattre, Prof. Mike Eaton, Prof. Claus-Michael Lehr, Dr Laurant Levy, Prof. Egbert Meijer, Dr Milada Sirova, Prof. Karel Ulbrich, Prof. Arto Urtti, Prof. Ernst Wagner, Dr Jaap Wilting

Introduction

Nanopharmaceuticals can be developed either as drug delivery systems or biologically active drug products. This sub-discipline was defined as the science and technology of nanometre size scale complex systems, consisting of at least two components, one of which is the active ingredient. In this field the concept of nanoscale was seen to range from 1 to 1 000 nm.

Over the last three decades Europe has been at the forefront of the research and development of nanosized drug carriers including liposomes, nanoparticles, antibodies and their conjugates, polymers conjugates, molecular medicine (including proteins) and aspects of nanobiotechnology including tissue engineering and repair.

There are a growing number of marketed nanosized drug delivery systems and imaging agents.



They include liposomal anticancer agents, antibody-drug conjugates, polymer-protein conjugates, nanoparticle-based imaging agents and an anticancer delivery system (see Appendix VI). There are also a large number of constructs (including the first polymer-based gene delivery system) in clinical development. These can be viewed as the first-generation Nanomedicines and future developments will build on these successes.

Scope of this discipline

The nanosized drug delivery systems currently under development are either self-assembling, or involve covalent conjugation of multicomponent systems, e.g. drug, protein and polymer. The materials used to create such drug delivery systems typically include synthetic or semi-synthetic polymers, and/or natural materials such as lipids, polymers and proteins. If classified by function, many materials used for drug delivery are bioresponsive and/or biomimetic. An increasing number of nanosystems are being proposed as drug carriers. They include micelles, nanoemulsions, nanoparticles, nanocapsules, nanogels, liposomes, nanotubes, nanofibres, polymer therapeutics and nanodevices. Magnetic nanoparticles are being developed for diagnostic imaging and disease targeting, for example, liver and lymph node targeting following intravenous administration.

For the past thirty years, Europe has pioneered the development of many of these technologies and research in the area of nanodrug delivery is still forging ahead. Pharmaceutical science is especially strong, but research is increasingly interdisciplinary both across Europe and indeed globally. There is already a number of major programmes and strategic initiatives in Europe promoting interdisciplinary research and training in drug delivery, although there has not been any clear emphasis within the

EU Framework 6 Programme (FP6) to promote networks of excellence and specific projects able to enhance activities in the area of Nanomedicine.

There are three principal goals of drug delivery research today: more specific drug delivery and targeting; greater safety and biocompatibility; and faster development of new, safe medicines. To achieve these goals the current nanotechnologies being applied to drug delivery and pharmaceutical research include the following:

Nanotechnologies

- Supramolecular chemistry-Self assembling drug carriers and gene delivery systems
- Nanoparticles and nanocapsules
- Antibody technologies
- Polymer-drug conjugates
- Polymer-protein and antibody conjugates
- Nano-precipitation, nanocrystals
- Emulsification technologies
- Liposome technology
- In situ polymerisation
- Tissue engineering and repair
- Dendrimer technologies
- Molecular imprinting

In parallel to the technology development there is a need to develop pharmaceutical formulations that can be conveniently administered to patients and that display acceptable shelf-life stability.

Validated analytical techniques are also needed to confirm the identity, strength and stability of complex nanomedicines. New chemical and physical techniques must be developed during scaling-up.

During research and development molecular imaging techniques (e.g. AFM) are increasingly being used, and in vitro (e.g. caco-2 cells, blood brain barrier models, and skin models) and in vivo models are being developed to understand better cellular and whole-body pharmacokinetics. There is also a need to examine carefully pharmacokinetic and pharmacodynamic correlations to allow carefully design of drug targeting and controlled release systems.

In the near future, nanodrug delivery systems and pharmaceutical research have the potential to contribute significantly to the furtherance of Nanomedicine. The key topics of investigation are:

- vectors that will overcome the biological barriers for effective gene delivery
- cancer targeting
- brain delivery
- combination of the potential of antibody targeting with nanoparticle and liposome technology.

With good interaction between academia and industry, increased European funding to strengthen the translational research and development, and building on past successes, these goals can be realised quickly. However, tremendous challenges also lie ahead. There is still a lack of communication in a field where the multidisciplinarity of the research continues to grow. At the research stage, chemistry-physics-pharmaceutical science-biology-medicine must work in concert. There is a concern that regulatory hurdles may become so high that the industry will be reluctant to accept the risk of developing innovative technology. In addition, because of the variable quality of the scientific representation within public debate and concerns raised about nanotechnology as a whole, there is an apprehension that the general public may be reluctant to accept new concepts and technologies.

2.1.5. Workshop on Clinical Use, Regulatory and Toxicology Issues

Workshop participants:
Dr Wolfgang Kreyling, Prof. Rogério Gaspar (chairs), Dr Paul J. A. Borm (co-chair)
Prof. Luc Balant, Dr Janna de Boer,
Dr Thomas Bruhn, Prof. Kenneth Donaldson,
Dr Benoit Dubertret, Prof. Ruth Duncan,
Prof. Mike Eaton, Prof. Mauro Ferrari,
Prof. Alberto Gabizon, Prof. Varban Ganev,
Dr Andreas Jordan, Prof. Harm-Anton Klok,
Prof. Jørgen Kjems, Dr Mihail Pascu,
Prof. Helmut Ringsdorf, Dr Valérie Lefèvre-Seguin,
Dr Ottila Saxl, Dr Milada Sirova, Prof. Karel Ulbrich

Introduction

As for any other conventional medicine, the entire life cycle of nanopharmaceuticals includes production, distribution, clinical administration, consumer safety (human body effects and side-effects), and waste disposal. While the clinical applications usually concern only the selected stages of the life cycle, toxicological effects may exist in all the stages. Both clinical applications and toxicology of nanopharmaceuticals must be studied and examined comprehensively.

When designing a clinical protocol for a nanopharmaceutical there are new challenges. Clinical trials and epidemiology studies may be significantly different from those for conventional diagnostic and therapeutic agents. Early dialogue and collaboration between scientists, clinicians, toxicologists and regulatory authorities are increasingly recognised as one of the important issues to ensure rapid clinical uses of safe nanopharmaceuticals.

Scope of this discipline

Nanoscale objects, typically but not exclusively with dimensions smaller than 100 nm, smaller than 200 nm for ultrafiltrable range and smaller than 1 000 nm for dendrimers, exhibit fundamentally different physical, chemical and biological properties from those of the corresponding mass materials. These distinctive properties, together with the nanoscale size which is in the same scale of the naturally occurring biomolecules, promise revolutionary potential applications in clinical practice. Nanomedicines or nanopharmaceuticals may therefore be defined as nanoscale material to be used for clinical diagnosis, treatment, and prevention of human disorders. Nanomedicine application depends on the structures and mechanisms which are functional only on nanoscale-mediated macro-molecular and supra-molecular assemblies.

In particular, the following areas were considered:

Technology	Application
Nanopharmaceuticals – in current use or entering routine use in the short-term future (within 5 years)	Cancer Antiviral agents Arteriosclerosis Chronic lung diseases Diabetes
Nanopharmaceuticals – with potential clinical applications in the longer term future (10 years)	Gene therapy Tissue engineering Tissue/cell repair
Nanodevices	Delivery of diagnostic and therapeutic agents

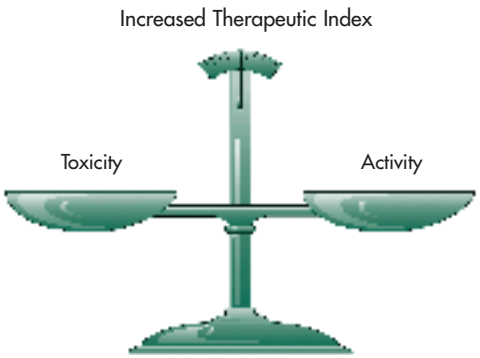
There are very strict regulations and approval processes for any medicine (via regulatory agencies such as FDA, EMEA etc.) or any material proposed for human use. It must undergo rigorous toxicology studies as part of the regulatory approval process. However, the special properties of nano-objects that are only exhibited at the nanoscale suggest that nanopharmaceuticals may also require a new array of toxicological and safety tests. It was agreed that new strategies in toxicology for Nanomedicine must go hand-in-hand with the development of nanopharmaceuticals in order to ensure the safe yet swift introduction of nanomedicines to clinical use.

The toxicology of nanopharmaceuticals, nano-imaging agents and nanomaterials used in device manufacture should be considered during their entire life cycle:

- stages of production/manufacture
- preclinical and clinical development (or for other uses e.g. veterinary)
- consumer and staff safety
- waste management/fate in environment.

Although the nanopharmaceuticals that have already entered routine clinical use have been rigorously tested with regard to safety, there have been comparatively few toxicological studies published on nanopharmaceuticals. However, this issue needs to be explored, based on the large literature in the toxicology field describing the effects of nanoparticles, either present in the environment as pollutants or made as a result of the industrial production of non-medical and non-biological materials.

Cancer Chemotherapy and Drug Targeting



Europe has considerable experience in the clinical development of nanopharmaceuticals (particularly in cancer). Pre-clinical toxicology to 'good laboratory practice' (GLP) has assessed antibody-drug conjugates, polymer-drug conjugates and nanoparticle-based chemotherapy. During the development of novel anticancer treatments there is always a careful evaluation of risk-benefit.

Since Europe has particular strengths in the research areas of toxicology of inhaled ambient or occupational fine and ultrafine particles there is an excellent opportunity to redress the current mismatch between studies on toxicology of nanomaterials and those involved in research and development of Nanomedicine-related technologies.

As there seems to be enormous prospects for the application of nanotechnology in medicine, the European Nanomedicine research community should act proactively to seize the opportunity to clearly define the ground rules for the related toxicological research, and the related clinical and industrial development of these important technologies.

As yet there are no regulatory authority guide-

lines specific to Nanomedicine. As the number of nanopharmaceuticals increases there is a need to review and define appropriate regulatory authority guidelines directed towards each new class of Nanomedicine. It would be timely to produce 'Good Clinical Practice' (GCP) guidelines that may be applied to the clinical development of specific families of drug delivery systems or therapeutics. Some examples of well-established categories of pharmaceuticals involving nano-objects are polymer-protein, polymer-drug conjugates and nanoparticle-associated chemotherapy. There may be specific clinical endpoints that are unique to these nanomedicines, and there may also be specific issues relating to good manufacturing practice (GMP) compliance.

Second generation nanopharmaceuticals are already being, or will be, developed based on first generation systems. An integrated strategy will be the key for toxicological evaluation of new nanomaterials that are emerging. There is a need for preclinical and clinical test standardisation and an evaluation of the environmental impact of these systems in the context of academic research and industrial development. On a case by case basis there is a need to define toxicokinetics, toxicogenomics, and toxicoproteomics. This field might be defined as 'Toxiconanomics'. This research effort should be conducted by virtual networks of basic and applied scientists using existing expertise as a starting point. Industrial collaboration should be used to establish standard reference materials.

2.2. Research Strategy and Policy

2.2.1. Organisation and Funding

Workshop participants:
Prof. Claus-Michael Lehr (chair),
Prof. A.W. McCaskie (co-chair)
Dr María José Alonso, Prof. Luc Balant,
Dr Janna de Boer, Prof. Salvatore Cannistraro,
Dr Rosita Cottone, Dr Nicole Déglon,
Dr Franz Dettenwanger, Prof. Thomas Kissel,
Prof. Helmuth Möhwald, Dr Mihail Pascu,
Prof. Clemens Sorg, Dr Christoph Steinbach,
Prof. Manuel Vázquez, Dr Petra Wolff

It was suggested that current funding mechanisms do not adequately address the needs of Nanomedicine. The structure of programmes and the diversity of sources (e.g. European, national, regional and charities) can obscure routes to funding. This is further limited by traditional borders between scientific disciplines; e.g. chemistry, physics, biology, medicine and engineering, which can effectively exclude transdiscipline and interface research. In many cases the funding opportunities are often restricted by the requirement of an industrial partner. Moreover, selection criteria can often be political, rather than based on scientific excellence. The fact that EU FP6 applications were channelled into main themes of 'Health' or 'Nanotechnology' was a contributory factor, leading to the ineffectiveness of FP6 to successfully support the stated Nanomedicine objectives of this scheme. The possibility of an EU Technology Platform in Nanomedicine was noted and welcomed.

It was noted that there is an opportunity to improve communication/coordination between the different funding agencies across Europe. There is a specific need to reflect the multidisciplinary nature of Nanomedicine in funding opportunities presented.

The funding opportunities available for basic technological research must initially be available for pure academic groups without an underlying requirement of an industry partner. All calls for proposals and applications should encourage the appointment of multiple partners from different disciplines with internationally leading expertise. The evaluation of such multidisciplinary proposals must be undertaken by a multidisciplinary expert panel using the same format used by the US National Institutes of Health (NIH) study groups. Whilst the European networking instruments (e.g. COST, Network of Excellence etc.) are considered

helpful, in the future there must also be enough funding to undertake basic and applied Nanomedicine research (that is, for salaries, instruments, and consumables).

Means to improve funding and organisation at the level of political bodies, policy makers and national organisations were identified. The fundamental requirements to progress Nanomedicine quickly are more investment for Nanomedicine R & D, greater understanding of the complexities of this multidisciplinary area, and a higher priority for specific technologies that will improve healthcare for society in Europe.

Specific opportunities include:

- Those aspects of Nanomedicine that have been realised and transferred into practice today have arisen from previous basic research programmes. Universities should be able to pursue a more entrepreneurial freedom and spirit to increase inventiveness that will feed the future technology pipeline.
- Nanomedicine should be discussed in terms of pharmacoeconomic value at an early stage with regulatory authorities, policy makers and healthcare stakeholders.
- The potential of Nanomedicine to create not only new products, but also new jobs (socioeconomic value) needs to be appreciated.
- Public awareness about the opportunities and *realistic* risks of Nanomedicine is necessary and can be brought about by educational programmes. National support for Nanomedicine would be enhanced when action groups and patient-support groups are more aware of the benefits that these technologies can already bring.

2.2.2. Commercial Exploitation

Workshop participants:
Dr Julie Deacon (chair), Dr Oliver Bujok, Dr Françoise Charbit, Dr John Davies, Dr Sjaak Deckers, Dr Benoit Dubertret, Prof. Mike Eaton, Rainer Erdmann, Dr Arne Hengerer, Dr Corinne Mestais, Dr Pierre Puget, Dr Jürgen Schnekenburger, Prof. Csaba Szántay

Transferring the technologies arising from Nanomedicine research into clinical reality and generating commercial value from research will rely on the generation of intellectual property, licensing, technology transfer, and collaborative product development involving both specialised small and medium enterprises (SMEs) as well as larger companies. To encourage rapid technology transfer there is a need to generate clusters or highly selected teams chosen for personal excellence, and not to fragment resources.

Nanomedicine is particularly multidisciplinary so there are many opportunities to cross-licence technologies; for example diagnostics and pharmaceuticals. Joint ventures involving confidential R&D relationships could be very successful, but with a complex supply chain, the intellectual property portfolio needs careful management. Good communication and project management skills are needed.

To be competitive and effective in commercialisation, speedy globalisation is imperative. European funding schemes often dictate the choice of partners. To be effective in Nanomedicine development a global perspective is needed involving growing partnership with the USA and other funding agencies. To encourage the establishment of more effective SMEs working in the Nanomedicine field, more focused funding and a fast response to grant applications are needed.

As Nanomedicine becomes fashionable, a good understanding of the end user-supplier interface is vital. Companies that appreciate the medical needs and the practicalities of their technology will be best placed to commercialise. There is a need to promote meetings and a technology directory to assist industry to network. However, Nanomedicine presents a complex array of end-users. The medical doctors' wish list of technologies is not yet commercially validated. Large companies have a time horizon for market entry that is too short for many new technologies, while the activities of SMEs is often too confidential to allow wide discussion. This can make dialogue difficult. There is a real need to increase confidence in Nanomedicine technologies by losing the hype and focusing resources to pick winners.

2.2.3. Interdisciplinary Education and Training

Workshop participants:
Prof. Hans Oberleithner (chair), Prof. Robert Henderson (co-chair) Dr Patrick Boisseau, Dr Paul J. A. Borm, Dr Luc Delattre, Prof. Varban Ganev, Dr Peter Hinterdorfer, Prof. Jørgen Kjems, Dr T.H. Oosterkamp, Dr Andrea Ravasio, Dr Kristina Riehemann, Prof. Arto Urtti, Dr Peter Venturini, Prof. Ernst Wagner, Dr Jaap Wilting

The standard of university education in Europe, in physics, chemistry, biology, pharmacy and medicine, to master's level, is very high. It was noted that specific Nanomedicine training should be developed rapidly to provide an educated workforce and researchers to support this rapidly growing field. New programmes providing education and training in Nanomedicine should encourage interdisciplinarity. master's courses, or early postgraduate medical or scientific training should be developed with a focus on Nanomedicine.

In recent years there has been a reduction in the basic science component of undergraduate medical degrees. Although this may be appropriate for many clinicians, there is a danger that there will be a shortfall in the number of clinician-scientists. These are the very people needed to support the transfer of Nanomedicine into routine clinical practice. Widespread adoption of MD/PhD degree programmes, with some provision for nanoscience training, should be encouraged to provide core scientific training for clinicians. In addition, new funding is needed to support the introduction of such courses, and also for postgraduate clinical training in nanoscience.

In Europe, training in different scientific disciplines is currently highly focused, which is a great strength. However, this presents the danger of individuals lacking knowledge outside their own field, possibly preventing productive communication across disciplines. It was proposed that formal interdisciplinary training programmes should be instituted, focusing on basic scientific topics; for example molecular biology, colloidal chemistry, cell physiology, surface chemistry, and membrane biophysics.

Several European Centres of Excellence should be established (possibly relating to the sub-disciplines of Nanomedicine) to provide an interdisciplinary environment in which participants can 'speak the same language', thus helping to bridge the gap between chemical, physical and biomedical scientists. This would provide the infrastructure for direct interactions between scientists, clinicians and entrepreneurs; e.g. 'Nanomedicine Centres'. Such centres could also be used to provide structures for undergraduate courses that encourage an interdisciplinary frame of mind and allow establishment of Erasmus-type programmes for Nanomedicine.

Importantly, both academic scientists and clinicians should have the opportunity and training to help them identify methods for commercial exploitation of their work.

2.2.4. Communication

Workshop participants:
Dr Ottila Saxl (chair), Prof. Ruth Duncan, Prof. Harm-Anton Klok, Dr Valérie Lefèvre-Seguin, Dr Mihail Pascu, Prof. Helmut Ringsdorf.

Communication issues were discussed in relation to: (i) difficulties in communication within the multidisciplinary scientific environment; (ii) communication between the scientists and the policy makers; and importantly (iii) the perception of the general public.

In general, government departments, research ministries and university faculties continue to operate in separate compartments. A paradigm shift in the way of operation is needed. Otherwise there is no doubt that Europe will lose out in developing a leading position in Nanomedicine, an area that demands a multidisciplinary approach. This will be exacerbated by the emphasis on converging technologies in FP7 as the basis of future products.

A major barrier to collaboration is the lack of understanding between scientists of different disciplines. This needs to be addressed by the establishment of more truly transdisciplinary research groups and more truly transdisciplinary conferences and workshops. The creation of transdisciplinary goal-driven 'clusters', virtual centres and 'poles' should also be actively encouraged. Partnerships should be encouraged between large medical centres and university research groups, leading to goal-oriented research. Transdisciplinary meetings should be held within medical centres and sponsored by a medical leader. This could be facilitated through available instruments at the European level. Additionally, the numbers of transdisciplinary PhDs should be increased, as well as transdisciplinary exchanges at every level – from secondary to tertiary.

The benefits and the *threats* of Nanomedicine need to be clearly articulated to the politicians and policy makers. Benefits include employment potential and the ability to meet the needs of the ageing population. Threats include losing out on important economic opportunities and not meeting the aims of the Lisbon agenda. Serious consideration needs to be also given to lobbying politicians by opinion leaders in the Nanomedicine world. There is also a lack of scientifically qualified politicians, and communication problems have already resulted in a lack of alignment of the regional programmes, the national programmes and the EU programmes.

In the recent past, many top quality transdisciplinary projects and/or papers have not been recog-

nised as such, as the reviewers lack the necessary knowledge. Failure to recognise the significance of our success in multidisciplinary activities has been a great loss to European scientific growth. One way forward is that the national and European funding agencies that provide funds and who audit research output take a lead in pushing for equal weighting for transdisciplinary research.

Nanotechnology has to counter two preconceptions in the mind of the general public. Nanotechnology was initially (and continues to be) popularised through science fiction, and many of the well-established nanoimages are figments of the imagination of Hollywood-inspired artists. Secondly, it suits sensation-seeking journalists to compare nanotechnology with the already discredited genetically modified organisms (GMO) technology. The fact that nanotechnology is such a broad area – covering most if not all areas of technological development, and particularly in the context of the present argument – can make the term Nanomedicine almost incomprehensible to the general public.

To avoid backlash, Nanomedicine-related developments must be presented in a realistic way, without overhyping. It is important to focus on the real benefits that people understand: better diagnostics, smaller doses, fewer side-effects, disease targeted therapy, better efficacy, etc.

The media must be handled intelligently and with caution. And there could be a benefit in providing them with carefully constructed ‘copy’ in advance of any new development. Individuals who have to interact with the press should receive special training. It was also considered important to improve the breadth of communication; through possibly organising thematic meetings aimed at informing focus groups. Nanomedicine awareness-raising activities need public funding (at all levels) in order to ensure a continued dialogue with all stakeholders.

3. European Situation and Forward Look – SWOT Analysis

All the technology based workshops held in Amsterdam from 1 to 5 March 2004 were independently invited to conduct a SWOT analysis regarding the current status of European activities in the field. There was considerable consensus across these groups and the results were summarised and presented at the Consensus Conference held at Le Bischenberg. Below is a summary of the most significant points agreed.

Strengths

Funding and Strategic Issues	Academic Research and Education	Environment for Research and Development	Commercial Exploitation	Technology
• The diversity of funding sources provides a wide range of funding opportunities	• The strong educational base in Europe and training style	• There are already several major European clusters and Centres of Excellence in the Field of Nanomedicine	• There are a number of world leading European companies in imaging/contrast agent and nano-pharmaceuticals areas	• Molecular and clinical imaging techniques, and contrast agent research and development are particular strengths
	• European programmes such as the EU Marie-Curie scheme and the ESF training courses provide good training opportunities although more focus should be put on Nanotechnology in Medicine	• Potential exists to rapidly expand Nanomedicine R & D	• There are a number of SMEs working in the technology and pharmaceutical areas relating to Nanomedicine	• Existing expertise in drug delivery research and the clinical development of nanopharmaceuticals
	• There are many leading academic groups in the sub-disciplines of Nanomedicine	• Visionary institutions such as the New Drug Development Office and Cancer Research UK have facilitated early phase cancer clinical trials and supported translational activities, especially for innovative nano-pharmaceuticals	• Ongoing standardisation efforts at the European Medicines Agency for the Evaluation of Medical Products (EMEA)	• Strong basic sciences, particularly in - antibody technologies - nanoparticle technologies - polymer therapeutics - gene delivery systems - biological models for cell and tissue-based in vitro screening • Leading research groups in ultrafine particle toxicology

Weaknesses

Funding and Strategic Issues	Academic Research and Education	Environment for Research and Development	Commercial Exploitation	Technology
• EU programmes lack long-term strategy as it changes every 5 years. Nanomedicine research needs both a short-and a long-term strategy.	• Insufficient integration of clinical research	• The size of many nanotechnology regional clusters and medical research centres is too small	• Inefficient translation of concept to product because of inadequate venture capital, excessive bureaucracy and lack of medical input	• Interfacing clinical medicine and basic research
• Low funding rates and complex administrative procedures have been problems associated with FP6	• Too much replication of R&D efforts in universities and in companies across Europe	• Small clusters often lack adequate funding	• Interaction with the numerous regulatory authorities, (fragmentation) and differences in regulations can deter those considering product development	• Interfacing basic biological sciences and materials sciences
• FP6 has not been effective for supporting research and development of Nanomedicine		• Specific guidelines, regulations and test protocols for Nanomedicine are still awaiting to be developed	• Lack of ability to interact with regulating agencies at the investigational new drug (IND) stage when developing new technologies, compared with USA	• Lack of competitive edge in chip-based technologies
• Too little funding for application-oriented and translational research		• Compared to the USA and Asia: requirement of ethical approval for many aspects of Nano-medicine research are more demanding	• Inadequate industrial investment in long-term (or basic) research and relatively few companies to cooperate with or assist with commercialisation	
• Lack of a coordinated European Research Council able to allocate funding based only on excellence without a political agenda		• Recent change in clinical trial regulations (new EU directive) will delay clinical trials for nanopharmaceuticals, particularly in cancer	• Ineffective organisation of the health system and inadequate provision of accredited labs can limit options for clinical research and development in the field of Nanomedicine	

Opportunities

Funding and Strategic Issues	Academic Research and Education	Environment for Research and Development	Commercial Exploitation	Technology
• Identification of Nanomedicine as a key area for funding in FP7. Explicitly removing the divide between Health and Nanotechnology	• European courses integrating the biological and physical sciences toward nanoscience, nanobiology, and most importantly nanotechnology applied to medicine	• Better use of human resources e.g. well-educated people coming from Eastern Europe • Increased collaborations between European companies (e.g. imaging and pharmaceutical) and academic institutions	• Better exploitation of innovation at the European level through easier access to venture capital, better dialogue with regulatory agencies and government support for R & D in Nanomedicine. Accelerate Nano-medicine research from lab to clinic and then the market	• Development of a new generation of nanosized materials and devices that can be used as a tool kit • Design of innovative diagnostics and biosensors
• Improved healthcare for European citizens	• Via new education programmes establish a technically skilled workforce able to address the challenges of Nanomedicine research and development	• Establish enhanced job opportunities and a competitive international position in Nanomedicine	• Move towards cost effective patient-individualised treatments, and point of care diagnostics	• Design of nanopharmaceuticals and implantable devices for improved drug delivery
• Establish Networks of Excellence in the sub-disciplines of Nanomedicine via coordination of recognised leading edge researchers and companies		• Proactive risk management with an immediate feed back to Nanomedicine development at the earliest time point	• Use experience with first generation anticancer nanopharmaceuticals to rapidly develop second generation medicines with increased specificity with less toxic side effects for a wider range of target diseases	• Design of vectors able to - assist drugs to better reach their target (transferring across biological barriers) - ensure biotech drugs reach their intracellular targets
• At the European and National level establish well defined goal oriented Nanomedicine focused projects building on specific technical expertise			• Reduced health costs by earlier detection of predisposition allowing use of preventative intervention, and more effective monitoring of chronic illness leading to improved therapy	• Development of nanomaterials able to control biological signalling and provide a biomolecular display for tissue engineering and to promote tissue repair

Threats

Funding and Strategic Issues	Academic Research and Education	Environment for Research and Development	Commercial Exploitation	Technology
• EU and/or national bureaucracy limiting the best use of funding for research and innovation	• Failure to respond quickly to the need for more multidisciplinary training targeted at Nanomedicine, leading to Inadequately trained workforce	• Continued erosion of the European pharmaceutical industry	• Difficulties in managing intellectual property with many different national patent organisations. Poorly capitalised companies can lose their intellectual property base	• Lack of scientific dissemination and truly interdisciplinary exchange in the field of Nanomedicine
• Continued fragmentation of efforts in the Nanomedicine field, particularly economic, political, and regulatory aspects	• Increasing lack of science (under)graduates • Too many young researchers leaving Europe, particularly to USA via brain-drain	• Pharmaceutical companies concentrating their research outside Europe	• Inability to secure sufficient funding (and time) to commercialise innovative products	• Mismatch between studies on toxicology of nanomaterials and Nanomedicine researchers in certain sub-disciplines
• Discrepancies between promises and facts in funding	• Researchers becoming unwilling to take on high risk projects because of the need to generate data (success) for subsequent project evaluation	• Overregulation and inadequate funding for small companies		• Failure to consider the environmental impact of new materials • Failure to consider the safety of new materials in respect of proposed applications
• Negative public and political perception. A different perception by the public on risks of the use of nanopharmaceuticals was noted, compared to the uses of nanotechnology in hi-tech products; e.g. computers and mobile telephones				• Lack of a balanced understanding of the risk-benefit of Nanomedicine-related products in their many forms and applications

4. Recommendations and Suggested Actions

4.1 General Recommendations

4.1.1. Priority areas in Nanomedicine for the next 5 years

- Engineering technology for immobilising cells or molecules on surfaces
- Programmes to generate reproducible and reliable platforms integrating micro- and nanotechnologies
- Methods to deposit such platforms and such components
- Proactive risk management with an immediate feedback to Nanomedicine development
- Clinical applications
- Development of satisfactory sensitivity of in vivo methods
- Developing of non-invasive in vivo diagnostic systems
- Implantable or injectable parenteral nanodevices for diagnosis and therapy

4.1.2. Priority areas in Nanomedicine for the next 10 years

- Understanding of the cell as a 3D complex system
- Bioanalytical methods for single-molecule analysis
- Nanosensing of multiple, complicated analytics for in vitro measurement of biochemical, genomic and proteomic networks, their dynamics and their regulation
- Nanosensing in vivo with telemetrically controlled, functional, mobile sensors
- Rapid fingerprinting of all components in blood samples

4.1.3. Commercial Exploitation

- European seed funds for nanotechnology applied to medicine
- Intellectual Property management
- Improved interactions with the EU regulatory system to promote rapid commercialisation of innovation
- Establishing incubators for innovative companies in nanomedical applications
- New reference organisation (such as EMBO) in nanobiotechnolgy/nanomedicine possibly with prestigious positions, scientific excellence, visibility, and own journal
- Support to clusters for internal cooperation and European coordination

4.1.4. Interdisciplinary Education and Training

- Trained people for technology management and transfer (PhD + MBA)
- Tailored education on management for scientists
- Fellowships to support academics gaining experience in industry
- Multidisciplinary training
- Fellowships for complementary education for scientists

4.2. Scientific Trends

4.2.1. Nanomaterials and Nanodevices

General directions should be:

- optimisation of existing technologies to specific Nanomedicine challenges
- development of new multifunctional, spatially ordered, architecturally varied systems for targeted drug delivery
- enhancement of expertise in scale-up manufacture, characterisation, reproducibility, quality control, and cost-effectiveness

Specific directions should be:

- new materials for sensing of multiple, complicated analytes for in vitro measurement
- new materials for clinical applications such as tissue engineering, regenerative medicine and 3D display of multiple biomolecular signals
- telemetrically controlled, functional, mobile in vivo sensors and devices
- construction of multifunctional, spatially ordered, architecturally varied systems for diagnosis and combined drug delivery (theranostics)
- advancement of bioanalytical methods for single-molecule analysis

4.2.2. Nanoimaging and Analytical Tools

Specific developments should include:

short term

- use and refinement of existing nanotechniques in normal and pathological tissues for the under-

standing of initiation and progression of disease
- development of novel nanotechniques for monitoring in real time cellular and molecular processes in vivo and for molecular imaging to study pathological processes in vivo, with improved sensitivity and resolution
- identification of new biological targets for imaging, analytical tools and therapy
- translation of research based on molecular imaging using nanoscale tools from animal models to clinical applications
- closing of the gap between the molecular and cellular technologies and the clinical diagnostic nanotechnologies

Specific developments should include:

longer term
- development of a multimodal approach for nano-imaging technologies
- design of non-invasive in vivo analytical nanotools with high reproducibility, sensitivity and reliability for use in pre-symptom disease warning signal, simultaneous detection of several molecules, analysis of all sub-cellular components at the molecular level, and replacement of antibodies as detection reagents by other analytical techniques

4.2.3. Novel Therapeutics and Drug Delivery Systems

Specific developments should include:

short term
- application of nanotechnology to develop multifunctional structured materials with targeting capabilities or functionalities allowing transport across biological barriers
- nanostructured scaffolds (tissue engineering), stimuli-sensitive devices and physically targeted treatments
- a focus on cancer, neurodegenerative and cardiovascular diseases and on local-regional delivery (pulmonary/ocular/skin)

Specific developments should include:

longer term
- a synthetic, bioresponsive systems for intracellular delivery of macromolecular therapeutics and bioresponsive/self-regulated delivery systems (smart nanostructures such as biosensors coupled to delivery systems)

4.2.4. Clinical Applications and Regulatory Issues

General directions should be:
- disease-oriented focus for Nanomedicine development in specific clinical applications
- case-by-case approach for clinical and regulatory evaluation of Nanomedicines
- highly prioritised communication and exchange of information among academia, industry and regulatory agencies with a multidisciplinary approach

4.2.5. Toxicology

General directions should be:
- improved understanding of toxicological implications of nanomedicines in relation to material properties and proposed use by the potentially predisposed, susceptible patient
- thorough consideration of the potential environmental impact, manufacturing processes and ultimate clinical applications in toxicological investigations for nanomedicines
- risk-benefit assessment for both acute and long-term effects of nanomedicines with special consideration on the nature of the target disease
- a shift from risk assessment to proactive risk management at the earliest stage of new nanomedicines discovery and development

4.3. Research Strategy and Policy

4.3.1. Organisation and Funding

Recommendations
- improved coordination and networking of research activities and diverse range of funding sources at the European, national and regional levels
- creation of new Nanomedicine-targeted funding schemes to better facilitate both transdisciplinary and interface research that is critical for success in Nanomedicine
- establishment of European Centres of Excellence in the field of Nanomedicine
- modification of funding mechanisms for basic technological research to permit academic-group-only applications
- development of funding procedures with sufficient scale and scope; for example with longer term funding rather than continuous short-term funding cycles, to enable research for seriously tackling goal-oriented problems
- establishment of economic and social benefits of Nanomedicine and communication of them to stakeholders and the public

Suggested Action
- coordinated funding of basic research in Nanomedicine through ESF EUROCORES and European Commission FP7 instruments (e.g. ERA-Net)

4.3.2. Commercial Exploitation

Recommendations

- establishment of a scheme supporting academic/commercial ventures, such as a European version of the Small Business Innovative Research program of the US National Institutes of Health
- involvement of clusters or highly selected teams, chosen for personal excellence or track record
- establishment of more manufacturing sites with 'Good Manufacturing Practice' designation to support small and medium enterprises for transferring projects more rapidly into clinical development

Suggested Actions

- liaise with regulatory authority for Good Manufacture Practice designation
- conduct policy study on the feasibility for a European Small Business Innovative Research programme

4.3.3. Interdisciplinary Education and Training

Recommendations

- establishment of formal interdisciplinary training courses, mainly at the undergraduate level, covering basic scientific disciplines such as molecular biology, colloidal chemistry, cell physiology, surface chemistry, and membrane biophysics
- institution of new programmes, at master's or early postgraduate level (with combined medical and scientific training), to support the rapidly developing field of Nanomedicine
- encouragement of more interdisciplinary MD/PhD degree programmes, with some provision for nanoscience, to provide core scientific training for both scientists and clinicians in the longer term

Suggested Action

- facilitate the establishment of interdisciplinary training courses, masters and MD/PhD programmes via ESF networking instrument (a la carte Programme), COST and European Commission instruments (e.g. Network of Excellence)

4.3.4. Communication

Recommendations

- promotion of more truly transdisciplinary conferences focusing on the specific themes of Nanomedicine to facilitate better communication between research disciplines
- encouragement of goal-oriented research partnerships between large medical centres and university research groups
- clearer articulation and better communication of the benefits of embracing Nanomedicine and the threats from inaction: the benefits consisting of employment potential and meeting the medical needs of the ageing population; and the threats including missed economic opportunities
- engagement of the scientific community in regular dialogue with the general public in order to discover likely public concerns early, and continuation of dialogue to address and alleviate public concerns by the presentation of clear facts
- supply of non-specialist information on potential benefits of Nanomedicine to the general public in a timely fashion, with the emphasis on the fact that Nanomedicine is based on mimicking the elegance of nature

Suggested Actions

- organise truly transdisciplinary conferences using the ESF Research Conference scheme or related schemes at the European Commission
- set up a communication entity, possibly in the form of a small enterprise, to report scientific findings and innovation to the public.

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5.3. Websites and General Information

It should be noted that many web sites contain relevant information but they are not necessarily designated "Nano"

- The world service for nanotechnology nanotechweb.org
- News.Nanoapex.com is one of the best nanotechnology news services on the web news.nanoapex.com/
- Científica – the nanobusiness company http://www.cientifica.com/
- Nanotechnology news at Chemical & Engineering News Chemical & Engineering News - Nanotechnology
- European Nanotechnology Gateway http://www.nanoforum.org/
- iNano website containing links to several companies and institutions that could be helpful in the start-up phase of new companies http://www.inano.dk/sw179.asp
- Pronano Swedish site for the promotion of nanotechnology in industry http://www.pronano.se/
- The Institute of Nanotechnology provides news and background information on new developments in nanoscience www.nano.org.uk

- Nanotechnology database, at Loyola College, Maryland, USA
  itri.loyola.edu/nanobase/
- The Foresight Institute
  www.foresight.org/NanoRev/index.html
- Nanonordic
  www.nanonordic.com/extra/page/
- The Royal Society: Nanotechnology and Nanoscience
  http://www.nanotec.org.uk/

Journals

It should be also noted that many journals contain relevant information but they are not necessarily designated "Nano".

- IEE Proceedings Nanobiotechnology
  www.iee.org/proceedings/nbt
- For the latest articles in nanoscience and nanotechnology, visit the AIP/APS Virtual Journal of Nanoscale Science and Technology www.vjnano.org
- Chemical & Engineering News, October 16, 2000: Nanotechnology
  pubs.acs.org/cen/nanotechnology/7842/7842 nanotechnology.html
- Nano Letters; pubs.acs.org/journals/nalefd/index.html
- Nanotechnology focuses on the interdisciplinary approach to nanoscale science
  www.iop.org/EJ/S/3/354/journal/0957-4484
- Scientific American : Nanotechnology
  http://www.sciam.com/nanotech/www.sciam.com/nanotech
- International Journal of Nanomedicine
  http://www.dovepress.com/IJN.htm
- Journal of Nanobiotechnology:
  http://www.jnanobiotechnology.com/home/
- Particle and Fibre Toxicology
  www.particleandfibretoxicology.com
- Journal of Nanoparticle Research
  www.springeronline.com/sgw/cda/frontpage/0,11855, 4-10100-70-35588310-0,00.html
- Journal of Aerosol Medicine
  http://www.liebertpub.com/publication.aspx?pub_id=24
- International Journal of Nanomedicine
  www.dovepress.com/IJN_ed_profile.htm
- Journal of Nanotoxicology
  http://www.tandf.co.uk/journals/titles/17435390.asp

North American Nanoinitiatives

- National Nanotechnology Initiative, the largest American nanocooperation, USA
  www.nano.gov
- NanoBioTechnology Center, a National Science Foundation Center, USA
  www.nbtc.cornell.edu/
- The Canadian National Research Council's National Institute for Nanotechnology
  www.nrc.ca/nanotech/home_e.html
- National Institute for Nanotechnology - University Alberta;
  http://www.nint.ca/
- Pacific Northwest National Laboratory's effort in nanoscience
  www.pnl.gov/nano/index.html
- Center for Nanotechnology, University of Washington
  http://www.nano.washington.edu/
- Center for Biological and Environmental Nanotechnology, Rice University (CBEN)
  http://www.ruf.rice.edu/%7Ecben/

6. Appendices

Appendix I

ESF Forward Look Workshop Participants Amsterdam, Netherlands, 1-5 March 2004

Workshop on Analytical Techniques and Diagnostic Tools, Amsterdam, 1 March 2004

Dr Patrick Boisseau (Chair)
CEA-Nano2Life
17 rue des Martyrs
38054 Grenoble Cedex 9 • France
patrick.boisseau@cea.fr

Dr François Berger
Centre Hospitalier Universitaire
Rue des Carabins-Ancienne
38043 Grenoble • France
Francois.Berger@ujf-grenoble.fr

Prof. H. Allen O. Hill
Inorganic chemistry laboratory
University of Oxford
South Parks Road
Oxford OX1 3QR • United Kingdom
allen.hill@chem.ox.ac.uk

Dr Jürgen Schnekenburger
Gastroenterologische Molekulare Zellbiologie, UKM
University of Münster
Domagkstr. 3A
48149 Münster • Germany
schnekenburger@uni-muenster.de

Prof. Yosi Shacham
University Research Institute for NanoScience and NanoTechnology
Tel Aviv University
Ramat Aviv, 69978 Tel Aviv • Israel
yosish@eng.tau.ac.il

Dr Dimitrios Stamou
Laboratory of physical chemistry of polymers and membranes (LCPPM)
EPFL
1051 ausanne • Switzerland
dimitrios.stamou@epfl.ch

Workshop on Nanoimaging and Manipulation, Amsterdam, 2 March 2004

Prof. Jean-Louis Coatrieux (Chair)
Lab. Traitement du Signal et de l'Image
Université de Rennes 1
Campus de Beaulieu
35042 Rennes Cedex • France
jean-louis.coatrieux@univ-rennes1.fr

Dr Andreas Briel
Schering AG
Drug Delivery Systems
13342 Berlin • Germany
Andreas.Briel@schering.de

Prof. Salvatore Cannistraro
Dipartimento di Scienze Ambientali
Istituto Nazionale per la Fisica della Materia
Università della Tuscia
01100 Viterbo • Italy
cannistr@unitus.it

Prof. Martyn Davies
Laboratory of Biophysics and Surface Analysis
School of Pharmacy, University of Nottingham
University Park
Nottingham NG7 2RD • United Kingdom
martyn.davies@nottingham.ac.uk

Dr Sjaak Deckers
Molecular Imaging and Diagnostics
Philips Medical Systems Nederland BV
P.O. Box 10.000
5680 DA Best • Netherlands
sjaak.deckers@philips.com

Prof. Paul Dietl
Institute of Physiology
University of Innsbruck
Fritz-Pregl-Str. 3
6020 Innsbruck • Austria
paul.dietl@uibk.ac.at

Rainer Erdmann
PicoQuant GmbH
Rudower Chaussee 29 (IGZ)
12489 Berlin • Germany
photonics@pq.fta-berlin.de

Dr Mauro Giacca
International Centre for Genetic Engineering and Biotechnology (ICGEB)
Padriciano 99
34012 Trieste • Italy
giacca@icgeb.org

Dr Corinne Mestais
CEA Grenoble
Département Système pour l'Information et la Santé
17, Rue des Martyrs
38054 Grenoble Cedex 09 • France
corinne.mestais@cea.fr

Prof. Hans Oberleithner
Institute of Physiology
University of Münster
Robert-Koch-Str. 27a
48149 Münster • Germany
oberlei@uni-muenster.de

Workshop on Nanomaterials and Nanodevices, Amsterdam, 3 March 2004

Prof. Jeffrey Alan Hubbell (Chair)
Laboratoire de médecine régénérative et
de pharmacobiologie
EPFL
1015 Lausanne • Switzerland
jeffrey.hubbell@epfl.ch

Prof. Wim Hennink (Co-chair)
Department of Pharmaceutics
Utrecht Institute for Pharmaceutical Sciences
Utrecht University
3508 TB Utrecht • Netherlands
w.e.hennink@pharm.uu.nl

Prof. João Pedro Conde
Department of Materials Engineering
Instituto Superior Tecnico
Av. Rovisco Pais 1
1096 Lisboa • Portugal
joao.conde@ist.utl.pt

Dr John W Davies
Polymer Laboratories Ltd
Essex Road
Shropshire
Church Stretton SY6 6AX • United Kingdom
john.davies@polymerlabs.com

Prof. Helmuth Möhwald
Max-Planck-Institute of Colloids and Interfaces
Wissenschaftspark Golm
14476 Potsdam • Germany
moehwald@mpikg-golm.mpg.de

Prof. José Rivas
Dpto. Física Aplicada, Campus Universitario Sur
Universidad de Santiago de Compostela
15782 Santiago de Compostela • Spain
farivas@usc.es

Workshop on Drug Delivery and Pharmaceutical Development, Amsterdam, 4 March 2004

Prof. María José Alonso (Chair)
Department of Pharmaceutical Technology
Faculty of Pharmacy
University of Santiago de Compostela
15782 Santiago de Compostela • Spain
ffmjalon@usc.es

Prof. Ruth Duncan (Co-chair)
Centre for Polymer Therapeutics
Welsh School of Pharmacy
Cardiff University
Redwood Building
King Edward VII Avenue
Cardiff CF10 3XF • United Kingdom
DuncanR@cf.ac.uk

Prof. Daan Crommelin
Department of Pharmaceutics
Utrecht Institute for Pharmaceutical Sciences
PO Box 80082
3508 TB Utrecht • Netherlands
d.j.a.crommelin@pharm.uu.nl

Prof. Patrick Couvreur
Faculté de Pharmacie
Universite de Paris-Sud
5 rue J-B Clement
92296 Chatenay-Malabry • France
patrick.couvreur@cep.u-psud.fr

Prof. Mike Eaton
UCB-Celltech
216 Bath Road
Slough, Berks SL1 4EN • United Kingdom
mike.eaton@ucb-group.com

Prof. Thomas Kissel
Institut für Pharmazeutische Technologie und
Biopharmazie
Philipps-Universität Marburg
Ketzerbach 63
35032 Marburg • Germany
kissel@staff.uni-marburg.de

Prof. Claus-Michael Lehr
Department of Biopharmaceutics and Pharmaceutical
Technology
Saarland University
Im Stadtwald, Bldg. 8.1
66123 Saarbrucken • Germany
lehr@rz.uni-sb.de

Prof. Egbert Meijer
Laboratory of Macromolecular and Organic Chemistry
Eindhoven University of Technology
Den Dolech 2 , STO 4.36
5600 MB Eindhoven • Netherlands
e.w.meijer@tue.nl

Workshop on Clinical Applications and Toxicology, Amsterdam, 5 March 2004

Dr Wolfgang Kreyling (Chair)
GSF National Research
Centre for Environment and Health
Institut für Inhalationsbiologie
Ingolstädter Landstrasse 1
85764 Neuherberg • Germany
kreyling@gsf.de

Dr Paul J. A. Borm
Centre of Expertise in Life
Sciences (CEL)
Hogeschool Zuyd
Nieuw Eyckholt 300
6419 DJ Heerlen • Netherlands
p.borm@hszuyd.nl

Prof. Kenneth Donaldson
ELEGI Colt Laboratory
School of Clinical Sciences and Community Health,
Medical School
University of Edinburgh
Wilkie Building, Teviot Place
Edinburgh EH 8 9AG • United Kingdom
ken.donaldson@ed.ac.uk

Prof. Alberto Gabizon
Shaare Zedek Med. Ctr.
Oncology Institute
POB 3235
Jerusalem 91031 • Israel
alberto@md.huji.ac.il

Dr Rogério Gaspar
Laboratory of Pharmaceutical Technology
Faculty of Pharmacy
University of Coimbra
3000 Coimbra • Portugal
rgaspar@ff.uc.pt

Dr Andreas Jordan
MagForce Applications
Center of Biomedical Nanotechnology
Campus Charite, CBN, Haus 30
Spandauer Damm 130
14050 Berlin • Germany
andreas.jordan@charite.de

Appendix II

ESF Consensus Conference Participants
Le Bischenberg, France, 8-10 November 2004

Steering Committee

Prof. Ruth Duncan (Chair)
Centre for Polymer Therapeutics
Welsh School of Pharmacy
Cardiff University
Redwood Building
King Edward VII Avenue
Cardiff CF10 3XF • United Kingdom
DuncanR@cf.ac.uk

Dr Wolgang Kreyling (Deputy-chair)
GSF National Research Centre for Environment
and Health
Institut für Inhalationsbiologie
Ingolstädter Landstrasse 1
85764 Neuherberg • Germany
kreyling@gsf.de

Dr Patrick Boisseau
CEA – Nano2Life
17 rue des Martyrs
38054 Grenoble Cedex 9 • France
patrick.boisseau@cea.fr

Prof. Salvatore Cannistraro
Dipartimento di Scienze Ambientali
Instituto Nationale per la Fiscica della Materia
Università della Tuscia
01100 Viterbo • Italy
cannistr@unitus.it

Prof. Jean-Louis Coatrieux
Lab. Traitement du Signal et de l'Image
Université de Rennes 1
Campus de Beaulieu
35042 Rennes Cedex • France
jean-louis.coatrieux@univ-rennes1.fr

Prof. Hans Oberleithner
Institute of Physiology
University of Münster
Robert-Koch-Str. 27a
48149 Münster • Germany
oberlei@uni-muenster.de

ESF Member Organisations and Representatives/Political Bodies

Dr Janna de Boer
The Netherlands Organisation for Health Research
and Development (NWO)
P.O. Box 93245
2509 AE The Hague • Netherlands
boer@zonmw.nl

Dr Oliver Bujok
VDI Technologiezentrum GmbH
Physikalische Technologien
Graf-Recke-STr. 84
40239 Düsseldorf • Germany
bujok@vdi.de

Dr Jean Chabbal
Dept. Microtech. Biol.&Health
CEA-L2t
17, Rue des Martyrs
38054 Grenoble Cedex 09 • France
jean.chabbal@cea.fr

Dr Françoise Charbit
CEA Grenoble
LETI-DTBS
17, Rue des Martyrs
38054 Grenoble Cedex 09 • France
francoise.charbit@cea.fr

Dr Rosita Cottone
Mission Affaires Européennes on sabbatical of BMBF
(Ministry of Research, Germany) Direction de
la Technologie Ministère délégué à la Recherche
1, rue Descartes
75005 Paris • France
rosita.cottone@technologie.gouv.fr

Dr Julie Deacon
UK Micro and Tanotechnology Network
Farlan Cottage
Lower Road
Cookham, Berks SL6 9HJ • United Kingdom
julie.deacon@pera.com

Dr Nicole Déglon
CEA/Service Hospitalier Frédéric Joliot
4, place du Général Leclerc
91401 Orsay Cedex France • France
Nicole.deglon@cea.fr

Dr Luc Delattre
Département de Pharmacie
Pharmacie Galénique et Magistrale
Université de Liège
Avenue de l'Hôpital, 1 – Bât. B36
4000 Liege 1 • Belgium
l.delattre@ulg.ac.be

Dr Franz Dettenwanger
VolkswagenStiftung
Kastanienallee 35
30519 Hannover • Germany
dettenwanger@volkswagenstiftung.de

Dr Mauro Ferrari
The National Cancer Institute
110U Davis Heart and Lung Research Institute
31 Center Drive MSC 2580
The Ohio State University
Room 10A52
473 West 12th Avenue
Columbus OH 43210-1002 • USA
ferrari@lvd1.bme.ohio-state.edu

Dr Valérie Lefèvre-Seguin
Direction de la Recherche, Ministère délégué
à la Recherche
1, rue Descartes • 75005 Paris • France
valerie.lefevre@recherche.gouv.fr

Dr Corinne Mestais
CEA Grenoble
Département Système pour l'Information et la Santé
17, Rue des Martyrs
38054 Grenoble Cedex 09 • France
corinne.mestais@cea.fr

Prof. Julio San Roman
CSIC
Institute of Polymers
Juan de la Cierva 3
28006 Madrid • Spain
jsroman@ictp.csic.es

Dr Christof Steinbach
Dechema e.V.
Theodor-Heuss-Allee 25
60486 Frankfurt a.M. • Germany
steinbach@dechema.de

Prof. Manuel Vázquez
Instituto de Ciencia de Materiales de Madrid, CSIC
Campus de Cantoblanco
28049 Madrid • Spain
mvazquez@icmm.csic.es

Dr Peter Venturini
National Institute of Chemistry
Hajdrihova 19
1000 Ljubljana • Slovenia
peter.venturini@ki.si

Dr Petra Wolff
Bundesministerium für Bildung und Forschung (BMBF)
Referat 511 Nanomaterialien
Heinemannstr. 2
53175 Bonn • Germany
petra.wolff@bmbf.bund.de

Academic Experts

Prof. María José Alonso
Department of Pharmaceutical Technology
Faculty of Pharmacy
University of Santiago de Compostela
15782 Santiago de Compostela • Spain
ffmjalon@usc.es

Dr Paul J.A. Borm
Centre of Expertise in Life Sciences (CEL)
Hogeschool Zuyd
Nieuw Eyckholt 300
6419 DJ Heerlen • Netherlands
p.borm@hszuyd.nl

Prof. Hans Börner
Max Planck Institute of Colloids and Interfaces
Department of Coloid Chemistry
Research Campus Golm
Am Mühlenberg 1
14424 Potsdam • Germany
boerner@mpikg-golm.mpg.de

Dr Benoit Dubertret
ESPCI, Laboratoire d'Optique Physique
CNRS UPRA0005
10, rue Vauquelin
75231 Paris Cedex 10 • France
benoit.dubertret@espci.fr

Prof. Alberto Gabizon
Shaare Zedek Med. Ctr.
Oncology Institute
POB 3235
Jerusalem 91031 • Israel
alberto@md.huji.ac.il

Prof. Varban Ganev
Medical University of Sofia
2 Zdrave Street
1431 Sofia • Bulgaria
ganev@medfac.acad.bg

Dr Mauro Giacca
International Center for Genetic Engineering
and Biotechnology (ICGEB)
Padriciano 99
34012 Trieste • Italy
giacca@icgeb.trieste.it

Dr Robert M. Henderson
Department of Pharmacology, University of Cambridge
Tennis Court Road
Cambridge CB2 1PD • United Kingdom
rmh1003@cam.ac.uk

Dr Peter Hinterdorfer
Institute for Biophysics
Johannes Kepler Universität Linz
Altenbergerstr. 69
A-4040 Linz • Austria
peter.hinterdorfer@jk.uni-linz.ac.at

Prof. Thomas Kissel
Institut für Pharmazeutische Technologie
und Biopharmazie
Philipps-Universität Marburg
Ketzerbach 63
35032 Marburg • Germany
kissel@staff.uni-marburg.de

Prof. Jørgen Kjems
Department of Molecular Biology
University of Arhus
C.F.Mollers Alle, Build. 130
DK-8000 Aarhus C • Denmark
kjems@biobase.dk

Prof. Harm-Anton Klok
Ecole polytechnique fédérale de Lausanne (EPFL)
Institute de matériaux, Laboratoire de polymères
Ecublens
CH-1015 Lausanne • Switzerland
harm-anton.klok@epfl.ch

Prof. Jean-Marie Lehn
Institut de Science et d'Ingénierie Supramoléculaires
Laboratoire de Chimie Supramoléculaire
ISIS/ULP
8, allée Gaspard Monge
BP 70028 • F-67083 Strasbourg Cedex
lehn@isis.u-strasbg.fr

Prof. Claus-Michael Lehr
Department of Biopharmaceutics and Pharmaceutical
Technology
Saarland University
Im Stadtwald, Bldg. 8.1
66123 Saarbrucken • Germany
lehr@rz.uni-sb.de

Prof. C.R. Lowe
Institute of Biotechnology
University of Cambridge
Tennis Court Road
Cambridge CB2 1QT • United Kingdom
c.lowe@biotech.cam.ac.uk

Prof. A.W. McCaskie
Surgical&Reproductive Sciences
Medical School, University of Newcastle upon Tyne
Newcastle upon Tyne NE2 4HH • United Kingdom
A.W.McCaskie@newcastle.ac.uk

Prof. Helmuth Möhwald
Max-Planck-Institute of Colloids and Interfaces
Wissenschaftspark Golm
14476 Potsdam • Germany
moehwald@mpikg-golm.mpg.de

Prof. Lars Montelius
Division of Solid State Physics
Department of Physics
Lund University
Box 117
SE-221 00 Lund • Sweden
Lars.Montelius@ftf.lth.se

Prof. Roeland J.M. Nolte
Department of Organic Chemistry
University of Nijmegen
Toernooiveld 1 - U 052
6525 ED Nijmegen • Netherlands
nolte@sci.kun.nl

Dr T.H. Oosterkamp
Leiden Institute of Physics
Leiden University
Niels Bohrweg 2
2333 CA Leiden • Netherlands
tjerk@phys.leidenuniv.nl

Dr Pierre Puget
Département Systèmes pour l'information et la santé
(DSIS)
LETI - CEA Grenoble
17, rue des Martyrs
38054 Grenoble cedex 9 • France
pierre.puget@cea.fr

Dr Andrea Ravasio
Department of Physiology
University of Innsbruck
Fritz-Pregl-Str. 3
6020 Innsbruck • Austria
andrea.ravasio@uibk.ac.at

Prof. Helmut Ringsdorf
University of Mainz
Raum 00.125
Düsenbergweg 10-14
55128 Mainz • Germany
ringsdor@mail.uni-mainz.de

Dr Jürgen Schnekenburger
Gastroenterologische Molekulare Zellbiologie, UKM
University of Münster
Domagkstr. 3A
48149 Münster • Germany
schnekenburger@uni-muenster.de

Dr Milada Sirova
Institute of Microbiology ASCR
Videnska 1083
142 20 Prague 4 • Czech Republic
sirova@biomed.cas.cz

Prof. K. Ulbrich
Czech Republic Academy of Science
Institute of Macromolecular Chemistry
Heyrovského námestí 2
CZ-162 06 Prague 6 • Czech Republic
ulbrich@imc.cas.cz

Prof. Arto Urtti
University of Kuopio
Department of Pharmaceutics
P.O.Box 1627
FIN-70211 Kuopio • Finland
Arto.Urtti@uku.fi

Prof. Ernst Wagner
Pharmaceutical Biotechnology
Department of Pharmacy
Ludwig-Maximilians Universität München (LMU)
Butenandtstr. 5-13
81377 Munich • Germany
erwph@cup.uni-muenchen.de

Dr Jaap Wilting
Utrecht Institute Pharmaceutical Sciences
University of Utrecht
Sorbonnelaan 16
3585 CA Utrecht • Netherlands
J.Wilting@pharm.uu.nl

Industrial & Regulatory Experts

Dr Andreas Briel
Schering AG
Drug Delivery Systems
13342 Berlin • Germany
Andreas.Briel@schering.de

Dr John W Davies
Polymer Laboratories Ltd
Essex Road
Church Stretton
Shropshire, SY6 6AX • United Kingdom
john.davies@polymerlabs.com

Dr Sjaak Deckers
Molecular Imaging and Diagnostics
Philips Medical Systems Nederland BV
P.O. Box 10.000 • 5680 DA Best • Netherlands
sjaak.deckers@philips.com

Prof. Mike Eaton
UCB-Celltech
216 Bath Road
Slough
Berks SL1 4EN • United Kingdom
mike.eaton@ucb-group.com

Rainer Erdman
PicoQuant GmbH
Rudower Chaussee 29 (IGZ)
12489 Berlin • Germany
photonics@pq.fta-berlin.de

Dr Rogério Gaspar
Laboratory of Pharmaceutical Technology
Faculty of Pharmacy
University of Coimbra
3000 Coimbra • Portugal
rgaspar@ff.uc.pt

Dr Arne Hengerer
Siemens Medical Solutions
MR MI
Karl-Schall-STr. 4
91054 Erlangen • Germany
arne.hengerer@siemens.com

Dr Laurent Levy
Nanobiotix
Rue Pierre et Marie Curie - BP27/01
31319 Labege Cedex • France
Laurent.levy@nanobiotix.com

Dr Kristina Riehemann
Integrated Functional Genomics (IFG)
University of Münster
von-Esmarch-Str. 56
48149 Münster • Germany
k.riehemann@uni-muenster.de

Prof. Csaba Szántay Jr.
Spectroscopic Research Division
Chemical Works of Gedeon Richter Ltd.
H-1475 Budapest
P.O.B. 27 • Hungary
cs.szantay@richter.hu

Nanotechnology Information Suppliers

Dr Ottila Saxl
The Institute of Nanotechnology
6 The Alpha Centre
University of Stirling Innovation Park
Stirling, FK9 4NF • United Kingdom
ottilia@nano.org.uk

ESF/EMRC/COST

Prof. Luc P. Balant
COST TC Medicine & Health
Department of Psychiatry
University of Geneva
2, Chemin du Petit-Bel-Air
1225 Chene-Bourg • Switzerland
luc.balant@medecine.unige.ch

Dr Thomas Bruhn
Institute of Experimental Dermatology
University of Münster
von-Esmarch-Str. 58
48149 Münster • Germany
tbruhn@uni-muenster.de

Nathalie Geyer
European Science Foundation
1, quai Lezay Marnésia
BP 90015 • 67080 Strasbourg Cedex • France
ngeyer@esf.org

Dr John Marks
European Science Foundation
1, quai Lezay Marnésia
BP 90015 • 67080 Strasbourg Cedex • France
jmarks@esf.org

Prof. Mihail Pascu
ESF-COST Office
Medicine and Health; Biomaterials
149, Avenue Louise
P.O. BOX 12
1050 Brussels • Belgium
mpascu@cost.esf.org

Prof. Clemens Sorg
Institute of Experimental Dermatology
University of Münster
von-Esmarch-Str. 58
48149 Münster • Germany
sorg@uni-muenster.de

Dr Hui Wang
European Science Foundation
1, quai Lezay Marnésia
BP 90015 • 67080 Strasbourg Cedex • France
hwang@esf.org

Appendix III

Projected Market for Nanomedicines

The market of nanomedicines is rapidly rising as new products are being approved. It is expected that this market will reach a significant economic potential within 5 to 10 years. Currently, little data is available on the market of nanomedicines in Europe.

*Market size worldwide 2003 for medical devices and pharmaceuticals**

Medical devices	€145 billion
Pharmaceuticals	€390 billion

Expected market growth: 7-9% annually

Within the market of pharmaceuticals, advanced drug delivery systems account for approximately 11% market share (€42.9 billion). This market is expected to expand rapidly as only a few products are currently in clinical application and many more in clinical trials or in the process of being approved. As an example, the current estimates for

Doxil®/Caelyx® (PEGylated liposomal doxorubicin) are $300 million (€251.32 million) sales per annum

Ambisome® (liposomal amphotericin B) are > $100 million (€83.77 million) sales per annum

* Vision paper and basis for a strategic research agenda for NanoMedicine, European Technology Platform on NanoMedicine - Nanotechnology for Health – EU publication September 2005

Appendix IV

European Projects and Networks Undertaking Nanomedicine Research

European Networks

EU funding opportunities in the Nanotechnology Research Area
www.cordis.lu/nanotechnology/

Communication on nanotechnology from the European Commission, 'Towards a European strategy on nanotechnology'
www.cordis.lu/nanotechnology/src/communication.htm

Illustrated brochure entitled 'Nanotechnology, Innovation for tomorrow's world' ftp://ftp.cordis.lu/pub/nanotechnology/docs/nano_brochure_en.pdf

The PHANTOMS Nanoelectronics Network scheme
www.phantomsnet.net

A general European site on European nanoscience and technology.
www.nanoforum.org/

European National Nanocentres

The Swiss 'National Centre for Nano Scale Science' at Universität Basel
www.nanoscience.unibas.ch/

Nanoscience @ Cambridge University
http://www.nanoscience.cam.ac.uk/

London Centre for Nanotechnology
http://www.london-nano.ucl.ac.uk/

Nanolink at University of Twente
Nanolink
www.mesaplus.utwente.nl/nanolink/

Centre of Competence Nano-Scale Analysis in Hamburg
www.nanoscience.de/
http://www.nanoanalytik-hamburg.de/shtml/index.shtmlhttp://www.nanoanalytik-hamburg.de/shtml/index.shtml

Centre for NanoScience based at Ludwig-Maximillians-Universität, München
www.cens.de/

Centre of Competence NanoBioTechnology, Saarland, Germany
www.nanobionet.de/

Centre of Competence NANOCHEM, Saarbrücken, Germany
www.cc-nanochem.de

The German Ministry of Education and Research supports six national Competence Centres
www.nanonet.de/nanowork/indexe.php3

Nano-World, The Computer-Supported Cooperative Learning Environment on Nanophysics, a Swiss Virtual Campus
www.nanoworld.unibas.ch/zope/nano/en

Center for NanoMaterials at Technische Universiteit Eindhoven, Holland
www.cnm.tue.nl

Center for Ultrastructure Research, Austria
www.boku.ac.at/zuf/

Institute of Nanotechnology at the Forschungszentrum Karlsruhe
http://hikwww1.fzk.de/int/english/welcome.html

DFG-Centrum für Funktionelle Nanostrukturen
http://www.cfn.uni-karlsruhe.de/index.html

Nanostructures Laboratory at MFA Research Institute for Technical Physics and materials science
http://www.mfa.kfki.hu/int/nano/

Paul Scherrer Institut - Laboratory for Micro- and Nanotechnology
http://lmn.web.psi.ch/index.html

Nano-Science Center at Københavns Universitet
http://www.nano.ku.dk/

MIC National Micro- and Nanotechnology Research Center at DTU
http://www.mic.dtu.dk/

NanoBIC - NanoBioCentrum at University of southern Denmark
http://www.sdu.dk/Nat/nanobic/index.php

European Projects

BIOMIN
Objectives: The aim of the project is to form nanostructure composites of biomaterials and inorganic compounds for applications in, e.g. implants.
Contact: Ralph Thomann
Email: r_thomann@igv-gmbh.de

BIOSMART
Objectives: To establish an infrastructure for coordinating research into the design and application of biomimetic materials and smart materials with biorecognition functions, including new porous biorecognition materials for tissue engineering.
Contact: Sergey Piletsky
Email: s.piletsky@cranfield.ac.uk

HEPROTEX
Objectives: To develop a joint research infrastructure for development of protective textiles. With new innovations in textiles, forms will become more widely used in surgical procedures than for just traditional uses such as wound care.
Contact: Hilmar Fuchs
Email: stfi@stfi.de

INCOMED
Objectives: The aim is to reduce 90% of implant complications, by way of an innovative method of coating objects with a thin layer of hydroxylapatite, bioactive glass or mixtures of both in order to give biocompatible surfaces.
Contact: Christoph Schultheiss
Email: christoph.schultheiss@ihm.fzk.de

INTELLISCAF
Objectives: The aim is to produce intelligent scaffolds using nanostructured particles and surfaces to give materials which will help regenerate tissues such as bone or skin on their implantation.
Contact: Soeren Stjernqvist
Email: info@teknologisk.dk

MENISCUS-REGENERATIO
Objectives: The aim is to use tissue engineering to produce an artificial meniscus with a structure similar to the natural tissue.
Contact: Claudio de Luca
Email: cdeluca@fidiapharma.it

EU 6th Framework Programme

Search: http://eoi.cordis.lu/search_form.cfm

Microrobotnic surgical instruments
Project Acronym: (none).
Objectives: To develop microrobotic surgical instruments for new types of surgery.
Contact: Georges Bogaerts
Email: geboconsult@lps-business.com

MOBIAS
Objectives: To develop a way to manufacture implants and scaffolds with several materials and to vary the composition throughout the structure, to give multiple functions.
Contact: Gregory Gibbons
Email: g.j.gibbons@warwick.ac.uk

NA.BIO.MAT
Objectives: The design and development of self-assembling biocompatible polymers, for applications in, e.g., tissue engineering.
Contact: Gaio Paradossi
Email: paradossi@stc.uniroma2.it

Nanoarchitecture
Objectives: Nanostructuring modification of biomaterials for tissue engineering and other biomimetic applications.
Contact: Vasif Hasirci
Email: chasirci@metu.edu.tr

NanoBone
Objectives: To apply nanotechnology, in terms of structuring, to bone repair and regeneration.
Contact: Fernando Monteiro
Email: fjmont@ineb.up.pt

Nanostres
Objectives: To use nanotechnology techniques to create implants and implant technologies for skeletal tissues.
Contact: Josep Anton Planell
Email: plannell@cmem.upc.es

NB-TISS-INTER-MED
Objectives: To redress the issue of the decreasing European market share in medical devices.
Contact: Ian McKay
Email: ian.mckay@pera.com

NMMA
Objectives: To carry out interdisciplinary research (for medical applications) into the possibilities nanotechnology offers for shaping surface and internal structure, and using molecular biology to control interactions between materials and cells.
Contact: Krzysztof Kurzydlowski
Email: KJK@inmat.pw.edu.pl

NONMETALLICIMPLANTS
Objectives: To create new/improved polymer materials for implants and scaffolds, with the necessary structure to optimise their function.
Contact: Jan Chlopek
Email: chlopek@uci.agh.edu.pl

SAM-MED-NET
Objectives: To gain a better understanding of self assembly mechanisms for applications in biomimetic materials (e.g. tissue engineering).
Contact: Frederic Cuisinier
Email: fred.cuisinier@odonto-ulp.u-strabg.fr

Appendix V

Nanomedicines in Routine Clinical Use or Clinical Development

Liposomal formulations in clinical use and clinical development

Product	Status	Payload	Indication
Daunoxome®	Market	daunorubicin	cancer
Doxil®/Caelyx®	Market	doxorubicin	cancer
Myocet®	Market	doxorubicin	cancer
Ambisome®	Market	amphotericin B	fungal infections
Amphotech®	Market	amphotericin B	fungal infections

Monoclonal antibody-based products in the market

Antibody	Target	Payload	Use
Therapeutic antibodies			
Rituxan®	CD20	inherent activity	CD20+ve Non-Hodgkin's Lymphoma
Herceptin®	HER2	inherent activity	HER2 +ve breast cancer
Antibody-drug conjugates			
Mylotarg®	CD33	calicheamicin	Acute Myeloid Leukaemia
Radioimmunotherapeutics			
Tositumomab®	CD20	[^{131}I]iodide	Non-Hodgkin's Lymphoma-targeted radiotherapy
Zevalin®	CD20	^{90}Yttrium	Non-Hodgkin's Lymphoma-targeted radiotherapy
Immunotoxins			
Anti-B4-blocked ricin	CD19	blocked ricin	Non-Hodgkin's lymphoma targeted immunotoxin
Anti-Tac(Fv)-PE38 (LMB2)	CD25	*Pseudomonas* exotoxin fusion protein	Haematological malignancies
PEG-antiTNF Fab CDP870	TNFα	Phase III	Rheumatoid arthritis and Crohn's disease

Nanoparticles as imaging agents and drug carriers

Product	Compound	Status	Use
Imaging Agents			
Endorem®	superparamagnetic iron oxide nanoparticle	Market	MRI agent
Gadomer®	Dendrimer-based MRI agent	Phase III	MRI agent-cardiovascular
Drug delivery			
Abraxane®	Albumin nanoparticle containing paclitaxel	Market	Breast cancer

Polymer Therapeutics in the market or transferred into clinical development

Compound	Name	Status	Indication
Polymeric drugs			
Poly(alanine, lysine, glutamic acid, tyrosine)	Copaxone®	Market	Multiple sclerosis
Poly(allylamine)	Renagel®	Market	End stage renal failure
Dextrin-2-sulphate	Emmelle® gel	Market	Phase III HIV/AIDS - a vaginal virucide formulated as a gel
Dextrin-2-sulphate		Phase III	HIV/AIDS - polymer administered intraperitoneally
Poly(I):Poly(C)	Ampligen®	Phase III	Chronic fatigue immune dysfunction (myalgic encephalomyelitis; ME)
Polyvalent, polylysine dendrimer containing SPL7013	VivaGel™	Phase I/II	Viral sexually transmitted diseases, formulated as a vaginal gel
Polymer-oligonucleotide conjugates			
PEG-aptamer	Macugen™	NDA filed	Age-related macular degeneration
Polymer-protein conjugates			
PEG-adenosine deaminase	Adagen®	Market	Severe combined immuno-deficiency syndrome
SMANCS	Zinostatin Stimalmer®	Market	Cancer - hepatocellular carcinoma
PEG-L-asparaginase	Oncaspar®	Market	Acute lymphoblastic leukamia
PEG-a-interferon 2b	PEG-intron™	Market	Hepatitis C, also in clinical development in cancer, multiple sclerosis, HIV/AIDS
PEG-a-interferon 2a	PEG-Asys®	Market	Hepatitis C
PEG-human growth hormone	Pegvisomant®	Market	Acromegaly
PEG-GCSF	Neulasta™	Market	Prevention of neutropenia associated with cancer chemotherapy
PEG-antiTNF Fab	CDP870	Phase III	Rheumatoid arthritis and Crohn's disease
Polymer-drug conjugates			
Polyglutamate-paclitaxel	CT-2103, XYOTAX™	Phase II/III	Cancer -particularly lung cancer, ovarian and oesophageal
HPMA copolymer-doxorubicin	PK1; FCE28068	Phase II	Cancer -particularly lung and breast cancer
HPMA copolymer-doxorubicin-galactosamine	PK2; FCE28069	Phase I/II	Cancer -particularly hepatocellular carcinoma
HPMA copolymer-paclitaxel	PNU166945	Phase I	Cancer
HPMA copolymer camptothecin	MAG-CPT / PNU166148	Phase I	Cancer
HPMA copolymer platinate	AP5280	Phase II	Cancer
HPMA copolymer platinate	AP5346	Phase I/II	Cancer
Polyglutamate-camptothecin	CT-2106	Phase I/II	Cancer
PEG-camptothecin	PROTHECAN™	Phase II	Cancer
Polymeric micelles			
PEG-aspartic acid-doxorubicin micelle	NK911	Phase I	Cancer

Appendix VI

European Companies Active in Nanomedicines' Development

A list of some companies active in nanomedicines' development. This list is not meant to be comprehensive.

iNano
website containing links to several companies and institutions that could be helpful in the start-up phase of new companies
Website: http://www.inano.dk/sw179.asp

Pronano
Swedish site for the promotion of nanotechnology in industry
Website: http://www.pronano.se/

Advanced Photonic Systems APhS GmbH
Advanced Photonic Systems manufactures lasers, laser systems and components, with a focus on fast and ultra fast-pulsed lasers.
Website: http://www.advanced-photonic-systems.com/

Bio-Gate Bioinnovative Materials GmbH
Bio-Gate develops and tests anti-infective materials using nanosilver, for medicine and other industries.
Website: http://www.bio-gate.de

DILAS, Diodenlaser GmbH
DILAS designs and engineers various products (standard or custom designed) in the field of High Power Diode Lasers
Website: http://www.dilas.de

JenLab GmbH
JenLab uses femtosecond laser technology to develop instruments for biotechnology and biomedical applications.
Website: http://www.jenlab.de

Kleindiek Nanotechnik
Kleindiek Nanotechnik produces micro and nano positioning systems, with high precision and resolution, combined with a large working range.
Website: http://www.nanotechnik.com

NEWCO Surgical
NEWCO Surgical is a supplier of innovative surgical instruments and accessories throughout the UK.
Website: www.newco.co.uk

Capsulution Nanoscience AG
uses LBL-Technology® for making unique capsules, allowing the manufacture of extremely precise nano- and micron-sized capsules.
Website: www.capsulution.com

Flamel Technologies
has developed Medusa which is nanoencapsulation technology to deliver native protein drugs.
Website: www.flamel.com

ImaRx Therapeutics
uses SonoLysis technology which employs tiny micro and nanobubbles injected into the bloodstream to enter into regions of thrombosis. When external ultrasound is applied, the microbubbles cavitate and dissolve blood clots into smaller particles.
Website: www.imarx.com

iMEDD
is a biomedical company developing advanced drug delivery systems based on MEMS technology. iMEDD's lead drug delivery platform, NanoGATE, is an implant that uses membranes containing pores with nanometre dimensions that control the diffusion of drugs at a molecular level.
Website: www.imeddinc.com

LiPlasome Pharma
has developed a prodrug and drug delivery platform that can be used for targeted transport of anticancer drugs. Their prodrug and drug delivery technology is based on smart lipid based nanocarriers (LiPlasomes) that can be applied for targeted transport of anticancer drugs.
Website: liplasome.com

MagForce Applications
is a group of companies that have developed the magnetic fluid hyperthermia method (MFH). This is a minimally invasive cancer therapy that attacks cancer at the cellular level whilst leaving healthy tissue largely unharmed. The method consists of two components; nanosized iron oxide particles (MagForce) and an external magnetic field applicator (MFH).
Website: www.magforce.de

MagnaMedics
uses its SensithermA therapy to help combat AIDS. The principle of the therapy is the selective overheating of the virus and the infected cells by means of magnetic nanoparticles. SensiTherm therapy is also used in the treatment of liver tumours.
Website: www.nanovip.com

Micromet AG
is using antibodies to create novel drugs that precisely and effectively combat human diseases such as cancer or rheumatoid arthritis.
Website: www.micromet.de

Nanobiotix
has developed their NanoBiodrugs™ which are nano-particles with a diameter smaller than 100nm. The core of the nanoparticle is a NanoProdrug in an inactive form that can then be activated by external physical activation. This generates a local therapeutic effect destroying the pathological cells. Activation is achieved by a magnetic field similar to that of an MRI machine, or by laser.
Website: www.nanobiotix.com

Nanogate Technologies
concentrates on inorganic-organic nanocomposites as well as self-organising nanostructures based on chemical nanotechnology
Website: www.nanogate.de

Nanomix Inc
Website: nano.com

NanoPharm AG
has developed nanoparticles as a drug delivery formulation using NANODEL technology. Drugs are bound to nanoparticles and then transported to their specific target. It is even possible to transport drugs across the blood-brain barrier.
Website: nanopharm.de

NOSE
Nanomechanical olfactory sensors.
Website: http://monet.unibas.ch/nose/

Novosom AG
specialises in the development and production of liposomes, liposomal nanocapsules and liposomal vectors.
Website: www.novosom.de

Pharmasol GmbH
has developed lipid nanoparticles as an alternative delivery system to polymeric nanoparticles.
Website: www.pharmasol-berlin.de

Psividia Ltd
is a biomedical technology company which has produced a material designed to enable drug molecules to be held in nanoscale pockets which release tiny pulses of a drug as the material dissolves. The rate of dissolution can be controlled so that delivery can be achieved over days or months.
Website: www.psividia.com

SkyePharma
is a leading developer, manufacturer and provider of drug delivery technologies. One of its technologies uses nanoparticles which allow targeted drug delivery in the lung.
Website: www.skyepharma.com

Companies Active in Tissue Engineering

Alchimer SA
Alchimer develops and produces coatings for biomedical implants and microelectronics.
Website: http://www.alchimer.com/

BioTissue Technologies AG
BioTissue produces autologous skin grafts, bone and cartilage implants.
Website: www.biotissue-tec.com

GfE Medizintechnik GmbH
GfE develops and produces titanium-coated ('titanized') implants.
Website: http://www.gfe-online.de/opencms/opencms/gfe/en/mt/index.html

IIP-Technologies GmbH
IIP has developed an artificial retina that can help restore some sense of vision.
Website: http://www.iip-tec.com/english/index.php4

Micromuscle AB
Micromuscle develops and produces electroactive components for medical devices.
Website: http://www.micromuscle.com

pSiMedica
pSiMedica has developed a form of silicon that is biocompatible and biodegradable. BioSilicon can be used in various medical applications.
Website: http://www.psimedica.co.uk

TransTissue Technologies GmbH
TransTissue creates replacement tissues such as bone and cartilage using tissue engineering.
Website: http://www.transtissue.com

NAMOS GmbH
NAMOS produces 'intelligent' surface coatings for materials using nanotechnology.
Website: http://www.namos.de/

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EUROPEAN SCIENCE FOUNDATION

European Science Foundation
1 quai Lezay-Marnésia, BP 90015
67080 Strasbourg cedex, France
Tel: +33 (0)3 88 76 71 00
Fax: +33 (0)3 88 37 05 32
www.esf.org

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