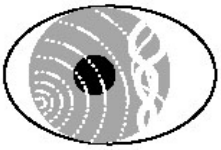


The European Group on Ethics in Science and New Technologies to the European Commission

Opinion on the ethical aspects of nanomedicine

- Opinion N° 21 -

- 17 January 2007 -

CONTENTS

ABSTRACT 5

I. HAVING REGARD TO 7

II. WHEREAS 11

1. Introduction 11

2. Scientific and technical background 13

2.1 Introduction 13

2.2 Nanomedicine: the state of the art 13
2.2.1 Diagnostic techniques 16
2.2.2 Imaging 17
2.2.3 Biomaterials 18
2.2.4 Drug development and delivery 19
2.2.5 Other potential health related applications of nanotechnologies 20
2.2.6 Cosmetic applications 21
2.2.7 Toxicological aspects 21

3. Legal background 23

3.1 The legal situation: an overview 23

3.2 EU legislation 24

3.3 World Trade Organisation (WTO) agreements and Trade-Related Aspects of Intellectual Property Rights (TRIPS) 30

3.4 Framework on ethics and human rights 31

3.5 Regulatory concerns 33

4. Ethics, governance and policies: Problems and concerns 36

4.1 Introduction 36

4.2 Toxicology and human health 37
4.2.1 Safety 37
4.2.2 Risk governance 38
4.2.3 The precautionary principle 39

4.3 Bioethical questions 39
4.3.1 Protection of individuals 39
4.3.2 Informed consent 40
4.3.3 Diagnostic complexity and increased personal responsibility 40
4.3.4 Third-party uses? 41
4.3.5 Medical and non-medical uses: therapy and enhancement? 41
4.3.6 Access from an individual perspective 42
4.4 Social ethics 42
4.4.1 Economic issues 42
4.4.2 Societal debates 44
4.4.2.1 Pluralism 44
4.4.2.2 Societal dialogue 45
4.4.3 Institutional/political issues 45
4.4.3.1 The individual and the state 46
4.4.3.2 Institutional and regulatory questions 46
4.4.3.3 Intellectual property rights 47
4.4.4 Research policies 48
4.4.4.1 Clinical research involving nanomedical applications 48
4.4.4.2 Nanotechnology in the 6th Research and Development Framework Programme (FP6) 48
4.4.4.3 Nanotechnology in the 7th Research and Development Framework Programme (FP7) 49
4.4.4.4 Military research and use 49
4.4.5 Questions of Justice 50
4.4.6 Anthropological questions: Changing the human condition 50

III. OPINION 53
5.1 Introduction 53
5.2 Scope of the Opinion 53
5.3 Fundamental values and rights 53
5.4 Safety 54
5.4.1 Risk assessment 55
5.4.2 The need for prospective technology assessment, including consideration of social effects 56

5.5 Legal issues 56
5.5.1 General issues 57
5.5.2 Intellectual property rights 57
5.6 Offering nanomedicine tests on the market 58
5.7 Information and consent 59
5.8 Economics and research funding 59
5.9 Communication and public trust 60
5.10 The need for interdisciplinary research on the Ethical, Legal and Social Implications (ELSI) of nanomedicine 60
5.11 Ethical deliberation on the concept of humanity, human rights, social and political conflicts in relation to Nanotechnology 61
5.12 Clinical research involving nanomedical applications 61
5.13 Medical and non-medical uses 62
5.14 Sharing of information and establishing databases 62
5.15 The need for revision of this Opinion 63

APPENDIX I 65
Examples of projects funded under FP6

APPENDIX II 67
Examples of ELSA projects in the programmes funded under FP6 in the area of nanomedicine

APPENDIX III 69
Extract from the Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies, produced by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)

APPENDIX IV 73
Nanomedicine, Nanotechnology for Health, from the European Technology Platform, Strategic Research Agenda for Nanomedicine, November 2006

APPENDIX V 163

Addendum requested from Professor Krzysztof Marczewski, EGE Member

ABSTRACT

Nanomedicine and nanotechnology in the EU Research Programme

Nanomedicine is an area of nanotechnology which raises high expectations with regard to its potentials in diagnostics, drug development and delivery, imaging and other health- related applications. It is a major research sector covered by the EU Research and Development Programme.

Under the 6th EU Framework Programme for research (FP6) the Commission has invested more than €1.36 Billion in nanotechnology (550 projects financed) and under the 7th Framework Programme for research (FP7) some €3.5 billion should be allocated to this research sector.

The first FP7 call for proposals on nanotechnology has been launched and it has been estimated that €300-400 million could be allocated to nanotechnology in 2007. Around €100 million per year is expected to be allocated to nanomedicine project proposals.

Like other research sectors, however, this new area of nanotechnology needs a proper analysis of its ethical implications.

The EGE Opinion on the ethical aspects of nanomedicine.

In its Opinion the EGE acknowledges that nanomedicine offers the possibility of new diagnostic, treatment and preventive methods that may open up promising areas of medicine. The Opinion focuses on ethics issues arising from nanomedicine but also discusses a number of problems raised by nanotechnology insofar as they concern primarily health-related issues.

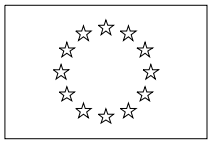
The EGE underlines the vital importance of addressing concern for safety with respect to nanomedical developments (and, in fact, nanotechnology in general) and therefore advocates the need to establish measures to verify the **safety of nanomedical products** and to ensure that nanomedical devices are properly assessed with regard to public health. The Group proposes that institutions already operating at European and national level to protect the safety of patients and citizens should be charged with the additional task of overviewing the safety and security aspects of new tools and devices in nanomedicine. The Group then underlines the need to properly address risk assessment at national and EU level and invites relevant stakeholders to devote adequate efforts to understanding and preventing risks that may be linked to nanomedicine.

As far as **public participation** is concerned, the Group argues that transparency (including openness about uncertainties and knowledge gaps) is essential for public trust in nanotechnology. The Group therefore proposes that initiatives should be taken at national and European level to prepare surveys of public perception of the benefits and risks of the applications of nanotechnologies, with special reference to

medical sectors. The Group also calls for initiatives to be taken to organise academic and public debates on problems and possibilities of present and near-future nanomedicine.

Additionally the Group underlines the need for: **prospective technology assessment**, including consideration of social effects (also in developing countries); **interdisciplinary research on the Ethical, Legal and Social Implications (ELSI)** of nanomedicine; the establishment of a European Network on Nanotechnology Ethics; and enhanced information exchange between research ethics committees in different Member States or among competent bodies in particular on toxicity studies, ELSI-related aspects of nanomedicine and informed consent procedures with regard to safety.

As far as the **legal implications** of nanomedicine are concerned, the EGE does not propose any new regulatory structures specifically dealing with nanomedicine at this point, and argues that any changes should be made within existing structures (with focus on implementation of existing regulations). The Group proposes, however, that possible cases of nanomedicine applications where there might be overlap between regulations, which could create uncertainty as to which regulations should be applied, should be explored by the relevant authorities so that the existing regulations can be implemented in an unambiguous way. In addition the EGE calls for comparative research on intellectual property rights and nanomedicine and advocate the needs to look further into the balance between knowledge protection and information dissemination.



OPINION OF THE EUROPEAN GROUP ON ETHICS
IN SCIENCE AND NEW TECHNOLOGIES
TO THE EUROPEAN COMMISSION

N° 21 **Original in English**

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ETHICAL ASPECTS OF NANOMEDICINE

Reference: Opinion produced at the request of José Manuel Barroso, President of the European Commission, dated 10.11.2005

Rapporteurs: Professor Göran Hermerén, Professor Krzysztof Marczewski and Professor Linda Nielsen

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The European Group on Ethics in Science and New Technologies (EGE),

Having regard to the Treaty establishing the European Community and in particular Article 6 of the common provisions concerning respect for fundamental rights;

Having regard to the EC Treaty, and in particular Article 152 on public health;

Having regard to the Charter of Fundamental Rights of the European Union of 28 September 2000, approved by the European Council in Biarritz on 14 October 2000 and proclaimed solemnly in Nice by the European Parliament, the Council and the Commission on 7 December 2000, and in particular Article 1 (Human dignity), Article 3 (Right to the integrity of the person) and Article 8 (Protection of personal data);[1]

[1] Official Journal C 364 of 18 November 2000, pp. 1 - 22.

Having regard to the Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee of 7 June 2005 "Nanosciences and nanotechnologies: an action plan for Europe 2005 – 2009"[2] and in particular section 5.1.(b) thereof, stating that "the Commission will ask the European Group on Ethics in Science and New Technologies to carry out an ethical analysis of nanomedicine";

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;[3]

Having regard to the Convention on the grant of European patents (European Patent Convention) of 5 October 1973 (text as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996, 10 December 1998 and 27 October 2005 and comprising the provisionally applicable provisions of the act revising the EPC of 29 November 2000);[4]

Having regard to Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use;[5]

Having regard to Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector;[6]

Having regard to Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use,[7] as amended in 2003 and 2005;

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use;[8]

Having regard to Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions;[9]

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[2] COM(2005) 243 final.
[3] Official Journal L 136 of 30 April 2004, pp. 1 - 33.
[4] http://www.european-patent-office.org/legal/epc/e/ma1.html.
[5] Official Journal L 159 of 27 June 2003, pp. 46 - 94.
[6] Official Journal L 201 of 31 July 2002, pp. 37 - 47.
[7] Official Journal L 121 of 1 May 2001, pp. 34 - 44.
[8] Official Journal L 311 of 28 November 2001, pp. 67 – 128.

Having regard to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data;[10]

Having regard to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices;[11]

Having regard to Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices;[12]

Having regard to Directive 76/768/EC of the European Parliament and of the Council of 27 July 1976 on the approximation of the laws of the Members States relating to cosmetic products[13]

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
Having regard to the Council of Europe Convention on Human Rights and Biomedicine, signed on 4 April 1997 in Oviedo[14]

Having regard to the Additional Protocols to the Council of Europe Convention on Human Rights and Biomedicine, in particular the Additional Protocol on Prohibition of Human Cloning and the Protocol on Biomedical Research;

Having regard to the Universal Declaration on the Human Genome and the Rights of Man adopted by Unesco on 11 November 1997,[15] the Declaration on Human Genetic Data adopted by Unesco on 16 October 2003 and the Universal Declaration on Bioethics and Human Rights adopted by Unesco on 19 October 2005;

Having regard to the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data adopted by the Council of Europe on 1 January 1981;[16]

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[9] Official Journal L 213 of 30 July 1998, pp. 13 - 21.
[10] Official Journal L 281 of 23 November 1995, pp. 31 – 50.
[11] Official Journal L 169 of 12 July 1993, pp. 1 - 43.
[12] Official Journal L 189 of 20 July 1990, pp. 17 - 36.
[13] Official Journal L 262, 27.9.1976, p. 169
[14] http://conventions.coe.int/treaty/en/treaties/html/164.htm.
[15] http://portal.unesco.org/shs/en/ev.php-URL_ID=2228&URL_DO=DO_TOPIC&URL_SECTION=201.html.
[16] http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm).

Having regard to the United Nations Declaration on Human Cloning adopted by the UN General Assembly on 8 March 2005;

Having regard to the hearings of experts and Commission departments by the EGE during their November 2005, December 2005, January 2006 and March 2006 meetings;[17]

Having regard to the "Vision Paper and Basis for a Strategic Research Agenda for NanoMedicine" published in September 2005 by the European Technology Platform on NanoMedicine;

Having regard to the Opinion on "The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies" (SCENIHR, 29.9.2005);[18]

Having regard to the "Reflection paper on nanotechnology-based medicinal products for human use" published in June 2006 by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency;

Having regard to the report "Ethics and nanotechnologies: a basis for actions" issued by the Quebec Science and Technology Ethics Committee;[19]

Having regard to EGE Opinion No 17 on "Ethical Aspects of Clinical Trials in Developing Countries";[20]

Having regard to EGE Opinion No 20 on "Ethical Aspects of ICT Implants in the Human Body";[21]

Having regard to the Roundtable organised by the EGE on 22 March 2006 in Brussels;

Having heard the EGE rapporteurs, Professor Göran Hermerén, Professor Krzysztof Marczewski and Professor Linda Nielsen;

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[17] See agendas on the EGE website: http://europa.eu.int/comm/european_group_ethics/index_en.htm.

[18] SCENIHR/002/05, available at: http://europa.eu.int/comm/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003.pdf.

[19] http://www.ethique.gouv.qc.ca/.

[20] http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf.

[21] http://europa.eu.int/comm/european_group_ethics/docs/avis20en.pdf.

II. WHEREAS:

1. INTRODUCTION

> "The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big".[22]

It is thanks to this statement that Richard Feynman has been considered the grandfather of the concept of nanotechnology, an expression coined by Norio Taniguchi, popularised by Eric Drexler, and ever more part of our daily life.[23,24] Characteristically, each of them had a different aspect of this fascinating new field of science and technology in mind.

Although, like nanotechnology, nanoscience is beginning to be familiar to the general public, some clarification of the meaning of the two terms is needed. The prefix "nano" indicates one thousand millionth or 10^{-9}. A nanometre is 10^{-9} metre. For comparison, a human hair has a diameter of about 80 thousand nanometres and a strand of DNA is about 2 nm wide.

Nanoscience is the study of the properties of materials and their manipulation at the atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale,[25] and nanotechnology is the development and practical applications of structures and devices on a nanometre scale in several fields including medicine.

Nanotechnology exploits the often distinctly different physical, chemical and biological properties of materials at sizes similar to those of molecules compared with those of the bulk material. "In nanometre scale structures, it is possible to control or change the fundamental characteristics of a material, including its melting point, magnetic properties, strengths, electrical and thermal conductivity, porosity, corrosiveness, even colour, and – most important in some cases - bio-compatibility, without changing the material's

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[22] Richard Feynman (1918-1988), Nobel Prize winner in Physics 1965, lecture given on 29 December 1959 at the annual meeting of the American Physical Society.

[23] Drexler, K.E. (1981) "Molecular engineering: An approach to the development of general capabilities for molecular manipulation", *Proceedings of the National Academy of Sciences USA* 78:5275-5278.

[24] Drexler, K.E. (1986) *Engines of Creation: The Coming Era of Nanotechnology*. New York, Anchor Press/Doubleday.

[25] The Royal Society & The Royal Academy of Engineering (July 2004) *Nanoscience and nanotechnologies: Opportunities and uncertainties.* London, ISBN 0 85403 604 0.

chemical composition".[26] In many cases nanotechnology includes technology which has been in use for a long time, and most of the concepts used are not strictly speaking new. For instance, the mode of action of all pharmaceutical products occurs at nano scale. Nanomedicine essentially provides tools that may be useful for well identified medical problems.

The European Science Foundation (ESF) defines nanomedicine as "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" .[27]

In the view of its advocates, nanomedicine may prove to be a very promising set of techniques, especially for the detection and treatment of cardiovascular conditions, certain types of cancer, and age-related and neurological degenerative illnesses. Although this discipline is in its infancy, it is advancing very rapidly. It has the potential to change medical science dramatically but it also raises urgent ethical issues.

Nanoscience is one of the most rapidly growing branches of science applied to medical questions.[28]

In addition, on 7 June 2005 the Commission adopted a Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee entitled "Nanosciences and nanotechnologies: an action plan for Europe 2005 – 2009" (COM(2005) 243 final). Section 5.1.(b) of the Communication states that "the Commission will ask the European Group on Ethics in Science and New Technologies to carry out an ethical

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[26] Philips Medical Systems Position in Nanomedicine, for communication to the European Commission, Michael H. Kuhn PhD, Jacques Souquet PhD.

[27] "ESF Forward Look on Nanomedicine", European Science Foundation, November 2005, available at: http://www.esf.org/publication/214/Nanomedicine.pdf (accessed 9 January 2006).

[28] According to data for 2005 "more than 130 nano-based drugs and drug delivery systems and 125 devices or diagnostic tests have entered preclinical, clinical, or commercial development" (Nanobiotech News, 4 January 2006, "2006 Nanomedicine, Device & Diagnostic Report"). This is an increase of 68% compared with the previous year. Over 4 000 scientific papers (25% published in 2006) in the Medline database are related to nanomedicine.

analysis of nanomedicine. This will identify the primary ethical concerns and enable future ethical review of proposed nanoscience and nanotechnology Research and Devlopment (R&D) projects to be carried out appropriately".

2. SCIENTIFIC AND TECHNICAL BACKGROUND

2.1 Introduction

The potential of nano-technologies[29] raises great hopes. Far-reaching claims are made by both opponents and proponents. The first difficulty in describing the state of the art accurately is to distinguish between science and science fiction, i.e. between the state of the art today, what may be around the corner tomorrow and what remains highly speculative. The ethical issues raised at these stages are not necessarily the same.

Today's nanotechnologies exploit the interaction of three technological developments:

- New and improved control of the size and manipulation of nano-scale building blocks and standardisation of nanodevices;
- New and improved characterisation of materials on a nano scale;
- New and improved understanding of the relationships between nanostructure and properties and how these can be engineered.

2.2 Nanomedicine: the state of the art

Potential applications of nanomedicine have been discussed in many of the reports on nanotechnology and nanoscience, for example those published in the UK (the Royal Society and the Royal Academy of Engineering[30]), Norway (Norwegian Research Council), the Netherlands (Dutch Health Council[31]) and Canada[32], as well as by Unesco[33]. An overview is also available in the

[29] For additional background see the Vision Paper and Basis for a Strategic Research Agenda for NanoMedicine published in September 2005 by the European Technology Platform on NanoMedicine, and annexed with permission to this Opinion, and the Strategic Research Agenda on Nanotechnology under the EU research programme (FP7), 5 June 2006. Micro-Nano-Bio Systems: Future RESEARCH AND DEVELOPMENTand New Challenges. FP7 Consultation Workshop. Brussels, 3 May 2006. See http://cordis.europa.eu/nanotechnology/src/past-highlights.htm.

[30] The Royal Society & The Royal Academy of Engineering (July 2004) *Nanoscience and nanotechnologies: Opportunities and uncertainties*. London, ISBN 0 85403 604 0.

[31] http://www.gr.nl/pdf.php?ID=1417&p=1.

[32] http://www.ethique.gouv.qc.ca/.

[33] http://portal.unesco.org/shs/en/ev.php-URL_ID=9648&URL_DO=DO_TOPIC&URL_SECTION=201.html.

proceedings of the Roundtable on Nanomedicine organised by the Commission and the EGE.[34]

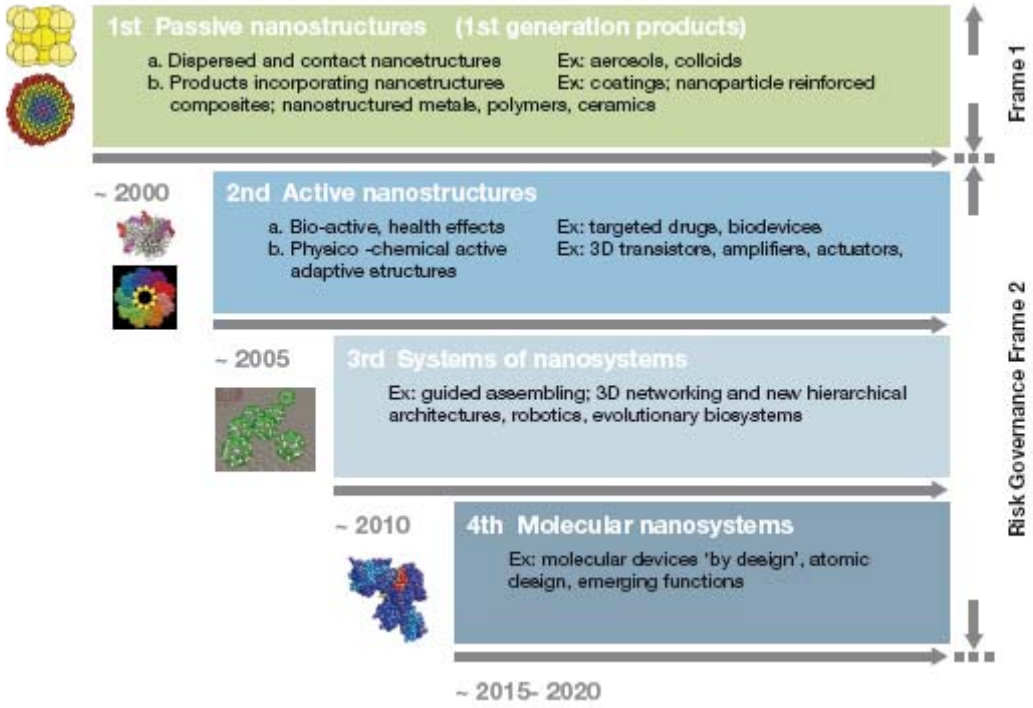
It has been claimed that clinical use in the short term includes therapies for cancer, antiviral and antifungal agents, arteriosclerosis, diabetes, and chronic lung diseases. In the longer term, clinical applications are likely to involve gene therapy and cell repair.

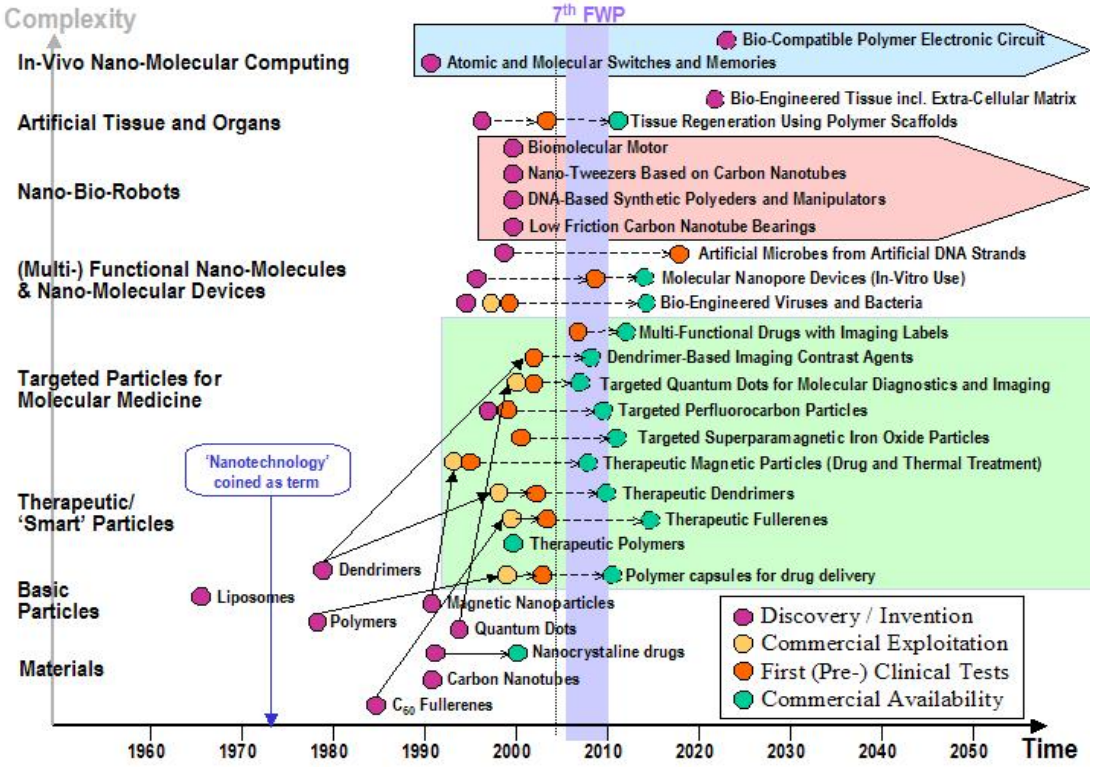
> "Progress in the development of nano-sized hybrid therapeutics and nano-sized drug delivery systems over the last decade has been remarkable. A growing number of products have already secured regulatory authority approval and, in turn, are supported by a healthy clinical development pipeline".[35]

According to an expert group of the European Medicines Evaluation Agency (EMEA), "the majority of current commercial applications of nanotechnology to medicine is geared towards drug delivery to enable new modes of action, as well as better targeting and bioavailability of existing medicinal substances. Novel applications of nanotechnology include nanostructure scaffolds for tissue replacement, nanostructures that allow transport across biological barriers, remote control of nanoprobes, integrated implantable sensory nanoelectronic systems and multifunctional chemical structures for drug delivery and targeting of disease."[36]

The diagrams below indicate what has already been achieved and what are the future prospects for nanomedicine[37]

[34] http://ec.europa.eu/european_group_ethics/publications/index_en.htm.
[35] Ruth Duncan, "Microscopic miracles: nanomedicines already bringing clinical benefits to thousands". Conference on 24 September 2004, Cardiff University.
[36] EMEA Committee for Medicinal Products for Human Use (CHMP) "Reflection paper on nanotechnology-based medicinal products for human use", June 2006.
[37] Philips Medical Systems Position in Nanomedicine, for communication to the European Commission, Michael H. Kuhn PhD, Jacques Souquet PhD and 'Nanotechnology risk governance, white paper' International risk governance council, Geneve, June, 2006..


1st Passive nanostructures (1st generation products)
a. Dispersed and contact nanostructures Ex: aerosols, colloids
b. Products incorporating nanostructures Ex: coatings; nanoparticle reinforced composites; nanostructured metals, polymers, ceramics
Frame 1
~ 2000
2nd Active nanostructures
a. Bio-active, health effects Ex: targeted drugs, biodevices
b. Physico -chemical active adaptive structures Ex: 3D transistors, amplifiers, actuators,
~ 2005
3rd Systems of nanosystems
Ex: guided assembling; 3D networking and new hierarchical architectures, robotics, evolutionary biosystems
~ 2010
4th Molecular nanosystems
Ex: molecular devices 'by design', atomic design, emerging functions
~ 2015- 2020
Risk Governance Frame 2


Complexity
7th FWP
In-Vivo Nano-Molecular Computing
Bio-Compatible Polymer Electronic Circuit
Atomic and Molecular Switches and Memories
Artificial Tissue and Organs
Bio-Engineered Tissue incl. Extra-Cellular Matrix
Tissue Regeneration Using Polymer Scaffolds
Nano-Bio-Robots
Biomolecular Motor
Nano-Tweezers Based on Carbon Nanotubes
DNA-Based Synthetic Polyeders and Manipulators
Low Friction Carbon Nanotube Bearings
(Multi-) Functional Nano-Molecules & Nano-Molecular Devices
Artificial Microbes from Artificial DNA Strands
Molecular Nanopore Devices (In-Vitro Use)
Bio-Engineered Viruses and Bacteria
Targeted Particles for Molecular Medicine
Multi-Functional Drugs with Imaging Labels
Dendrimer-Based Imaging Contrast Agents
Targeted Quantum Dots for Molecular Diagnostics and Imaging
Targeted Perfluorocarbon Particles
Targeted Superparamagnetic Iron Oxide Particles
Therapeutic Magnetic Particles (Drug and Thermal Treatment)
'Nanotechnology' coined as term
Therapeutic/ 'Smart' Particles
Therapeutic Dendrimers
Therapeutic Fullerenes
Therapeutic Polymers
Polymer capsules for drug delivery
Dendrimers
Basic Particles
Liposomes
Magnetic Nanoparticles
Polymers
Quantum Dots
Nanocrystaline drugs
Materials
Carbon Nanotubes
C60 Fullerenes
Discovery / Invention
Commercial Exploitation
First (Pre-) Clinical Tests
Commercial Availability
1960
1970
1980
1990
2000
2010
2020
2030
2040
2050
Time

The following paragraphs present some of the key scientific and technological aspects of nanomedicine, as background to address ethical issues of nanomedicine.

2.2.1 Diagnostic techniques

New in vitro diagnostic tests based on nanodevices may shift diagnosis to a pre-symptomatic stage and allow pre-emptive therapeutic measures with less invasive methods of extraction. The technology may therefore allow the use of cost-effective diagnostic systems with higher performance in terms of resolution, sensitivity, specificity, reliability, reproducibility and integration.
Diagnostic techniques can be either *in vitro* or *in vivo*. *In vitro* techniques are used in a wide variety of analyses including blood, urine and biopsies. Nanotechnologies may be used to improve the performance of DNA chips and protein chips, and offer the potential to enhance resolution down to a single-molecule analysis of standard samples.[38] A nanowire array might test a mere pinprick of blood (which is minimally invasive) in just minutes, providing a nearly instantaneous scan for many different cancer markers. Such devices could open up substantial new possibilities in the diagnosis of cancer and other complex diseases.[39,40] The first so-called "Lab-on-a-chip" devices are already being manufactured: such a device might offer many of the diagnostic functions of a medical laboratory. In addition, hand-held diagnostic kits may be used to detect the presence of several pathogens at once and could perhaps be used for wide-range screening in small peripheral clinics. These techniques have been greatly improved in recent years and they are becoming more reliable, inexpensive, and miniaturised. If the efforts are successful they may offer simple, rapid and inexpensive testing both for large numbers of patients (as in screening for epidemic diseases) and in the testing of multiple parameters with one sample (as in the diagnosis of complex conditions).

In vivo techniques include biosensors, implants and surgical tools. Subcutaneous chips are already being developed to continuously monitor key body parameters including pulse, temperature and blood glucose. Implantable sensors can also work with devices that administer treatments automatically if required, e.g. fluid injection systems to dispense drugs. It is expected that systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical treatments will soon be commercialised. In addition, "the integration of minimally invasive

[38] Sano Y, Shirai K, Takahata N, Hirata T, Sturchio NC. Nano-SIMS analysis of Mg, Sr, Ba and U in natural calcium carbonate. Anal Sci. 2005 September 21 (9), 1091-7.
[39] http://www.nanotechweb.org/articles/news/4/9/17/11 (accessed 31 December 2005).
[40] Herr JK, Smith JE, Medley CD, Shangguan D, Tan W. Aptamer-conjugated nanoparticles for selective collection and detection of cancer cells. Anal Chem. 2006 May 1;78(9):2918-24.

diagnostics with information technology for remote monitoring of the patient's condition may produce a radical shift of the point of care from the hospital or clinic into the home".[41]

Diagnostic techniques based on nanotechnologies are already available.[42] However, in the more distant future, miniaturised devices with biocompatible surfaces could remain in the body to constantly monitor and report certain markers to medical practitioners (for cancer or cardiovascular conditions in high-risk patients, for instance).

2.2.2 Imaging

Techniques such as tomography, nuclear magnetic resonance or ultrasound scanning have enormously expanded the classical use of X-rays in producing images of increasing quality of the human body that are already widely used in multiple types of diagnosis, including analysis of functions of the human brain. Imaging includes also analysis of microscopic images of tissues used in pathology. Nanotechnologies may allow a more precise diagnosis. As an example, ultra small, super-paramagnetic iron oxides, with a diameter of less than 50 nm, allow the imaging of organs and have been successfully evaluated for improved lymph node metastases detection in various clinical trials.

There are many other techniques in use or at the design stage that use nanoparticles to assist in the imaging process or that use nano-techniques to provide images of living systems.[43,44] These techniques can be both in vivo,

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[41] Rickerby D.G. "Societal and Policy Aspects of the Introduction of Nanotechnology in Healthcare", International Journal of Health Technology and Management.

[42] A method for the rapid collection and detection of leukemia cells using a novel two-nanoparticle assay (Herr JK, Smith JE, Medley CD, Shangguan D, Tan W. Aptamer-conjugated nanoparticles for selective collection and detection of cancer cells. Anal Chem. 2006 May 1;78(9):2918-24); possible use of nanocapsules of liquid perfluorocarbons as ultrasound contrast agents to visualise very small vessels in the human body (Pisani E, Tsapis N, Paris J, Nicolas V, Cattel L, Fattal E. Polymeric nano/microcapsules of liquid perfluorocarbons for ultrasonic imaging: physical characterization. Langmuir. 2006 Apr 25;22(9):4397-402); a bi-enzyme-based Clark electrode developed for the determination of 3-hydroxybutyrate (Kwan RC, Hon PY, Mak WC, Law LY, Hu J, Renneberg R. Biosensor for rapid determination of 3-hydroxybutyrate using bi-enzyme system. Biosens Bioelectron. 2006 Jan 15;21(7):1101-6); nano-liquid chromatography-mass spectrometry to analyse atenolol enantiomers present in human urine samples of a patient under atenolol (antihypertensive medicament) therapy (D'Orazio G, Fanali S. Use of teicoplanin stationary phase for the enantiomeric resolution of atenolol in human urine by nano-liquid chromatography-mass spectrometry. J Pharm Biomed Anal. 2006 Feb 24;40(3):539-44).

[43] Hauge Bunger M, Foss M, Erlacher K, Bruun Hougaard M, Chevallier J, Langdahl B, Bunger C, Birkedal H, Besenbacher F, Skov Pedersen J. Nanostructure of the neurocentral growth plate: Insight from scanning small angle X-ray scattering, atomic force microscopy and scanning electron microscopy. Bone. 2006 Jun 10; [Epub ahead of print].

for example contrast agents introduced in the body, and ex vivo, such as specific markers used in histology. In the more distant future a combination of improved in vivo agents, scanners and software could offer diagnostic support to the practitioner (e.g. displaying real-time statistics about similar symptoms).

2.2.3 Biomaterials

The biomaterials in current use are generally based on metallic alloys, ceramics, polymers and composites. Significant efforts to mimic biological materials with man-made materials are being made in order to improve their function within biological systems. Nanotechnologies may provide new approaches in this direction. For example, the nanotechnologies currently developed may be used to increase the mechanical properties and biological compatibility of prosthetic and dental implants, catheters, wound dressings and medical instruments. Furthermore, nanotechnology can help to understand and mimic the structures and biochemical pathways that lead to natural healing, with the future potential to induce and support healing beyond the normal capabilities (e.g. after massive loss of tissue, in the restoration of neural structures or even in the restoration of complete organs).

By applying bioactive nanoparticle coatings on the surface of implants, it will be possible to bond the implant more naturally to the adjoining tissue and significantly prolong the implant lifetime.

In addition to the above described applications, implants for knee joints coated with nano-crystalline diamond films have properties such as extreme hardness, wear resistance, low friction and high biocompatibility. Silver nanoparticles are also being used in antibacterial coatings for implants, catheters, wound dressings and medical instruments. Further examples include the following:

- A self-sterilising lancet coated with a titanium dioxide photocatalytic nano-layer has been developed for self-monitoring of blood glucose.[45]
- Novel dental materials might have longer life-spans, biocompatibility and other properties. Nano-indentation could also be used to measure the quality of resins for dental restoration.[46]

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[44] Plotkin M, Gneveckow U, Meier-Hauff K, Amthauer H, Feussner A, Denecke T, Gutberlet M, Jordan A, Felix R, Wust P. 18F-FET PET for planning of thermotherapy using magnetic nanoparticles in recurrent glioblastoma. Int J Hyperthermia. 2006 Jun;22(4):319-325.

[45] Nakamura H, Tanaka M, Shinohara S, Gotoh M, Karube I. Development of a self-sterilizing lancet coated with a titanium dioxide photocatalytic nano-layer for self-monitoring of blood glucose. Biosens Bioelectron. 2006 Sep 18.

- Cell encapsulation with nano-membranes might allow completely new ways of treating diseases such as diabetes.

2.2.4 Drug development and delivery

Drug delivery may be one of the main applications of nanotechnologies in medicine. Pharmaceuticals embedded or enclosed in targeted nanocarriers may allow a new degree of specificity and efficacy in the delivery of drugs.

A key characteristic of nano-pharmaceuticals is their complexity: they can combine several characteristics. They could deliver therapeutic molecules directly across biological barriers (such as the blood-brain barrier or the blood-retina barrier) by bearing specific molecules or charges on their outer shell. At the same time this shell could include specific reagents such as antibodies that bind to specific targets (e.g. molecules which are typical for cancer or for inflammation). The carrier could be made of physiologically stable material which only disintegrates on binding to its target (or on receiving an external signal, administered by the practitioner). This would allow the delivery of high-potency pharmaceuticals which either could have adverse effects when administered systemically or may not be administered successfully by conventional methods at all.

Early clinical trials have already commenced for nano-pharmaceuticals, and a number of pharmaceuticals already available are not marketed as nanomedicines but would actually fulfil the definition. The benefit of new drug delivery systems for the patient will be fewer side-effects, improved efficacy and the treatment of diseases and disease stages that currently cannot be effectively treated.[47] Some examples of drug delivery systems are nano-emulsions, conjugates, multi-component systems, liposomal anticancer agents, antibody drug conjugates, and nanoprecipitation.[48] Methods could be combined (e.g. first isolating diseased tissue from the vascular system, then locally releasing a substance which induces cell death). Novel forms of therapy are possible too (for instance a new form of thermotherapy: iron nanoparticles can be enriched in cells of malign brain cancer and will create local heating when the practitioner places the patient in an external magnetic field – thereby enhancing the effects of chemo- and radiation-therapy).

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[46] Hosoya Y. Hardness and elasticity of bonded carious and sound primary tooth dentin. J Dent. 2006 Feb;34(2):164-71.

[47] Sethuraman VT, Bae YH. Stimuli-sensitive polymeric micelles as anticancer drug carriers. Anticancer Agents Med Chem. 2006 Nov;6(6):525-35; Thorne SH. Strategies to achieve systemic delivery of therapeutic cells and microbes to tumors. Expert Opin Biol Ther. 2007 Jan;7(1):41-51.

[48] Bilati U, Allemann E, Doelker E. Development of a nanoprecipitation method intended for the entrapment of hydrophilic drugs into nanoparticles. Eur J Pharm Sci. 2005 Jan;24(1):67-75.

Novel drug release coatings for stents will reduce restenosis without potential adverse effects.

In conjunction with pharmacogenetics and pharmacogenomics, nanomedicine may help to offer "personalised" pharmaceutical therapy, when the individual mechanisms of drug response are better understood.

Another possibility would be the combination of miniaturised biosensors with drug reservoir units for implantation; a wireless integrated system could regulate drug release, receive sensor feedback, and transmit updates.[49]

2.2.5 Other potential health related applications of nanotechnologies

(a) *Regenerative medicine*

The potential applications of nanotechnology in regenerative medicine also include improvement in the activation of genes that stimulate regeneration of living tissues; production of nano- and micro-engineered biocompatible membranes; improvement in the performance and duration of neural prostheses; faster regeneration of novel bone substitutes; and creation of a new lymphocyte factory that re-establishes normal immune response in a patient.

According to the Vision Paper and Basis for a Strategic Research Agenda for NanoMedicine, nanotechnology may "allow for improvement of non-resorbable biomaterials and effective manipulation of biological interactions at the nanometer level, which will dramatically increase the functionality and longevity of implanted tissues.

Similarly, it may be possible in the future to surround implanted tissues with a nanofabricated barrier that would prevent activation of the rejection mechanisms of the host, allowing a wider utilisation of donated organs".

(b) *Stem cell therapy*

Stem cell therapy combined with nanotechnology, based on magnetic cell sorting, also offers promising possibilities for the regeneration of diseased tissue. Stem cells may be identified, activated and guided to the place of damage within the body with the use of cell–signalling molecules as a source of molecular regeneration messengers.

[49] Staples M, Daniel K, Cima MJ, Langer R. Application of micro- and nano-electromechanical devices to drug delivery. Pharm Res. 2006 May 5.

(c) *Implants*

With regard to the use of electronic nanodevices, it has also been advocated that nano- and related micro-technologies might be used to develop a new generation of smaller and potentially more powerful devices to restore loss of vision. Another future approach may be the use of a miniature video camera attached to a blind person's glasses to capture visual signals processed by a microcomputer worn on the belt and transmitted to an array of electrodes placed in the eye. Another uses a sub-retinal implant designed to replace photoreceptors in the retina.

For hearing, an implanted transducer may be pressure-fitted onto a bone in the inner ear, causing the bones to vibrate and move the fluid in the inner ear, which stimulates the auditory nerve.[50]

2.2.6 Cosmetic applications

One major area of health related non-medical nanotechnological applications is in the field of cosmetics. A number of cosmetics products using nanotechnology are already on the market[51]. The market is growing at about 10% a year and companies believe that nanotechnology will help to create a new generation of products. Toxic effects connected with the use of nanocosmetics have not been reported so far, but both US Food and Drug Administration and the Royal Society in Britain have stressed a lack of knowledge in this area[52].

2.2.7 Toxicological aspects

Nanotechnologies are employed in a wide variety of applications ranging from automobile construction to building techniques, from textiles to cosmetics. Although these technologies are not nanomedical applications in themselves, the use of nanomaterials may have health effects when they are dispersed in the environment. Toxic effects of some nanoparticles have been already demonstrated in cells, tissues and small animal experiments.

Some materials used at nano scale may increase the probability of nanoparticles entering the body and circulating or being absorbed into specific organs. Nanoparticles may act in a different way in tissues such as the respiratory organs and may be catabolised in a different way by the organism and recycled differently by the environment, when compared with

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[50] See also EGE Opinion No 20 "Ethical Aspects of ICT Implants in the Human Body".

[51] Ruetsch SB, Kamath YK, Kintrup L, Schwark HJ. Effects of conditioners on surface hardness of hair fibers: an investigation using atomic force microscopy. J Cosmet Sci. 2003 Nov-Dec;54(6):579-88.

[52] http://www.timesonline.co.uk/article/acessed 2007-01-16

larger particles. Nanoparticles can deposit in the respiratory tract after inhalation. There is currently little evidence from skin penetration studies but only a few specific nanoparticles have been investigated in a limited number of test systems, and extrapolation of this data to other materials is not possible.[53]

It is important to monitor the possible adverse effects on health arising from the use of free new nanoparticles for diagnostic, therapeutic or cosmetic purposes. Such adverse effects may be due to accumulation in tissue or organs; to the consequences on cellular metabolism of the organism involved, including potential protein conformational change – e.g. prions; as well as to the possible promotion of tumour formation. There are examples indicating that known and widely accepted toxicological methods are not sufficient to detect possible damaging effects of nanoparticles.[54]

[53]Borm PJ, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K, Schins R, Stone V, Kreyling W, Lademann J, Krutmann J, Warheit D, Oberdorster E. The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol. 2006 Aug 14;3:11.

[54] Wang B, Feng WY, Wang TC, Jia G, Wang M, Shi JW, Zhang F, Zhao YL, Chai ZF. Acute toxicity of nano- and micro-scale zinc powder in healthy adult mice. Toxicol Lett. 2006 Feb 20;161(2):115-23.

3. LEGAL BACKGROUND

The current legal systems in Europe were not designed for nanomedicine as such; but this does not mean that nanomedicine is unregulated. The legal background is primarily derived from European Union legislation, from other international instruments and from general principles underlying national legislation. These legal principles are mostly to be found in texts concerning different subject matters, including medicinal products, medical devices, data questions and general bioethical principles on information, consent, safety and justice.

3.1 The legal situation: an overview

Many reports mentioned in section 2.2 address legal questions, but specific legislation on nanomedicine has not been introduced in European Union Member States.

Most of the existing regulations result from transposition of the relevant EU legislation into the national legal systems. This is supplemented by some global provisions, issued by the World Trade Organisation (WTO), and an international framework on ethics and human rights. The latter is only to a limited extent legally binding. These rules[55] are described briefly in the following (according to their legal force), focusing on their importance for nanomedicine, with special reference to definitions, procedures and the content of the provisions.

(A) European Union (EU) legislation on products, clinical trials, data and patents

- Medicinal products
- Medical devices
- Cosmetics
- Chemicals
- Clinical trials
- Data protection (personal data)
- Patents
- Other relevant EU legislation

(B) Global provisions issued by the World Trade Organisation (WTO)

- General Agreement on Tariffs and Trade (GATT)

[55] As the topic of this Opinion is nanomedicine, the description focuses on human health. Legislation on the environment, foodstuffs etc. is thus not described.

- Sanitary and PhytoSanitary (SPS) agreement on trade
- Trade-Related Aspects of Intellectual Property Rights (TRIPS)

(C) International framework on ethics and human rights

- Council of Europe Convention for the protection of human rights and fundamental freedoms
- Council of Europe: Convention on human rights and biomedicine – known as the Bioethics Convention (Oviedo)
- EU Charter of Fundamental Rights.
- Unesco Declaration on the human genome and human rights
- Unesco Declaration on bioethics and human rights

Legislation adopted by the European Union is binding for the Member States, but there are differences in the nature of obligations. Legislation related to the placing of products on the EU market, e.g. medical devices, medicinal products and cosmetics, constitutes a harmonised system at Member State level, whereas legislation on Good Clinical Practice may be supplemented by national rules, as Community law establishes minimum provisions. The data protection and patent provisions are binding for the EU Member States.

WTO agreements ratified by a great number of nations form the legal ground rules for international commerce. They are binding for the States that have signed and ratified them.

The international framework on ethics and human rights is legally binding only to a limited extent. The Council of Europe Convention on Bioethics, based on the Convention for the Protection of Human Rights and Fundamental Freedom (4.11.1950), is binding for the States that have signed and ratified it, but not all EU countries have done so.[56] However, European projects funded under the EU research framework programmes also have to comply with the principles enshrined in that Council of Europe Convention. The Unesco Declarations and the EU Charter of Fundamental Rights are not legally binding, but they have moral authority. All three types of rules may be supplemented by national regulation.

3.2 EU legislation

There is a wide range of Community legislation related to issues relevant for nanotechnology and nanomaterials, currently in existence or being

[56] As of November 2006, the Convention has been signed by 21 EU Member States and ratified by 13 of them. See http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.

elaborated. These issues primarily have to do with risk assessment. Examples of legislation relevant for nanomedicine are the following:

(a) Medicinal products marketed in the European Union are covered by comprehensive EU legislation.[57]
Medicinal products are defined in the EU legislation as follow:

> "Medicinal product:
> Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product." (Art. 1.2; 2001/83/EC[58])

All medicinal products marketed in the European Union must obtain an EU product authorisation. Directive 726/2004 lays down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishes a European Medicines Evaluation Agency (EMEA). EMEA's task, according to its mission statement, is

> "to contribute to the protection and promotion of public and animal health by mobilising scientific resources from throughout the EU to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health care professionals developing efficient and transparent procedures, to allow timely access by users to innovative medicines through a single European marketing authorisation, and in particular through a pharmacovigilance network and the establishment of safe limits for residues in food producing animals".

The European regulatory system for medicinal products offers two routes for authorising medicinal products:

A "centralised procedure" with applications made directly to EMEA, leading – if approval is obtained – to the grant of a European marketing authorisation by the Commission. Use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products.

A "mutual recognition" procedure, which is applicable to the majority of conventional medicinal products. Applications are made to the Member States selected by the applicant and the procedure operates by mutual recognition of national marketing organisations. Purely national

[57] Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2003/94/EC, Directive 2003/63/EC.
[58] http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_311/l_31120011128en00670128.pdf

authorisations are still available for medicinal products to be marketed in one Member State.

Both procedures are based on a wide range of requirements laid down in implementing rules and – de facto binding – guidance documents. National clinical trials preceding an EU authorisation must observe the rules laid down in the Declaration of Helsinki, which means, among other things, that they must be assessed by an ethical review committee.[59] Seen in an international context, this EU regulatory system is unique in providing a network between all national regulatory bodies, coordinated by EMEA.

(b) Medical devices are also covered by EU regulation, but the Directive on medical devices[60] does not make placing on the market subject to a prior marketing authorisation issued by public authorities.

> A medical device is defined as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software necessary for its proper application intended by the manufacturer to be used for medical purposes for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, … investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means". The Directive does not apply to human blood, blood products, blood cells of human origin, human tissue engineered products, etc.

However, depending on risks involved, devices can only be placed on the market if they have been subject to a conformity assessment procedure involving a third party, a so-called Notified Body, designated by a Member State. The Directive deals primarily with risk management. Manufacturers are obliged to carry out an assessment of the risks and to adopt a risk management strategy. This means that they have to adopt measures to eliminate risks, or to reduce risks as far as possible, take the necessary protection measures in relation to risks that cannot be eliminated and, as a last resort, inform users of the residual risks due to any shortcomings of the

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[59] "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence." See http://www.wma.net/e/policy/b3.htm.

[60] Directive 93/42/EEC concerning medical devices and 90/385/EEC relating to active implantable medical devices. See: http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31993L0042&model=guicheti.

protection measures adopted and advise any other protective measure regarding risks that cannot be eliminated. The Directive on medical devices includes a risk-benefit analysis.

(c) Cosmetics

Cosmetic products are also covered by an EU Directive.[61] A "cosmetic product" is defined in Article 1 as:

> "any substance or preparation intended to be placed in contact with the various external parts of the human body or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition". According to Article 2, "a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorised agent or by any other person responsible for placing the product on the Community market".

The Directive lays down requirements in the form of a number of positive and negative lists of ingredients. The basic obligation on a manufacturer is to carry out a risk assessment. The manufacturer must have available an assessment of the safety for human health of the finished product. To that end, the manufacturer must take into consideration the general toxicological profile of the ingredients, their chemical structure and their level of exposure. The risk assessment must take particular account of the specific exposure characteristics of the areas on which the product will be applied or of the population for which it is intended. There must be inter alia a specific assessment for cosmetic products intended for use on children under the age of three and for cosmetic products intended exclusively for use in external intimate hygiene.

In contrast to the so-called "New Approach" type legislation (see below), the Cosmetics Directive does not provide for verification of the manufacturer's risk assessment by a third party before the product is placed on the market. This means that whether the legal requirements are met depends ultimately on assessment by manufacturer.

(d) Chemicals are embraced by one set of rules concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH),[62] which

[61] Directive 1976/768/EEC. See: http://ec.europa.eu/enterprise/cosmetics/html/consolidated_dir.htm.

[62] The REACH Regulation was formally adopted on 18 December 2006 by the Council of Environment Ministers following the vote in second reading of the European Parliament on

introduces changes to the current regulatory system, inter alia by placing the burden of risk assessment on manufacturers instead of authorities, widening the scope for registration of chemicals, replacing decentralised implementation by a centralised European system, and replacing a set of rules that have grown over time by a single regulatory system.[63]

(e) Clinical trials for medicinal products are covered by an EU Directive on Clinical Trials,[64] which was amended in 2003[65] and 2005[66]. The purpose is to rationalise the procedure involving documentation and administration required for conducting clinical trials, and to ensure that patients are afforded the same protection in all EU Member States. Before clinical trials may commence a number of criteria must be satisfied, including the weighing of predictable risks and drawbacks as regards the therapeutic benefit for each trial subject and society as a whole; respect for the trial subject's right to physical and mental integrity and right to personal privacy; and the obtaining of informed consent.

(f) Data protection is covered by the Directive on the processing of personal data and the protection of privacy in the electronic communications sector.[67] Article 8 provides protection regarding health data and establishes

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13 December 2006. REACH will enter into force on 1 June 2007. The text of the Regulation was published on 30 December 2006 in Official Journal of the European Union L 396 (Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. See: http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm).

[63] "*Article 1: Aim and scope*

1. The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.

2. This Regulation lays down provisions on substances and preparations within the meaning of Article 3. These provisions shall apply to the manufacture, placing on the market or use of such substances on their own, in preparations or in articles and to the placing on the market of preparations.

3. This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle."

[64] Directive 2001/20/EC.

[65] Directive 2003/63/EC.

[66] http://clusters.wallonie.be/servlet/Repository/Directive_2005/28/EC_EN__comp.PDF?IDR=5482.

[67] Directive 2002/58/EC, Directive 95/46/EC.

exemptions from the provisions laid down in the Directive for data required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy.[68]

(g) The Patent Directive,[69] on protection of biotechnological inventions, is designed to ensure effective legally harmonised protection of patents, and in doing so encourage innovation and promote investment in the field of biotechnology, and to establish legal certainty. The inventor secures exclusive rights to control commercial exploitation of his invention for 20 years and, in return, he must disclose a detailed description of his invention, making the new knowledge available to all. This disclosure enables others (researchers etc.) to build on the knowledge gained. The patent may be a product claim or a process claim.[70]

The standard criteria for patentability include novelty, inventive step and industrial application. According to Article 3, "biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature". The Directive contains provisions laying down restrictions based on ethical concerns, i.e. *ordre public* or morality (Article 6[71]).

In addition, diagnostic, therapeutic and surgical methods are traditionally excluded from patenting. This exclusion was intended to maintain the sharing of medical knowledge and know-how for the benefit of patients. It does not concern products or drugs used for medical purposes. In Europe there is also a traditional academic exemption, mentioned in most national laws, which

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[68] "Article 8: The processing of special categories of data. 1. Member States shall prohibit the processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life. … 3. Paragraph 1 shall not apply where processing of the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy." See:
http://europa.eu.int/ISPO/legal/en/dataprot/compenfr.html.

[69] Directive 98/44/EC.

[70] See also EGE Opinion No 16 on "Ethical aspects of patenting inventions involving human stem cells" (http://ec.europa.eu/european_group_ethics/docs/avis16_en.pdf).

[71] According to the Directive on biological inventions, "inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation".Directive 98/44/EC, Article 6(1).

allows further research without paying a licence to the inventor, if such research is not commercial.

The Directive above also states (Article 7) that the EGE "evaluates all ethical aspects of biotechnology".

(h) Other EU legislation

Other European Union legislation of specific importance for risk assessment issues includes Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EC;[72] Regulation (EC) No 1946/2003 on transboundary movements of genetically modified organisms;[73] Directive 90/219/EEC on the contained use of genetically modified micro-organisms;[74] and Council Directive 98/81/EC amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms.[75]

3.3 World Trade Organisation (WTO) agreements and Trade-Related Aspects of Intellectual Property Rights (TRIPS)

(a) The mission of the World Trade Organisation (WTO) is to develop a multilateral system of trade, the aim of which is to lower customs and trade barriers, and to abolish discrimination in international trade. The World Trade Organisation pledges to work for sustainable development and protection of the environment. The heart of the WTO system is the agreements, negotiated and signed by a large majority of the world's trading nations and ratified by their parliaments. These agreements are the legal ground rules for international commerce.

The General Agreement on Tariffs and Trade (GATT) and the Sanitary and Phyto Sanitary (SPS) agreement include measures that might impact on trade between nations and stipulate, for example, that measures may not be introduced in breach of the principle of non-discrimination if these are based on the precautionary principle. In cases where "relevant scientific evidence is insufficient", a Member may, according to Article 5(7), "adopt sanitary or phytosanitary measures on the basis of available pertinent scientific information, including that from the relevant international organisations as well as from sanitary or phytosanitary measures applied by other members. In such circumstances, Members shall seek to obtain the additional

[72] http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_106/l_10620010417en00010038.pdf.
[73] http://europa.eu/eur-lex/pri/en/oj/dat/2003/l_287/l_28720031105en00010010.pdf.
[74] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0219:EN:HTML.
[75] http://europa.eu/eur-lex/pri/en/oj/dat/1998/l_330/l_33019981205en00130031.pdf.

information necessary for a more objective assessment of risk and review the sanitary or phytosanitary measure accordingly within a reasonable period of time".

(b) The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement also contains a provision (Article 25(2)) allowing Member States to exclude from patentability inventions that are contrary to *ordre public* or morality or in order to protect human, plant or animal life, or in order to avoid serious detriment to the environment. It is unclear how the clause on morality in the TRIPS agreement will be implemented for nanomedicine.[76] "Diagnostic, therapeutic and surgical methods for the treatment of humans and animals" may be excluded from patentability (Article 27(3)(a)), something which may impact on the patentability of nanomedicinal products (or on patentability in the domain of nanomedicine).

3.4 Framework on ethics and human rights

As already mentioned, the Council of Europe Convention on Human Rights and Biomedicine (the Oviedo Convention) is legally binding for those States that have signed and ratified it. Other relevant documents (such as the Unesco Declaration and the EU Charter of Fundamental Rights) are not legally binding, but have moral authority.

(a) The *Council of Europe* has issued the Oviedo Convention – Convention on Human Rights and Biomedicine. Its main purpose is to protect individuals against exploitation arising out of treatment or research. The article on the purpose and object of the Convention states that the Parties "shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine". The Convention also concerns equitable access to health care, professional standards, protection of genetic heritage and scientific research. It contains

[76] In the Patent Directive (98/44/EC) there are two major exclusions from patentability: "*ordre public*" and "morality". Where the commercial exploitation or publication of the invention would be contrary to morality or affect *ordre public*, patentability is excluded (not immoral experimentation leading to the invention). The TRIPS agreement permits exclusion on these grounds. There have been few exclusions on the grounds of morality, although Article 6(2) of the Patent Directive provides examples (stressing that these are non-exhaustive) of possible "immoral" inventions which shall be unpatentable: (a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes; and (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

several detailed provisions on informed consent. The Convention is supplemented by a number of additional protocols.[77]

(b) The *Universal Declaration on the Human Genome and Human Rights*, adopted by Unesco's General Conference in 1997 and subsequently endorsed by the United Nations General Assembly in 1998, deals with the human genome and human rights. Since the Declaration was drafted in 1997 it does not refer explicitly to nanomedicine, but modifications that are targeted to DNA may fall within its scope. It states, among other things, that the "human genome underlies the fundamental unity of all members of the human family as well as the recognition of their inherent dignity and diversity". The Declaration asserts that "dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity". Moreover, the Declaration prohibits financial gain from the human genome in its natural state, and affirms that the benefits of advances in the technologies should be made available to all, and that freedom of research is "necessary for the progress of knowledge". The Declaration also contains provisions on the informed consent principle.
The recently adopted Unesco *Universal Declaration on Bioethics and Human Rights* (adopted on 19 October 2005) also contains specific provisions on ethical issues related to medicine, life sciences and associated technologies and advocates several ethical principles, including human dignity, consent, autonomy and responsibility, privacy, equity and justice, solidarity and benefit sharing.[78] The Declaration is not legally binding, but is a reference point for the protection of human rights and ethics.

(c) The *European Charter of Fundamental Rights*[79] emphasises that the Union is founded on the indivisible and universal values of human dignity, freedom, equality and solidarity and on the principles of democracy and the rule of law. It contributes to the preservation of these common values while respecting the diversity of the cultures and traditions of the peoples of Europe, as well as the national identities of the Member States and the organisation of their public authorities. The Charter formulates a common set of basic shared values at EU level.[80] Respect for human dignity, a ban on human reproductive cloning, respect for people's autonomy, non-

[77] http://www.coe.int/t/e/legal_affairs/legal_cooperation/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.
[78] http://portal.unesco.org/shs/en/file_download.php/46133e1f4691e4c6e57566763d474a4dBioethicsDeclaration_EN.pdf.
[79] Approved on 28 September 2000 and proclaimed by the European Parliament, the Council and the Commission on 7 December 2000.
[80] For example Article 1 (respect for human dignity), Article 3 (ban on human reproductive cloning, respect for people's autonomy, non-commercialisation of biological components derived from the human body, prohibition of eugenic practices), Article 8 (data protection issues), Article 13 (freedom of science).

commercialisation of biological components derived from the human body, prohibition of eugenic practices, protection of people's privacy, freedom of science: these are examples of values enshrined in the Charter, which was adopted at the Summit of Nice in 2001.

3.5 Regulatory concerns

The regulatory concerns include a number of questions:

a. Does regulation embrace the relevant areas of nanomedicine, so that no major area is left out?
b. Is the legislation clear and comprehensive, without overlap?
c. Does regulation secure adequate protective measures, including evaluation of health-related risks?
d. Is the implementation of existing regulations adequate?
e. Is the present patent system adequate to deal with problems regarding knowledge protection and information dissemination in nanomedicine?
f. What are the challenges for future regulatory discussions?

a. Does regulation embrace the relevant areas of nanomedicine, so that no major area is left out?

There is extensive regulation of areas where nanomedicine is used in products. Medicinal products and medical devices are subject to strict rules. Cosmetics are also subject to rules requiring inter alia risk assessment, but without verification of the manufacturer's risk evaluation. These provisions will probably embrace the products for which nanomedicine is being used. A regulatory framework is in place for research in humans and clinical trials, but informed consent may present a challenge: see below in the ethical section (4.3.1). Patents are possible, but the distinction between products and drugs, on the one hand, and diagnostic, therapeutic and surgical methods, on the other, may be blurred. These problems are dealt with in part 4 of this text.

b. Is the legislation clear and comprehensive, without overlap?

The lack of a clear legal definition of nanomedicine, and the fact that current regulation is based on other characteristics where nanomedicine was not part of the considerations on which the wording was based, present a problem, as it may be unclear whether nanomedicine is to be placed within or outside the scope of certain legislation. Some nanomedicinal innovations may fall within several categories of regulation which may apply

simultaneously. For example, nanomedical products may combine different mechanisms of action, be they mechanical, chemical, pharmacological or immunological. There may therefore be a risk not only of uncertainty as to which regulation(s) are applicable, but also of there being a plethora of regulatory provisions that are of relevance. Both situations are problematic from a legal point of view.

Most important is the fact that it is not in the present legal situation always obvious which directives etc. apply and how they should be interpreted. Clarity would enable scientists, producers of nanomedicine etc. to make sure they operate on safe ground, and European society would feel more secure knowing which safeguards are required and applied.

Uncertainty and overlap may result in a situation where the manufacturer may have to apply different systems or can choose between different systems with different procedures and different risk evaluations and assessments.

c. *Does regulation secure adequate protective measures, including evaluation of health-related risks?*

Risk assessment is included in virtually all product legislation relevant to nanomedicine. There is an obligation on the producer to carry out, although to different degrees, a risk assessment and to adopt risk-management measures for the risks covered by individual directives and regulations. As a general rule these risks are defined broadly. This is the case for medical devices, cosmetic products, chemicals, etc. In the case of medical devices the risk assessment and risk management approach is supplemented by a risk/benefit analysis; clearly identified risks that have been reduced as far as possible can be accepted, provided the benefits outweigh the possible adverse effects. Finally, as part of their post-market obligations, manufacturers have to set up a risk management scheme in relation to aspects not covered by the marketing authorisation.

Wide experience has been built up in the sector regarding new risks. EMEA has created the Innovation Task Force (ITF) to ensure EMEA-wide coordination of scientific and regulatory competence in the field of emerging technologies, including nanotechnologies, and to provide a forum for early dialogue with applicants on regulatory, scientific or other issues that may arise from the development.

d. Is the implementation of existing regulations adequate?

Even if regulation includes provisions on risk assessment, this only provides adequate protection if the implementation includes sufficient scientific expertise and the risk actually can be assessed and managed. Specific efforts are needed to develop measures for implementing existing regulations that would respond to the implications of nanomedicine.

e. Is the present patent system adequate to deal with problems regarding knowledge protection and information dissemination in nanomedicine?

The aim of the patent system is to encourage innovation by striking a balance between knowledge protection and information dissemination. There is, however, a risk of excessively broad patents being granted and the risk that the research exemption and the exemption for diagnostic and therapeutic purposes can be challenged. These factors make the present patent system less well adapted to deal adequately with, on the one hand, knowledge protection and, on the other, information dissemination in the area of nanomedicine, especially if combined with a liberal policy of granting patents. The balance between disclosure and inventors' rights is skewed.

f*. What are the challenges for future laws and regulations?*

The challenges are primarily:

- the risk evaluation for nanomedicine may not be adequate in all areas;

- the implementation of risk evaluation measures should be carried out in a scientifically sound and transparent manner;

- there is a need for legal clarity in a number of areas especially where regulations and/or areas overlap;

- ethical dimensions must be taken into account in legal provisions on nanomedicine.

4. ETHICS, GOVERNANCE AND POLICIES: PROBLEMS AND CONCERNS

4.1 Introduction

All areas of science and new technology developed within the European Union must be consistent with the ethical principles stated in the European Charter of Fundamental Rights. The overall principle of human dignity is spelled out in several chapters of the Charter, both as protective or negative rights (rights not to be unjustly hindered in actions, be it on the individual or the institutional level; and rights to be protected against maltreatment or unjustified risks caused by the actions of others) and as positive rights (rights to be upheld in people's everyday lives and/or raising the standard of living for those who do not have the means to fully participate in the activities of European society).

Against this background the questions arising are: How should the dignity of people participating in nanomedicine research trials be respected? How can we protect the fundamental rights of citizens that may be exposed to free nanoparticles in the environment? How can we promote responsible use of nanomedicine which protects both human health and the environment? And what are the specific ethics issues, such as justice, solidarity and autonomy, that have to be considered in this scientific domain?

All these questions call for a proper assessment of issues related to dignity, safety, individual and social ethics, public policy, the economy, societal debates, and socio-cultural anthropology.

As can be seen from the structure set out in the table of contents, social, economic, political and ethical concerns will be separated below, though in reality they are interrelated in complex ways and need to be properly addressed if nanomedicine is to be used in a way which is ethically sound, democratically discussed and respectful of citizens' rights.

Furthermore, it is important on the one hand to distinguish between:

- Present, near-future and more distant future (futuristic) uses;
- Specific and non-specific problems;
- Medical and non-medical issues;
- Traditional and new concepts of health and disease.

On the other hand, it is also important to recognise that these distinctions raise additional problems. Nevertheless, because nanomedicine may affect citizens, both directly (trials) or indirectly (possible exposure to free

nanoparticles into the environment), it is important to underline the safety of this technology in order to protect their rights, their property and their aspirations.

4.2 Toxicology and human health

4.2.1 Safety

Safety issues of nanotechnology and nanomedicine have been addressed in several reports across the world. The SCHENIR report and the White Paper *Nanotechnology risk governance* published in June 2006 by the International Risk Governance Council are two examples of reports on risk governance issues of nanotechnologies. Other examples have already been referred to in section 3.2 of this Opinion.

While using different approaches and methods, the above reports agree in stressing the lack of data on possible risks associated with nanomedicine and nanotechnology with regard to the human health and ecological consequences of nanoparticles accumulating in the environment.

For example, the Dutch Health Council report on the health significance of nanotechnology argues that "there is still a lack of understanding about the possible dangers of new, synthetic nanoparticles. This applies to the nature of possible health and environmental impacts as well as to their severity … there are good grounds for thoroughly investigating the toxicological properties of nanoparticles that do not readily dissolve or degrade".

In addition (to quote the Unesco report on the ethics and politics of nanotechnology[81]), the issue of the safe and responsible use of nanomedicine and nanotechnology raises "two concerns: the hazardousness of nanoparticles and the exposure risk. The first concerns the biological and chemical effects of nanoparticles on human bodies or natural ecosystems; the second concerns the issue of leakage, spillage, circulation, and concentration of nanoparticles that would cause a hazard to bodies or ecosystems."

For clarity, however, a distinction needs to be drawn here between risks for the patients undergoing an application of nanomedicine (for example risks of toxic effects on a person involved in clinical trials or a medical treatment) and health-related risks associated with the toxicological and eco-toxicological effects of nano-pollution (impact of free nanoparticles on public health and the environment).

Since this Opinion deals with nanomedicine, the key concerns in terms of risk assessment refer mainly to the first kind of risk. But the impossibility of

[81] http://unesdoc.unesco.org/images/0014/001459/145951e.pdf.

drawing a precise borderline between the two dimensions will make it necessary to comment on risks to health also in a broad sense. Risk assessment is therefore conceived here not only as a technical element for the safe governance of nanotechnology but rather as a factor conducive to the protection of the human dignity and autonomy of the persons directly (medical applications) or indirectly (exposure to free nanoparticles) involved, as well as the protection of the environment.

As far as nanomedicine is concerned, the risk assessment issues refer to possible health effects in terms of toxicity for the patients involved. For example, how do we check that, because of their greater capacity to pass through biological systems (for instance, crossing the blood-brain barrier and penetrating into the brain), nanodevices designed for drugs delivery would not induce negative side-effects for the patients (for example, because of possible accumulation of cross-effects in tissue or organs; or consequences with regard to the cellular metabolism of the organism involved)? Or how can we devise valid animal testing models to monitor such side-effects? Or how can we promote the safe use of nanomedicine and prevent some potential protein conformational change or possible promotion of tumour formation in the absence of adequate toxicological data?

Concerns have also been raised about the potential health risks for individuals other than patients due to the spread of free nanoparticles in the environment. The recycling of free and bound nanoparticles, and the possibility that such particles may pollute water, air and soil, raise issues about safety, and how the interests of the industry, competing for market shares, are to be balanced against other interests.

4.2.2 Risk governance

Concerns are also raised by the difficulties of identifying, estimating and managing risks in an area where there are considerable uncertainties and knowledge gaps, and when the short-term and long-term risks may be different. Similar concerns are raised by benefit management. These issues have been dealt with in several already published reports.[82]

In this context, the temptation of exaggerating benefits ("hype") should also be considered. The competition for research funds may, with the assistance of media and science fiction writers, contribute to creating nanomedical hype with regard to the curability of all diseases. Likewise, concerns need to be documented too, in order to avoid hyped-up hopes being replaced by hyped-up fears. The risks associated with nanotechnologies are well addressed in the SCENIHR report.

[82] See the White Paper *Nanotechnology risk governance* published in June 2006 by the International Risk Governance Council and the references in that report.

In addition to more technical risk governance, a broader approach must be developed that is better able than present instruments to adjust to possible changes, in the environment, in societies, in market economics or in national policies.

4.2.3 The Precautionary Principle

As stated in EGE Opinion No 20,[83] the Precautionary Principle does not necessitate impassable boundaries or bans. It is a general risk management tool (which was originally restricted to environmental matters). The Commission Communication of February 2000 states that:

> "The precautionary principle is not defined in the Treaty, which prescribes it only once - to protect the environment. But in practice, its scope is much wider, and specifically where preliminary objective scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community" (Communication Summary, paragraph 3).[84]

The basic constituents of the Precautionary Principle and the prerequisites for its application are the existence of a risk, the possibility of harm, and scientific uncertainty concerning the actual occurrence of this harm. Having referred to the Precautionary Principle the risk manager has to decide on precautionary actions which are proportionate to the potential harm being mitigated and which do not attempt to create "zero risk" situations. The risk management actions should be aimed at identifying the "acceptable risk" threshold with regard to the values at stake – and respect for the human body is undoubtedly one of the values deserving the highest legal protection. Though rooted in fundamental requirements, the Precautionary Principle is a dynamic tool that can follow developments in a sector and continuously verify that the conditions for the acceptability of a given innovation are fulfilled – thereby enhancing governance.[85]

4.3 Bioethical questions

4.3.1 Protection of individuals

The protection offered by international declarations and guidelines applies to both health care and medical research; it includes the obligation to obtain

[83] http://ec.europa.eu/european_group_ethics/docs/avis20_en.pdf.
[84] http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf.
[85] See the White Paper *Nanotechnology risk governance* published in June 2006 by the International Risk Governance Council and the references in that report.

free and informed consent from patients and participants in research and specifies the measures to be taken when patients and participants in research are for various reasons (minors, mentally incapacitated, etc.) unable to give consent.

The principles stated in the above declarations and guidelines also specify the obligations to protect individuals and societies against unpredictable risks on the basis of the precautionary principle and a risk-benefit analysis, which includes also long-term risks and benefits. The principles mentioned above are also applied to health-related risks of nanotechnology, not only in the medical contexts, which are in focus here, but also in other contexts where nanotechnologies are used.

Some particular problems, which will also be addressed in this text, include how to deal with medical information, considering the knowledge gaps and uncertainties, and with predictive information where more extensive information becomes available much more rapidly than before.

4.3.2 Informed consent

Consent may not be too difficult to obtain - but when is it informed? And when is it free? Informed consent requires the information to be understood. How is it possible to give information about future research possibilities in a rapidly developing research area and to make a realistic risk assessment in view of the many unknowns and the complexities?

In view of the knowledge gaps, and the complexity of the matter, concerning the long-term effects of nanomedical diagnostic and therapeutic tools, it may be difficult to provide adequate information concerning a proposed diagnosis, prevention and therapy needed for informed consent. Here the distinction between invasive and non-invasive procedures is very important, since they raise different concerns.

4.3.3 Diagnostic complexity and increased personal responsibility

Nanomedicine offers new diagnostic possibilities, where the results will be available with unprecedented speed, magnitude, and precision at the molecular level. The results may be complex and difficult to interpret. New disease dispositions not known today may be discovered. However, the increased speed of the diagnosis and the implications for personal responsibility are hardly new in principle; these issues have been discussed extensively in the context of genetic testing.[86] Genetic testing can, like

[86] The EGE has addressed the manifold problems in previous opinions. They also apply to genetic tests using nanomedical devices.

nanomedicine, provide tools for predictive information. With the use of micro-array analysis, for example, the speed of this kind of genetic diagnostics will increase further.

This trend in nanomedicine reinforces tendencies in health care where the improved precision, the increasing number of options and the speed of the diagnostics will on the one hand enhance personal freedom, at least theoretically. But it can also, on the other hand, create anxiety by increasing individual responsibility for the choices made. This may lead to a shift of responsibility between doctors and patients so that the responsibility of patients for their health will increase. If the most enthusiastic advocates of nanomedicine are right, it may also affect the very concepts of health and disease.

4.3.4 Third-party uses?

What are the implications of nanomedicine for problems raised in cases where the information obtained by refined nanomedical diagnostic methods is used by third parties, in particular insurance companies and employers? Will these have access to the extensive diagnostic data that may be collected from citizens? If so, under what conditions?

If there is a risk that the traditional system of insurance, based on solidarity and the principle of equal ignorance, can be undermined by the availability of new and more precise diagnostic tools based on nanotechnology, and we want to keep the traditional system, we need to think about how to limit the access to this more precise information. These issues are not in principle new, however – they have been discussed already in the literature and in the EGE Opinion on Genetic testing in the workplace.[87]

4.3.5 Medical and non-medical uses: therapy and enhancement?

Another issue that may raise concerns here is the fine line between medical and non-medical uses of nanomedical methods for diagnostic, therapeutic and preventive purposes.

The borderline between medical and non-medical applications is not all that clear, but it is possible to give examples illustrating fairly clear cases of both. Non-medical applications include intentional changes in or to the body due to

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See EGE Opinion No 18, 28.7.2003: Ethical aspects of genetic testing in the workplace (http://ec.europa.eu/european_group_ethics/docs/avis18_en.pdf): http://ec.europa.eu/research/conferences/2004/genetic/report_en.htm; Opinion No 16 of the Group of advisers to the European Commission on the ethical implications of biotechnology (GAEIB) (http://ec.europa.eu/european_group_ethics/docs/opinion6_en.pdf).

[87] http://ec.europa.eu/european_group_ethics/docs/avis18_en.pdf.

what a person wants, when these wants are not related to medical needs, even if such medical needs are difficult to define clearly.

Another problem is that non-medical applications can allow us to obtain information about solutions to health problems, as was discussed in our previous Opinion on ICT implants.[88] So there are several problems with the medical/non-medical distinction apart from the well-known ones discussed for example in the context of cosmetic surgery.

Concerns have also been expressed that new nanomedical tools can be used not only to transgress the border between medical and non-medical uses but also to open the door to ethically problematic enhancements, for the reasons discussed in the Opinion on ICT implants. This raises questions not only for the state but also for the individual: how can we preserve the plurality of life-styles and avoid the transformation of the medical system into a mere service system for whatever desire individuals may have?

4.3.6 Access from an individual perspective

Access to health-care and new medical technologies is often seen as a challenge for fair health-care systems. Individuals may struggle to gain access to nanomedical innovations, even taking on considerable financial costs. If they cannot afford new diagnostics, drugs, or therapies offered to them, they may feel left behind or even as second-class citizen. Apart from the social question of discrimination and injustice, how do individuals cope with the gap between availability in principle and non-availability in their concrete lives? Simultaneously to the development of new nanomedical diagnostics, drugs, and therapies, this question needs to be addressed as part of a societal and ethical debate. This may also apply to some nanomedical applications.

4.4 Social ethics

Social ethics addresses questions that are of economic, social and public concern and issues concerning governance and institutions.

4.4.1 Economic issues

In January 2006, following a decision taken at the Hampton Court Summit during the UK Presidency of the EU, an Independent Expert Group on Research, development and Innovation produced a report on how research should be fully integrated into the EU's strategy plan for economic growth and economic development. The Group, chaired by the former Prime Minister of Finland, Mr Esko Aho, provided a clear and comprehensive analysis of the

[88] http://ec.europa.eu/european_group_ethics/docs/avis20_en.pdf.

fundamental steps to be taken to bring research into the core of economic development: from investment of 3% of Gross Domestic Product in research to the creation of an innovation-friendly market, from financial mobility and venture capital to mobility in organisation and knowledge. The report indicated nanotechnology as one of the most promising research areas for economic development, innovation and the goals of the Lisbon agenda.[89]

There are numerous companies involved in the invention, development and marketing of drugs, delivery systems, analytical tools and diagnostic systems based on, or using, nanomaterials. For an estimation of the economic impact and the market potential of nanomedicine, see the forecasts in section 3 of the Vision Paper (reprinted here as an Appendix).

Investment in nanotechnology is very large throughout the world. In 2004 the British Royal Society[90] quoted EU sources indicating the amount of funding for this technology as follows:

Europe	Current funding for research in nanotechnology is about €1.6 billion in 2005, two thirds of which comes from national and regional programmes. With the launch of its nanotechnology strategy in 2003, the UK Government pledged £45 million (around € 68.63 million) per year from 2003 to 2009.
Japan	Funding rose from USD 400 million (around € 307 million) in 2001 to USD 800 million (around € 614 million) in 2003 and reached USD 1 000 million (around € 768 million) in 2005.
US	The United States' 21st Century Nanotechnology Research and Development Act (passed in 2003) allocated nearly USD 3.7 billion to nanotechnology from 2005 to 2008 (which excludes a substantial amount of defence-related expenditure). This compares with USD 750 million in 2003. About USD 1 250 million was allocated at the federal level in 2005.
China	USD 83.3 million (around € 70 million) in 2004
Singapore	USD 8.4 million (around € 6.4 million) in 2004
Others	About USD 400 million (around € 307 million) in 2004

The US National Science Foundation estimates that the nanotechnology market will be worth USD 700 billion (around € 537.7 billion) by 2008 and exceed one trillion dollars annually by 2015. Biomaterials and medical

[89] http://ec.europa.eu/invest-in-research/pdf/download_en/aho_report.pdf.
[90] The Royal Society & The Royal Academy of Engineering (2004) *Nanoscience and nanotechnologies: Opportunities and uncertainties.*

devices represent a fast emerging market that is estimated at about USD 260 billion worldwide, including Europe's share[91].

4.4.2 Societal debates

4.4.2.1 Pluralism

As stated in our previous Opinion No 15,[92] pluralism is a characteristic of the European Union, mirroring the richness of its traditions and adding the need for mutual respect and tolerance. Respect for different philosophical, moral or legal approaches and for diverse cultures is implicit in the ethical dimension of building a democratic Europe. This is relevant also for the moral controversies prompted by nanomedicine.

Respect for pluralism is in line with Article 22 of the European Charter of Fundamental Rights, on "Cultural, religious and linguistic diversity" and with Article 6 of the Amsterdam Treaty, which ensures the protection of fundamental rights at EU level, based in particular on international instruments as well as common constitutional traditions, while also stressing respect for the national identity of all Member States.

In European societies, pluralism of life-styles, values and beliefs is presupposed and respected within society itself as much as at the level of institutions. Social and ethical pluralism requires that a culture of debate and communication needs to be established wherever and whenever wide-ranging changes to the lives of individuals, or in social practices, take place or are liable to take place in the future.

The European Union has furthermore taken several steps in the development of ethical standards to guide decisions in the medical field *within* the constraints of the principle of respect for the rights of individuals, respect for multiculturalism, dialogue and tolerance.

These standards do not hinder deliberation and ethical evaluation of new technologies; on the contrary, they stimulate such evaluation and provide the necessary criteria.

[91] The European Union has invested around € 1.4 billion in nanomedicine under FP6 and this amount is expected to be more than doubled under FP7. (see section 4.4.4.2 and 4. 4.4.3)
[92] "Ethical aspects of human stem cell research and use" (http://ec.europa.eu/european_group_ethics/docs/avis15_en.pdf).

4.4.2.2 Societal dialogue

Public participation is of vital concern in democratic states. But such participation also raises questions.[93] In what way, and on what terms, can the public be an active partner in these debates? How can the development of nanomedicine and nanotechnology be tailored to the benefit of the public? How can we ensure that the public participates not only in discussions associated with nanotechnology and nanomedicine but in the overall design of research and development policy?

This raises wider issues of trust and confidence building between the scientific community and the public, including the need to promote proper debate (in particular on uncertainties), and ultimately leads to issues of deliberative democracy, including questions about who draws the lines between what is allowed, acceptable, and what is not; and who overviews those who draw the lines. The role of the media in such a process has to be taken into account.

Public participation and discourse about new and emerging technologies is important. What ways or means can be used to engage the general public about issues raised by the use of nanotechnological applications in medicine? Consensus conferences, public opinion surveys, and preparation of proper communication tools accessible to the general public (including new audiovisual tools) are all examples of possible actions to be taken to promote proper interaction between the public and the scientific and decision-making community (including industry, academia and NGOs). The participation of the public in all stages of the development of this innovative research sector is therefore important not only for the public acceptance of nanomedicine and nanotechnology, but also for the adoption of a nanotechnology strategy where public concerns are approached and discussed from the beginning.

4.4.3. Institutional/political issues

Nanomedicine is part of a process that can already be observed in other areas of research and technological development, demanding new models of governance, or structures to fashion the relations between society, the economy and research institutions. Depending on what policies on funding and, for example, patenting are chosen in this area, research and development in nanomedicine will take different paths. How can societies

[93] As part of the preparatory work on this Opinion the Group held on 21 March 2006 in Brussels a roundtable debate on the ethical aspects of nanomedicine, in order to discuss the topic with scientific experts, lawyers, philosophers, representatives from the European Parliament and international organisations, representatives of patients, industry, religions, and other interested parties. See:
http://ec.europa.eu/european_group_ethics/activities/index_en.htm.

remain at least partly autonomous in their decisions, when the development of nanomedicine is closely connected to the economic prosperity of a given society and plays a part in international competition on the global market?

4.4.3.1 The individual and the state

The basic rights of individuals are protected by the conventions and declarations mentioned in section 4.4. These rights include protection of human dignity, integrity and autonomy, protection of privacy and of confidentiality of personal data, as well as protection of the right not to know and of property rights.

These rights must be protected by the Member States. The conventions establish the basis for a legal system to prevent and punish violations of these rights. Within these constraints, freedom of research and free movement of goods and services is respected and encouraged.

The concerns raised by nanomedicine for the relationship between the individual and the state include in particular the following: How can privacy be protected, when more and more information can be used for surveillance rather than only for medical reasons? Where can the line be drawn between useful data storage within the medical context and non-medical data storage? What strategies are implemented to protect the individual's privacy in both contexts?

4.4.3.2 Institutional and regulatory questions

The development and implementation of new technologies does not take place in a vacuum. What kind of prospective technology assessment will take place in the Member States and at European level? Which institutions are responsible for this work and on what assumptions are such technology assessments being carried out? What role should be played by what institutions in the debate on the ethical dimension?

The broader perspective of technology development includes intellectual property rights, the protection of the health and safety of individuals other than patients, and research funding. Some of these issues are dealt with by particular institutions in the Member States. Against the background of the obligation for European communities to improve the standard of living in particular for those who do not have sufficient resources, technology development in this broader context raises further concerns.

Nanotechnologies have major applications in fields outside of medicine – but some of them will also have implications for individual and public health. This is true in particular for cosmetic applications but may also be relevant for

military applications and agrifood. The implications cannot always be completely separated from medical concerns.

Regulatory issues arise at different levels, with regard not only to clinical research and testing of new drugs but also to the development of new technologies. The relationship between development and use of commercial technologies on the one hand and the freedom and integrity of citizens on the other raises issues that have to be settled politically.

4.4.3.3 Intellectual property rights

Patenting of biomaterial for medical use has become an issue of ethical concern where and insofar as it may limit the provision of medical treatment on financial grounds. Patent law represents an attempt to strike a balance between several legitimate interests. Researchers and companies should be able to protect their intellectual property rights and benefit financially from their investment, but regulation will be needed in order to protect patients. European Patent law does not permit patenting of "methods for treatment of the human or animal body by surgery or therapy".[94] These issues will need to be subjected to ethical analyses, particularly when systems involving both tissues and nanomaterials are available for surgical procedures. Some have argued that there may be a conflict over patentability if a new product is both a pharmaceutical and a "diagnostic, therapeutic and surgical method" used for humans or animals. The European Patent Convention specifically excludes from patentability methods for "treatment of the human or animal body by surgery or therapy or diagnostic methods", but permits patents on products (substances or compositions) used in these methods.[95] It is possible that a nanoproduct may be patented even if it constitutes a method, given the wording of the Article. In addition, the TRIPS agreement (Article 27) permits the exclusion from patentability of "diagnostic, therapeutic and surgical methods for the treatment of humans or animals". It therefore seems that the material itself may be patented in Europe, but the associated method may only be patentable in the United States. Recital 35 of the Patent

[94] European Patent Convention, Article 52(4): "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

[95] Article 52(4): "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

Directive[96] provides as follows:

> "Whereas this Directive shall be without prejudice to the provisions of national patent law whereby processes for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body are excluded from patentability".

4.4.4 Research policies

4.4.4.1 Clinical research involving nanomedical applications

The usual guidelines for clinical trials and research ethics (Declaration of Helsinki, Oviedo Convention, CIOMS guidelines,[97] etc.) will be applied by research ethics committees in approving research proposals. As with other new technologies, concerns may be raised by the difficulties of meeting some of these requirements in the nanomedicine area, in particular those concerning confidentiality of patient data and data protection generally, since such data may be used by many different specialists.

4.4.4.2 Nanotechnology in the 6th Research and Development Framework Programme (FP6)

One of the objectives of the theme "The nano revolution" in FP6 is "to develop intelligent materials for applications in sectors such as transport, energy, electronics and biomedicine representing a potential market of several billion Euros".[98]

The European Technology Platform on NanoMedicine was launched in September 2005 with the publication of the Vision Paper and Basis for a Strategic Research Agenda for NanoMedicine.[99] The European Technology Platform on NanoMedicine has the following policy objectives:

- Establish a clear strategic vision in the area, resulting in a Strategic Research Agenda;
- Decrease fragmentation in nano-medical research;
- Mobilise additional public and private investment;
- Identify priority areas;

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[96] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions. Official Journal L 213 of 30 July 1998, pp. 13 – 21.

[97] The relevant European and International regulatory framework that applies to research and may be used by research ethics committees is available at: http://ec.europa.eu/research/science-society/page_en.cfm?id=2995.

[98] http://europa.eu.int/comm/research/fp6/index_en.cfm?p=3.

[99] ftp://ftp.cordis.lu/pub/nanotechnology/docs/nanomedicine_visionpaper.pdf.

- Boost innovation in nano-biotechnologies for medical use.

Three key priorities have been confirmed by the stakeholders:

- Nanotechnology-based diagnostics including imaging;
- Targeted drug delivery and release;
- Regenerative medicine.

In addition to the technology-oriented research projects financed under the relevant programmes of FP6, the Commission has also financed projects dealing with Ethical, Legal and Social Implications of nanotechnology. Examples of ELSI projects under FP6 are presented in the Appendix to this Opinion.

4.4.4.3 Nanotechnology in the 7th Research and Development Framework Programme (FP7)

The proposal for a Decision of the European Parliament and of the Council concerning the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007 – 2013) (COM(2005) 119 final, 6.4.2005) covers nine themes.[100] One of them is entitled "Nanosciences, Nanotechnologies, Materials and New Production Technologies". Annex I describes each theme and health applications are mentioned when reference is made to the integration of new knowledge and technologies in these areas.

4.4.4.4 Military research and use

There is no open access to military research. A new generation of weapons could be created with nanotechnologies that could have disastrous consequences for health and the environment. EU Member States have signed and ratified international conventions on chemical and biological weapons that are in the process of being revised. This would provide an opportunity to include new technological developments, including the use of nanotechnology for military purposes. In any event, the use of these technologies in a military situation does not preclude the obligation to inform those exposed to these products.

Attempts have been made to document the resources spent on military research involving applications of nanotechnologies, and to describe the direction of this research.[101] This research, though not in focus in the

[100] http://www.cc.cec/sg_vista/cgi-bin/repository/getdoc.cgi?full_file_name=COMM_PDF_COM_2005_0119_F_EN_ACTE.pdf.

[101] See Altmann, Jürgen. Nanotechnology and preventive arms control, Osnabrück: Deutsche

present report, clearly raises concerns about its potential impact on safety and human welfare, which need to be addressed in a different context.

4.4.5 Questions of justice

According to the EU treaties, the role of the European Union and the Member States is to guarantee fair exchange and fair distribution of goods, equal participation and equal access to these goods. This is also in line with the provisions of the earlier European Convention for the protection of human rights and fundamental freedoms (1950).

To achieve these goals, injustice due to socio-economic or ethnic conditions, age or gender status should be corrected by taking "affirmative action" in order to improve the chances of participation and access. The development and introduction of nanomedical tools (drugs, diagnostic methods and therapies) are – like any new or emerging technology – to be assessed against this background.

The central questions relating to justice for present and near-future applications of nanomaterials and nanotechnologies in medicine are:

- To what extent is there fairness in the exchange of pharmaceutical goods (drugs, devices, analytical tools)?
- To what extent is fairness of distribution guaranteed, in the private as well as in the public health sector?
- To what extent can every citizen gain access to the benefits of nanomedicine in Europe? And globally?
- What, if any, measures are taken to correct existing inequalities at national, European and global level with a view to the development of nanomedicine?

4.4.6 Anthropological questions: Changing the human condition

The overarching anthropological questions have to do with our view of ourselves and, in this context, the extent to which this view will be affected by the applications of nanotechnologies in medicine. Nano-scale implants and devices may have an impact on autonomy, integrity, self identity and freedom. In particular, what are the implications of the "man/machine" distinction, and in the perception of it, on a social level? How do our concepts of human beings change? What is the role of the media, literature and films

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Stiftung Friedensforshung (DSF), 2005 (also available electronically) and Altmann, Jürgen, Military nanotechnology: potential application and preventive arms control, London: Routledge , 2006.

(e.g. science fiction)? Such questions can be answered by social, cultural and ethical research in dialogue with biomedicine. Research of this kind may improve the communication between science, humanities and society[102].

[102] See EGE Opinion N. 20

II. OPINION

5.1 Introduction

The Group acknowledges that nanomedicine offers the possibility of new diagnostic, treatment and preventive methods that may open up promising areas of medicine.

5.2 Scope of the Opinion

The scope of this Opinion is ethical issues raised by nanomedicine in the sense indicated by the European Science Foundation definition quoted in the introduction and repeated here: 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.

In this context, the Group will consider nanomedicine including a number of issues raised by nanotechnology insofar as it concerns primarily health-related issues.

5.3 Fundamental values and rights

Nanomedicine, like many other domains, raises issues about protection of the fundamental rights enshrined in various European documents, such as the Charter of Fundamental Rights, the European Convention on Human Rights and its five protocols, as well as the Oviedo Convention and its protocols.

These rights are rooted in the principle of human dignity and shed light on core European values, such as integrity, autonomy, privacy, equity, fairness, pluralism and solidarity.

As stated in many European and international documents, the interests of science are legitimate and justified insofar as they are compatible with human dignity and human rights. New technologies are scrutinised with respect to the prospects of contributing to the improvement in human well-being they are aiming at, and with respect to possible threats to human well-being, be it at European or global level.

According to the Treaty (Article 152), the principle of subsidiarity applies to public health policies at EU level and Community actions should complement national policies.[103]

[103] Article 152 allows incentive measures designed to protect and improve human health to be adopted under the codecision procedure. Harmonisation of national laws and regulations is, however, expressly prohibited. Article 152 also confers on the Council the power, again under the codecision procedure, to set "high standards of quality and safety of organs and

As stated in the United Nations Millennium Development Goals, the Group considers that there is a moral duty to make affordable health care and biomedical technologies available to all those who need them on a fair and equitable basis,

5.4 Safety

In order to safeguard the core values mentioned above, including the precautionary principle, concern for safety with respect to nanomedical developments (and, in fact, nanotechnology in general) is of vital importance. Measures should be established to verify the safety of nanomedical products and to ensure that nanomedical devices are properly assessed with regard to public health.

In particular, the uncertainties and knowledge gaps associated with new nanotechnology-based diagnostics, therapies and preventive measures should be identified. These uncertainties need to be characterised and measures have to be developed in order to reduce them as far as possible. Research needs to be carried out to develop new methods for risk management specific to individual nanotechnology applications.

The Group proposes that relevant authorities should carry out a proper assessment of the risks and safety of nanomedicine. Such risk assessment should cover the whole life cycle of the products, from production to handling of waste. The same level of safety currently applied to medicine and medical devices should then apply to nanomedical products.

The Group considers it essential that reliable and cost-effective systems for toxicology screening of nanomaterials are developed (including instruments to quantify exposure and to characterise nanostructures in detail). The required animal testing should strictly follow the 3R principles (Refinement, Reduction, and Replacement); before starting in vivo testing, relevant data has to be gathered about the produced quantity, quantity and fate of uncontained nanostructures, and risk of exposure.

The Group proposes that institutions already operating at European and national level to protect the safety of patients and citizens should be charged with the additional task of overviewing the safety and security aspects of new tools and devices in nanomedicine. Networking of relevant bodies, at national, European and international level should then be encouraged to favour the proper implementation of safety measures and the adoption of common and validated standards.

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substances of human origin, blood and blood derivatives". Nevertheless, the power in question is still one which complements the powers of the Member States.

The Group also proposes that capacity building on how to address accidents and other unexpected situations should be encouraged and shared at European and international level. Publication of any results, whether positive or negative, which are relevant for safety must be part of the research contract.

5.4.1 Risk assessment

The Group recognises that "understanding and preventing risk often has a low priority in the competitive world of research funding" and bringing products to the market and believes that "without strategic risk research public confidence in nanotechnologies could be reduced through real or perceived dangers".[104] The lack of knowledge and data regarding the toxicity of nanoparticles in humans and in the environment is a cause of concern. The existing methodologies for risk assessment are inadequate (see the SCENIHR report) and need to be adapted or new methods devised.

The Group proposes that this should be considered a top priority for researchers and the relevant authorities and that data on adverse effects have to be communicated without delay to the public.

The Group considers it necessary for appropriate safety research to be carried out and information provided to the public before medical devices and medicinal products derived from nanotechnologies are marketed. The Group asks the European Commission to examine existing regulations in order to propose any amendment that might be needed.

The Group proposes that initiatives be taken at national and European level to stimulate/facilitate cooperation between institutions dealing with risk assessment.

The Group considers it paramount that no nano-based products enter the market without risk assessment, thereby securing their safety with regard to users' health. For example cosmetics are of particular interest in relation to risk assessment as nanocosmetics penetrate the skin and may cross the blood-brain barrier. On this basis we recommend that consideration be given to the question whether specific measures should be implemented regarding nanocosmetics, including evaluating whether verification of the manufacturer's risk assessment should be introduced in certain cases.

[104] Maynard AD (2006) *et al* "Safe handling of Nanotechnology" Nature 444(16) 267-269.

5.4.2 The need for prospective technology assessment, including consideration of social effects

In the rapidly developing fields of nanomedicine Research and Development, in addition to the usual retrospective risk assessment there is a need for prospective technology assessment at national and European level, not just for post factum evaluations.

Prospective technology studies should be performed with special reference to the health impact of nanoparticles; this would also involve prospective technology assessment of possible adverse events that may derive from nanotechnology or nanomedicine.[105] As suggested in the Canadian report,[106] scenarios need to be elaborated about possible adverse events related to the use of nanotechnologies in medicine, and responses should be prepared to deal with these events in such scenarios.

The Group proposes that such prospective technology assessment should consider issues of safety (agri-food and environment) and security (including dual use, impacts of bioterrorism and military research). Social effects should also be addressed, e.g. how new nano-scale technologies applied in medicine will affect social, economic and institutional structures, with particular concern for justice (equal access and participation in decision-making) and fair distribution of goods.

Furthermore, the Group suggests that the Commission should, inter alia, fund a study of the social effects of nanomedicine in the developing countries. Such research should also focus on macroeconomic trends, trade implications and possible international problems, and in particular examine the risk of creating a nano-divide which could widen the gap between the developed and developing countries.

5.5 Legal issues

As can be seen from the legal background (see section 3), many regulations, which are relevant also for nanotechnology-based applications in nanomedicine, are already in place. Implementing these regulations is of crucial importance to safeguard the core values mentioned above.

[105] On this issue, see also the already quoted Report on ethics and nanotechnology produced in Quebec in November 2006:
http://www.ethique.gouv.qc.ca/eng/ftp/Resume_nanos_ang.pdf.
[106] http://www.ethique.gouv.qc.ca/eng/ftp/Resume_nanos_ang.pdf.

5.5.1 General issues

The Group does not propose new broad regulatory structures that specifically deal with nanomedicine at this point. Changes should primarily be made within existing structures. The focus should then be on the implementation of existing regulations.

Monitoring is needed to ensure that regulatory systems exist to address all nanomedicinal products. Moreover the difference in the content of regulations e.o. regarding the conditions of risk evaluation, the responsibility for its performance and the involvement of third parties should be addressed by the relevant Authorities.

Nanomedical products may combine different mechanisms of action, be they mechanical, chemical, pharmacological or immunological, for instance. The mechanism of action is a key factor in deciding whether a product should be regulated as a medicinal product or a medical device.[107]

The Group proposes that possible cases of nanomedicine applications where there might be overlap between regulations, which could create uncertainty as to which regulations should be applied, should be explored by the relevant authorities so that the existing regulations can be implemented in an unambiguous way.

The Group proposes that networking between relevant authorities should be encouraged in order to deal in an optimal way with the problems outlined above, and that – if necessary – new specific implementing measures should be derived from the current regulations.

The Group stresses that the protection offered by the Data Protection Directive has to be properly applied to the type of health data obtained and collected by nano-based DNA chips, nano-scale sensors and devices.[108] This should be addressed in detail by the Article 29 Working Group.

Product liability legislation addresses many of the problems that may be associated with the new materials, but as the risks are not readily assessed and assessable, liability based on negligence and lack of knowledge becomes a serious ethical problem. This requires careful scrutiny and monitoring.

5.5.2 Intellectual property rights

According to the current regulatory system for patenting, some exemptions are allowed with regard to the patentability of therapeutic and surgical procedures. The exemptions in the present patent system are based on a balance of interests whereby diagnosis, therapy and research should be

[107] Directive 2001/83/EC, as amended, Article 1(2)(b).
[108] http://ec.europa.eu:8082/european_group_ethics/docs/avis20_en.pdf.

available to patients without patents being a hindrance. This is likely to be blurred because the new nanomaterials may logically fall within more than one category. To protect the ethical position that has led to these exemptions it is important to ensure that patents in these new areas do not alter the current balance. There are risks of overly broad patents being granted that may hinder their therapeutic availability.[109]

This is also the case for nanomedicine. The Group therefore draws attention to the need for research into the manner in which the patent system can properly balance the need to reward innovation and ensure availability. This could lead to a more general review of the nature of the patent system in relation to new technologies that do not easily fit into a system devised in the 19th Century, possibly with a focus on use or process patents rather than product patents. There is a need to look further into the balance between knowledge protection and information dissemination.

Comparative research on the merits and short comings of different patent systems in various parts of the world is needed.

5.6 Offering nanomedicine tests on the market

Medical tests of various kinds are currently offered for sale on the market, especially via Internet and other media, without medical prescription. In the near future such tests may also be based on applications of nanomedicine.

The Group emphasises that the first concern is the scientific validation of these tests, including their clinical utility, and the accuracy, interpretation and communication of the results. Such validation is considered a necessary (but not sufficient) condition for the acceptability of putting such tests on the market.

In order to protect consumers' rights, the Group proposes that policies be developed to monitor the introduction of tests directly marketed to consumers, in line with the relevant documents of the Council of Europe.[110]

[109] EGE Opinion No 16 on Ethical aspects of patenting inventions involving human stem cells (http://ec.europa.eu/european_group_ethics/docs/avis16_en.pdf).

[110] The Convention on Human Rights and Biomedicine (Oviedo Convention, Art. 12 in particular) and its Additional Protocols are available at: http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.

5.7 Information and consent

The requirement for informed consent is of crucial importance in both medical research and health care. But both the lack of knowledge and the uncertainties that exist create problems for the attempts to provide adequate and understandable information and obtain consent that cannot exclusively be met by informed consent forms signed by patients.

It is especially important to consider these problems in the context of developments that may contribute to a shift of responsibilities from the doctor to the patient.

The Group considers it important that initiatives are taken on different levels to help ensure that decision-making is in the long-term interest of the concerned citizens themselves.

Against this background, the Group encourages further efforts at national and European level to develop improved methods of providing information and obtaining consent e.g. through research projects under the ELSI (Ethical, Legal and Social Implications) programme.

5.8 Economics and research funding

Research funding affects research in nanomedicine, and emerging research in nanomedicine will affect research funding. Research funding in general raises ethical issues concerning the criteria used in priority setting. The Group acknowledges that nanomedicine offers promising opportunities to meet the need of patients and therefore should be funded. However, the overall goals of health-related research must be seen in the context of fair distribution and the overall goal of alleviation of the global health status. In this context, patenting and private gain derived from research funded by public money raises the issue of the fair sharing of burdens and benefits between taxpayers and companies, and should therefore be further explored.

Against this background the Group proposes that further initiatives be taken at national and European level to clarify the ways in which public investments in this area will benefit the citizens of Europe. The initiatives should be conducive to European economic growth and social welfare but also contribute to the UN Millennium Development Goals.

5.9 Communication and public trust

Transparency is essential for public trust. This also holds for openness about uncertainties and knowledge gaps. Such transparency and openness should not be limited only to safety issues but should also extend to funding of research and development.

The Group proposes that initiatives should be taken at national and European level to prepare surveys of public perception of the benefits and risks of the applications of nanotechnologies, with special reference to medical sectors.

The Group also recommends that there should be an EU website on ethics and nanomedicine which is updated regularly, and where citizens can find information and raise questions.

The Group finally proposes that initiatives be taken to organise academic and public debates on problems and possibilities of present and near-future nanomedicine.

The Group draws attention to the question of labelling of nanomedical products and recommends a thorough analysis of this issue by the Commission.

5.10 The need for interdisciplinary research on the Ethical, Legal and Social Implications (ELSI) of nanomedicine

The Group proposes that a considerable amount – up to 3% – of the budget invested in research in nanotechnology should be set aside for ELSI research. This is comparable to the budget allocated to ELSI research under FP5 (3% of the Life Science budget) and following the HUGO approach in the Human genome project (3% ELSI research).

With respect to nanomedicine, cooperation between different academic disciplines, research centres, hospitals and other important players is required for progress in this area and should be promoted at the different levels of nanomedicine research and applications.

The Group proposes that initiatives to support ELSI research should be taken at both national and European levels and that there should be an ELSI programme within FP7 to promote research in the various fields of application mentioned in the ESF definition.

5.11 Ethical deliberation on the concept of humanity, human rights, social and political conflicts in relation to Nanotechnology

In addition to technology-induced ELSI studies, the Group also suggests that initiatives be taken at European level to promote more research on philosophical, ethical and anthropological questions raised by recent developments in nanomedicine, looking into the broader questions of nanomedicine, among other things individual responsibility, including the shifts in the concept of the self, personal identity, societal goals and global health care.

For this purpose, a dedicated European Network on Nanotechnology Ethics should be established and financed by the Commission under FP7. The Network should, among other things, cluster experts from different fields, promote deeper understanding of the ethical issues arising from nanotechnology and nanomedicine, promote education in the fields above, and facilitate interaction between the community of ethicists and nanotechnologists and the embedding of ethics into research practices in nanomedicine and nanotechnology.

5.12 Clinical research involving nanomedical applications

Nanomedicine, like other clinical research, is subject to the relevant EU legislation requiring trials to be approved by local or regional ethics committees. Member States are thus responsible for making sure that there is an adequate ethical review process also for research projects involving studies of nanomedical devices on human beings.

In addition to research on nanomedicine carried out at national level, a number of pan-European or international research trials are being performed; the Group therefore proposes that initiatives should be taken to enhance information exchange between research ethics committees in different Member States.

The Group underlines the need to share relevant information among competent bodies and to properly address informed consent procedures with regard to safety. The Group also draws attention to the specific problems that nanomedicine may give rise to in terms of toxicity and environmental problems.

5.13 Medical and non-medical uses

Medical and non-medical uses of new medical technologies have been an issue for several years. Nanomedicine is expected to broaden the overlap between medical and non-medical uses in specific ways: on the one hand, the distinction between therapeutic goals and enhancement goals may become less clear, if, for example, predisposition tests are available more easily and cheaply. Especially in the reproductive context of Pre-Implantation Genetic Diagnosis, the line between “negative” and “positive” selection may be blurred.

In other areas, such as where the cosmetic industry deals with common allergies and the medical field addresses the same symptoms, the distinction may become even more difficult to draw than today.

Future applications are difficult to foresee today. For example, it may become difficult to ensure that neurological stimulation of brain activity is restricted to therapeutic and diagnostic use. Therefore, appropriate monitoring and guidelines of the use of nanotechnology in this field should be implemented.

Maintaining the distinction between medical and non-medical uses is important with respect to European research funding policies, too, because non-medical research funding of nanomedicine may not be advocated as easily as research funding within the medical sphere. The Group proposes that enhancement technologies should not be given priority. Health care concerns must be met first.

The Group suggests that this concern should be explored both under the ELSI programme and within a European network (involving ethicists and scientists) devoted to exploring the ethical aspects of different applications of nanotechnologies.

5.14 Sharing of information and establishing databases

Relevant scientific and ELSI information related to nanomedicine is not always collected or publicly available. Against this background the Group underlines the importance of sharing of information in order to safeguard some of the values mentioned above (sections 4.3 and 4.5). The Group therefore proposes that initiatives be taken at European level to establish databanks, not only on scientific aspects of nanomedicine, for instance the biodistribution of nanoparticles and results of toxicity studies, but also on ELSI-related aspects of nanomedicine.

5.15 The need for revision of this Opinion

Since research in the area of nanomedicine is undergoing rapid development, this text should be reconsidered and possibly revised in the light of scientific, legal and social developments within the next five years.

The European Group on Ethics in Science and New Technologies

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APPENDIX I

Examples of projects funded under FP6

EXPERTISSUES[111]	Novel Therapeutic Strategies for Tissue Engineering of Bone and Cartilage Using Second Generation Biomimetic Scaffolds
AUTOBONE[112]	Production unit for the decentralised engineering of autologous cell-based osteoinductive bone substitutes
NANOTEMPLATES[113]	Templates for Engineered Nano-Objects for use in Microwave, Electronic Devices and Biomedical Sensing Applications
HIPPOCRATES[114]	A Hybrid Approach for Bone and Cartilage Tissue Engineering using Natural Origin Scaffolds, Progenitor Cell and Growth Factors
BARP+[115]	Development of a bioartificial pancreas for type I diabetes therapy
RAMATI[116]	Rapid manufacturing of titanium implants
I-IMAS[117]	Intelligent Imaging Sensors for Industry, Health and Security
CORNEA ENGINEERING[118]	Three-dimensional-reconstruction-of human corneas by tissue engineering
GENSENSOR-	Nano-biotechnical components of an advanced bio-

[111] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74345&DOC=18&QUERY=2.
[112] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74411&DOC=11&QUERY=2.
[113] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74330&DOC=17&QUERY=2.
[114] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=73827&DOC=24&QUERY=2.
[115] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=73827&DOC=24&QUERY=2.
[116] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74329&DOC=77&QUERY=1.
[117] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74395&DOC=90&QUERY=1.
[118] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74357&DOC=95&QUERY=1.

NANOPARTS[119]	analytical microarray system
MUSTWIN[120]	Micromachined Ultrasound transducers for wide range application in Medical imaging and Non Destructive Testing
CELLPROM[121]	Cell Programming by Nanoscaled Devices
GANANO[122]	New Generation of GaN-based sensor arrays for nano- and pico-fluidic systems for fast and reliable biomedical testing

[119] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74415&DOC=99&QUERY=1.
[120] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74398&DOC=107&QUERY=1.
[121] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74334&DOC=112&QUERY=1.
[122] http://icadc.cordis.lu/fep-cgi/srchidadb?CALLER=FP6_PROJ&ACTION=D&RCN=74403&DOC=123&QUERY=1.

Appendix II

Examples of ELSA projects in the programmes funded under FP6 in the area of nanomedicine

Nanotechnology Capacity Building NGOs (NANOCAP)

Goals: To give support to environmental NGOs and trade unions to develop their own position in the debate on nanotechnology based on scientific information. To give academic and industrial RESEARCH AND DEVELOPMENT performers tools to introduce "responsible nanotechnology". To develop preliminary recommendations for public authorities to address ethics and health, safety and environmental risk issues.

Deepening Ethical Engagement and Participation in Emerging Nanotechnologies (DEEPEN)

Goals: Development of a deepened ethical understanding of issues related to emerging nanotechnologies through an interdisciplinary approach utilising insights from philosophy, ethics, and the social sciences.

Development of ways to map de-facto ethics embedded in the world of nanoscience and technology actors, and on that basis develop ways of enhancing ethical reflexivity in the nanoscience and technology world. Instigation of a programme of cross-European empirical research aimed at unravelling the ethical categories of lay people to ethical issues posed by emerging nanotechnologies. Organising new public fora where citizens, stakeholders, experts and decision-makers can develop common understandings of such dilemmas. Development of recommendations for integrating ethical reflection into nanoscience practice and into governance and regulatory processes.

Nanobiotechnology: Responsible Action on Issues in Society and Ethics (Nanobio-RAISE)

Goals: To bring together the key relevant players in the field including committed ethicists, Delft University of Technology, European Commission Nano2Life Network of Excellence, European Federation of Biotechnology's Task Group on Public Perceptions of Biotechnology, EuropaBio, DECHEMA (Fachsektion Nanotechnologie), Royal Institute for Technology in Stockholm, Church of Scotland Society, Religion and Technology Project , SMEs and major companies using nanobiotechnology. Horizon-scan for the scientific and commercial developments which are likely to cause public and political concern. To clarify the ethical issues and public concerns involved or as they arise, and recommend and carry out strategies for public communication to address the emerging questions, take on board the experiences and lessons learned from the European GM debate of the last decade and apply them with this project to the nanobiotechnology discussions, incorporate the recommendations of the European Commission's Communication "Towards a European Strategy for Nanotechnology" and the results of its Nanoforum public consultation which surveyed European public opinion on these issues, prepare for the relevant actions in the European Commission's Action Plan for Nanotechnology to be

recommendations of the European Commission's Communication "Towards a European Strategy for Nanotechnology" and the results of its Nanoforum public consultation which surveyed European public opinion on these issues, prepare for the relevant actions in the European Commission's Action Plan for Nanotechnology to be published in Spring 2005 and the Technology Platform on Nanotechnology foreseen in its Seventh Framework Programme commencing in 2006.

Additionally there are two projects of relevance: The SSA (specific support action) **Nanologue** (http://www.nanologue.net/) addresses Nanomedicine, and the **Network of Excellence Nano2Life** (http://www.nano2life.org/) specifically addresses ethical and social aspects of nanobiotechnology. The **European Technology Platform** on Nanomedicine also addresses such issues.

Appendix III

Extract from the Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies, produced by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (SCENIHR/002/05. European Commission Health & Consumer Protection Directorate-General, Directorate C - Public Health and Risk Assessment, Unit C7 - Risk assessment. Adopted by SCENIHR during its 7th plenary meeting on 28-29 September 2005)

1. *Are existing methodologies appropriate to assess potential and plausible risks associated with different kinds of nanotechnologies and processes associated with nano-sized materials as well as the engineered and adventitious products of nanotechnologies?*
2. *If existing methodologies are not appropriate to assess the hypothetical and potential risks associated with certain kinds of nanotechnologies and their engineered and adventitious products, how should existing methodologies be adapted and/or completed?*
3. *In general terms, what are the major gaps in knowledge necessary to underpin risk assessment in the areas of concern?*

Question 1

Although the existing toxicological and eco-toxicological methods are appropriate to assess many of the hazards associated with the products and processes involving nanoparticles, they may not be sufficient to address all the hazards. Specifically, particular attention needs to be given to the mode of delivery of the nanoparticle to the test system to ensure that it reflects the relevant exposure scenarios. The assays may need to be supplemented by additional tests, or replaced by modified tests, as it cannot be assumed that current scientific knowledge has elucidated all the potential adverse effects of nanoparticles.

For exposure, the use of mass concentration data alone for the expression of dose is insufficient, and the number concentration and/or surface area need to be included. Equipment that enables routine measurements in various media for representative exposure to free nanoparticles is not yet available. The existing methods used for environmental exposure assessment are not necessarily appropriate for determining the distribution, partitioning and persistence of nanoparticles in the various environmental compartments.

Given the above uncertainties, the current risk assessment procedures require modification for nanoparticles.

Question 2

Three different situations can be identified where existing methodologies are considered unsuitable:

- Routine methodologies have not yet been made available and / or have not been included in the testing guidance and/or achieved regulatory acceptance.
- Scientific research has identified a phenomenon to be evaluated and existing methodologies need to be adapted.
- Advances in nanotechnology may require additional methodological principles and developments.
- Included in the areas of requirements for new or modified methodologies are:
- Appropriate methodologies must be made available for the routine and careful characterisation of the physico-chemical properties of nanoparticles.
- Methodologies and equipment need to be developed that enable routine measurements, in various media, of representative exposure to free nanoparticles.
- Although conventional toxicity and ecotoxicity tests have been shown to be useful in evaluating the hazards of nanoparticles, some methods may require modification and some new testing methods may also be needed in order to optimise this process of hazard evaluation, including the assessment of whether nanoparticles can exacerbate pre-existing medical conditions.
- In this context, although again some potentially suitable methods exist for the detection of nanoparticle translocation, these need to be developed further and incorporated into new testing strategies and guidelines for the assessment of the systemic distribution of nanoparticles.

More specifically the above mentioned methodologies need to provide information on how nanoparticles distribute in human tissues and in environmental compartments. This information can then be used in the exposure assessment algorithm provided in figure 6 in section 3.10.5 of this opinion.

Question 3

In general, and in spite of a rapidly increasing number of scientific publications dealing with nanoscience and nanotechnology, there is insufficient knowledge and data concerning nanoparticle characterisation,

their detection and measurement, the fate (and especially the persistence) of nanoparticles in humans and in the environment, and all aspects of toxicology and environmental toxicology related to nanoparticles, to allow for satisfactory risk assessments for humans and ecosystems to be performed.

The major gaps in knowledge that need to be filled in relation to improved risk assessment for the products of nanotechnology include:

- The characterisation of the mechanisms and kinetics of the release of nanoparticles from a very wide range of production processes, formulations and uses of the products of nanotechnology.
- The actual range of exposure levels to nanoparticles, both to man and to the environment.
- The extent to which it is possible to extrapolate from the toxicology of non-nano sized particles and other physical forms e.g. fibres of the same substance to the toxicology of nanosized materials, and between nanoparticles of different size ranges and shape.
- Toxicokinetic data following exposure, so that target organs can be identified and doses for hazard assessment determined. This includes dose response data for the target organs, and knowledge of the subcellular location of nanoparticles and their mechanistic effects at the cellular level.
- Information from the occupational exposure and associated health effects on workers involved in the manufacture and processing of nanoparticles.
- The fate, distribution and persistence and bioaccumulation of nanoparticles in the environment and environmental species including micro-organisms.
- The effects of nanoparticles on various environmental species, in each of the environmental compartments and representative of different trophic levels and exposure routes.

In addition, there are several aspects of the fundamental properties of nanoparticles that require elucidation, including the ability of nanoparticles to act as vectors of chemicals, micro-organisms and interactions with other stressors.

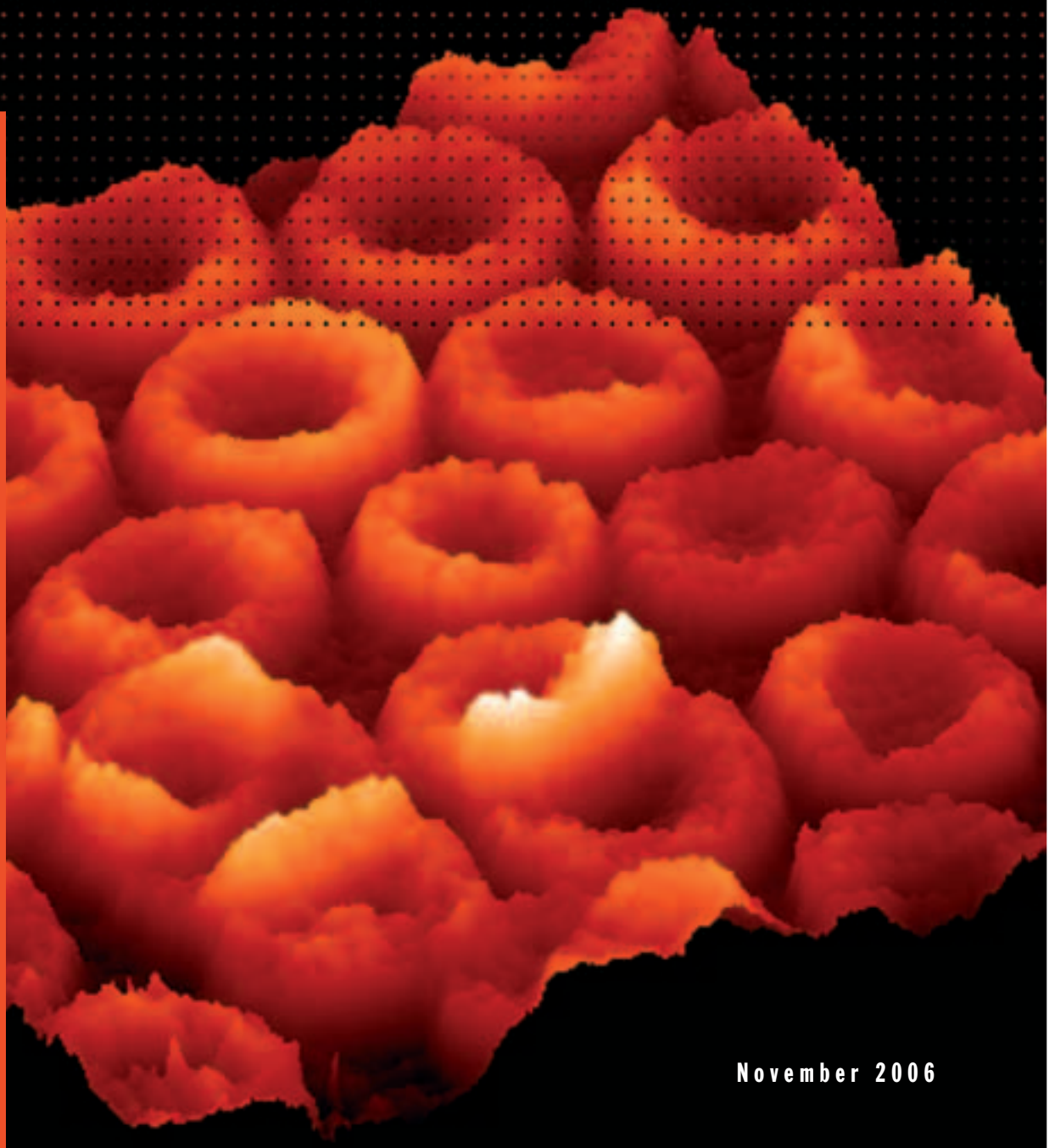
Appendix IV:

Nanomedicine, Nanotechnology for Health, from the European Technology Platform, Strategic Research Agenda for Nanomedicine, November 2006

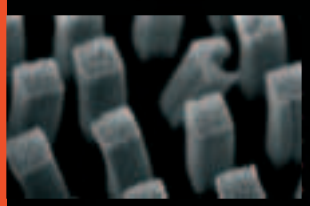
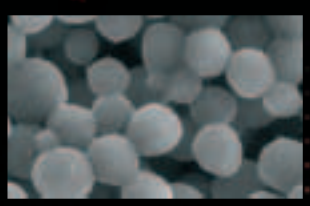
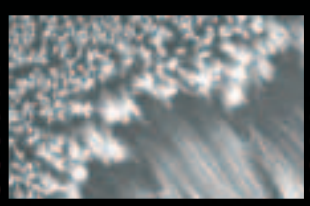
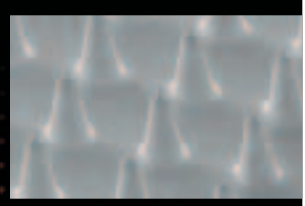
Nanomedicine
Nanotechnology for Health

European Technology Platform

Strategic Research Agenda for Nanomedicine



November 2006

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This brochure has been produced thanks to the efforts of the stakeholders group of the European Technology Platform on NanoMedicine.

A great deal of additional information on the European Union is available on the internet. It can be accessed through the Europa server (http://ec.europa.eu).

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Nanomedicine
Nanotechnology for Health

European Technology Platform

Strategic Research Agenda for Nanomedicine

November 2006

Executive Summary 1
1. Introduction 2
1.1. Nanomedicine: Answering Clinical Needs 2
1.2. The Impact of Nanomedicine on the Care Process 3
1.2.1. Preventive Medicine 3
1.2.2. Diagnosis 3
1.2.3. Therapy 3
1.2.4. Follow-Up Monitoring 4
1.3. Selected Disease Areas 4
1.3.1. Cardiovascular Diseases 4
1.3.2. Cancer 5
1.3.3. Musculoskeletal Disorders 6
1.3.4. Neurodegenerative Diseases and Psychiatric Conditions 6
1.3.5. Diabetes 7
1.3.6. Bacterial and Viral Infectious Diseases 8
1.4. Outlook 9

2. Technology Development driven by Healthcare Needs 10
Technologies for Therapeutic Benefits 10
2.1. Nanotechnology based Diagnostics and Imaging 10
2.1.1. Introduction 11
2.1.2. In Vitro Applications 11
2.1.3. In Vivo Imaging 11
2.1.4. Medical Devices 12
2.1.5. Strategic Research Priorities 12
2.2. Targeted Delivery 15
2.2.1. Introduction 15
2.2.2. Strategic Research Priorities 15
2.3. Regenerative Medicine 18
2.3.1. Introduction 18
2.3.2. Intelligent Biomaterials and Smart Implants 19
2.3.3. Bioactive Signalling Molecules 20
2.3.4. Cell Based Therapies 21
2.3.5. Strategic Research Priorities 21

3. Providing the Environment to Facilitate Nanomedicine 24
3.1. Ethical and Social Aspects of Nanomedicine 24
3.2. Public Acceptance of Nanomedicine 25
3.3. Risk Assessment 26
3.4. Regulatory Framework 26
3.5. Intellectual Property Rights 28
3.6. Required Research Infrastructure 28
3.7. Education and Training Needs 29

4. Making it Happen 30

Strategic Research Priorities 32
Diagnostics 32
Targeted Delivery 33
Regenerative Medicine 34

Strategic Research Agenda of the ETP NanoMedicine: Members & Contributors 35

Key References 38

Images 39

Executive Summary

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

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

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

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

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

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

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

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

1. Introduction

1.1. Nanomedicine: Answering Clinical Needs

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

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

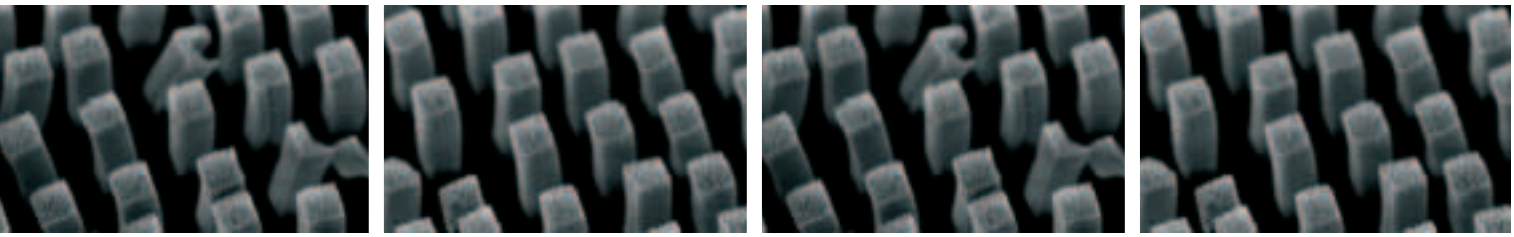
Nanomedical research should be initiated and supported in those areas of the care process, where the benefit for the patient is highest and should focus on diseases that have the highest socio-economical impact. The major diseases that impose the highest burden on society should be addressed first such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

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

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

Nanomedicine

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



1.2. The Impact of Nanomedicine on the Care Process

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

1.2.1. Preventive Medicine

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

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

Biomarkers

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

1.2.2. Diagnosis

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

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

1.2.3. Therapy

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

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

1.2.4. Follow-Up Monitoring

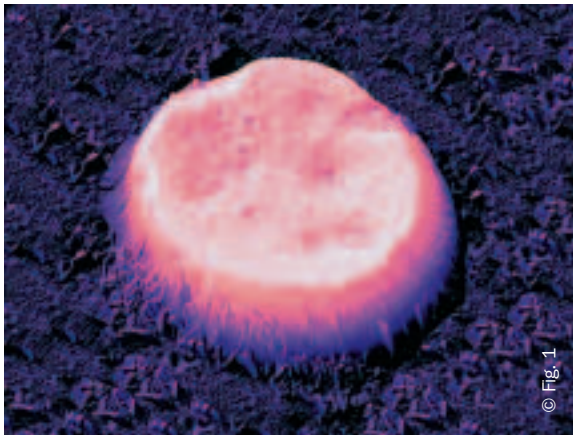
Medical reasons may call for an ongoing monitoring of the patient after completing the acute therapy. This might be a regular check for reoccurrence, or, in the case of chronic diseases, a frequent assessment of the actual disease status and medication planning. Continuous medication could be made more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

1.3. Selected Disease Areas

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

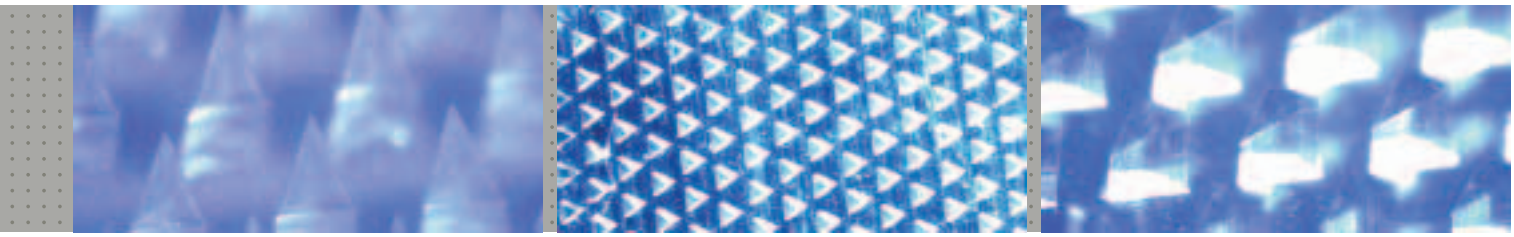
1.3.1. Cardiovascular Diseases

Cardiovascular diseases remain the most frequent cause of death in the European Union and in the world, according to the World Health Organisation, with myocardial infarction and stroke accounting for about half of all deaths in Europe. The underlying cause of cardiovascular disease is in most cases the formation of a plaque in the blood vessels. The formation of plaque can lead to a stenosis of the blood vessels, accompanied by a decreased tissue perfusion and a lack of oxygen. In acute cases, such as an infarct or a stroke, the plaque becomes unstable and ruptured leading to an acute clogging of the blood vessel with death or disability as the consequence. Many aspects of cardiovascular diseases at present, for example the biochemistry of unstable plaques, are not completely understood. Cardiovascular diseases are often associated with risk factors such as little exercise, high cholesterol that are typical for western life-style; however, recent research also indicates inherited causes.


© Fig. 1

Nanomedicine is anticipated to aim for improvements in early diagnosis, acute intervention and follow-up-therapy. For early diagnosis, nanotechnology could be used to realise new in vitro diagnostic tests for atherosclerosis or even for the presence of highly unstable plaque. While today's imaging procedures only indicate the presence of a stenosis, research should try to develop imaging methods that visualise plaques that are at the brink of rupturing.

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



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

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

1.3.2. Cancer

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

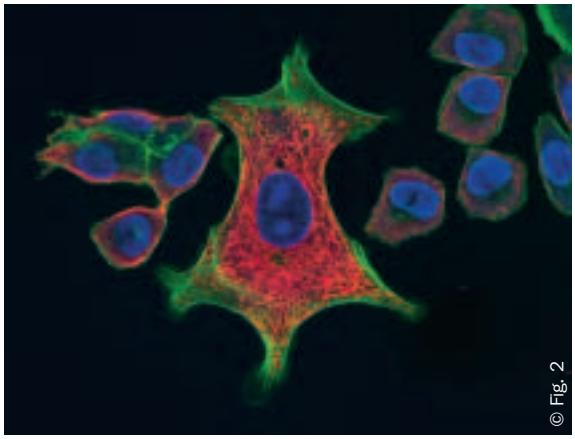
Especially in cancer, early diagnosis is of utmost importance. Late-stage metastatic cancer is difficult to cure and treatment leaves severe side-effects, suffering for the patient, and high costs. Diagnostic tests that allow measurement of a biomarker panel are necessary to catch the disease at on-set.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

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

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

1.3.3. Musculoskeletal Disorders

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



© Fig. 2

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

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

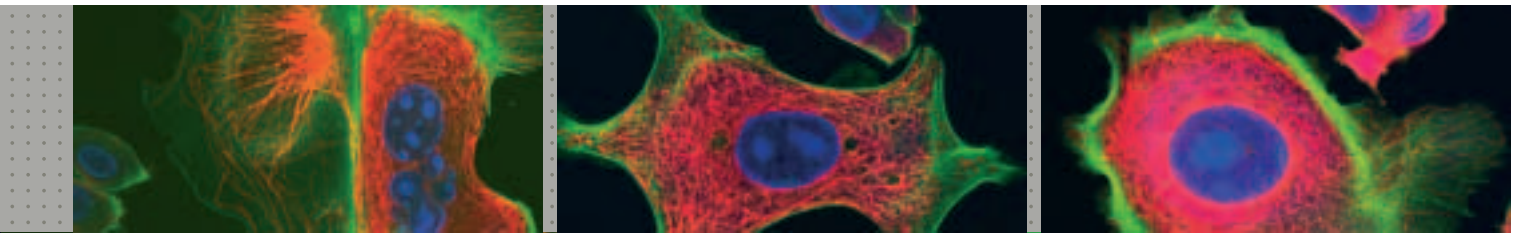
Both arthritis and diabetic nephropathy are thought to be ultimately a consequence of modern European life-style. It is expected that treatments for these diseases may well impact other inflammatory diseases such as Crohn's disease and psoriasis. At present, nanomedicines for these diseases are under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

1.3.4. Neurodegenerative Diseases and Psychiatric Conditions

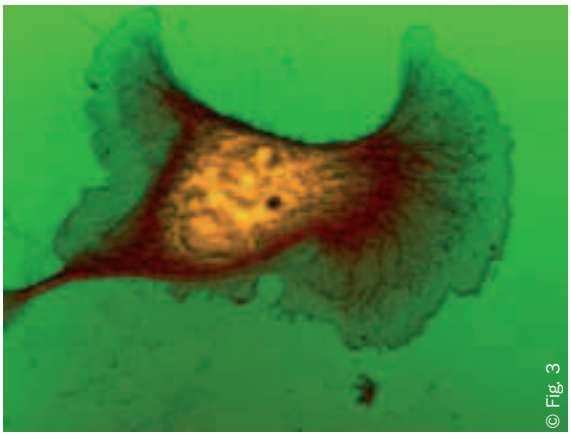
Age-associated neurodegenerative conditions like Alzheimer's and Parkinson's disease will strongly increase in prevalence over the next decade due to changing demographics. Neurodegenerative diseases come with a diminution in quality of life, while necessary patient care puts a financial and social burden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

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

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



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



© Fig. 3

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

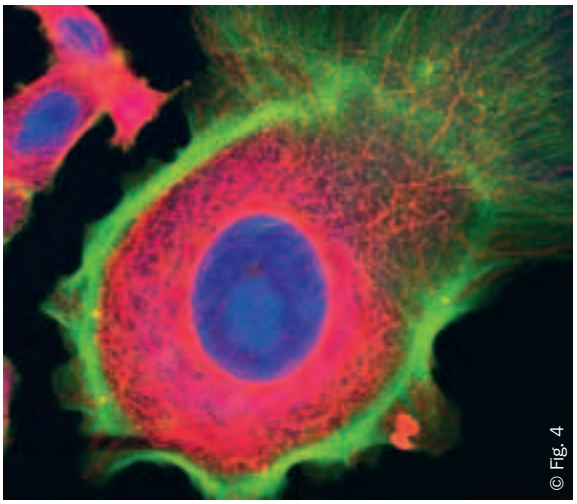
Regenerative medicine has enormous potential for neuro-degenerative conditions, an area where there is no therapy available that reverses or cures the disease. Treating the symptoms and slowing down further degeneration is often all that can be achieved today. Recent findings have shown that adult stem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

1.3.5. Diabetes

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

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

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



© Fig. 4

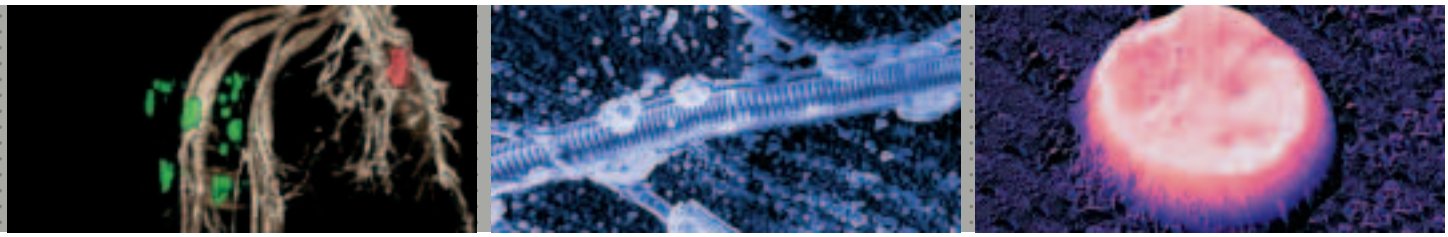
The need for daily injections and blood measurements worsens compliance in millions of patients, promoting earlier appearance of the devastating and costly complications. The development of a glucose sensor that allows non-invasive monitoring of the blood glucose level is one of the important clinical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

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

1.3.6. Bacterial and Viral Infectious Diseases

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

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



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

1.4. Outlook

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

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

Seamlessly connecting Diagnostics, Targeted Delivery and Regenerative Medicine

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

2. Technology Development driven by Healthcare Needs

Technologies for Therapeutic Benefits

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

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

2.1. Nanotechnology based Diagnostics and Imaging

2.1.1. Introduction

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

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

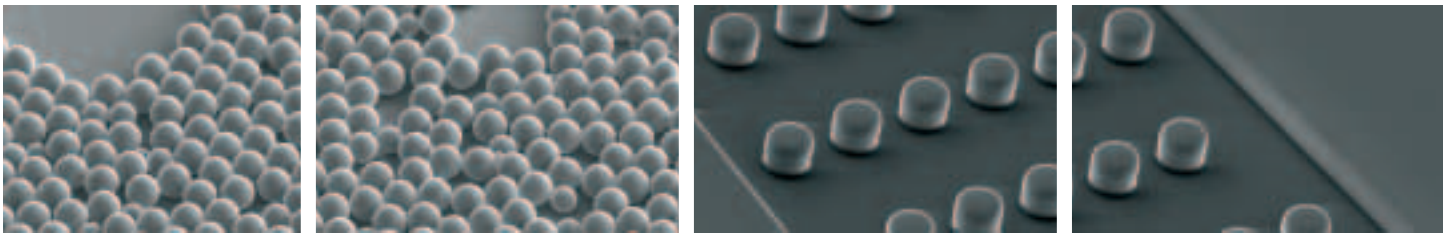
In vitro diagnosis for medical applications has traditionally been a laborious task. Blood and other body fluids or tissue samples are sent to a laboratory for analysis, which could take hours, days or weeks, and could be highly labour intensive. Steadily, miniaturisation, parallelisation and integration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

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

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

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

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



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

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

2.1.2. In Vitro Applications

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

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

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

2.1.3. In Vivo Imaging

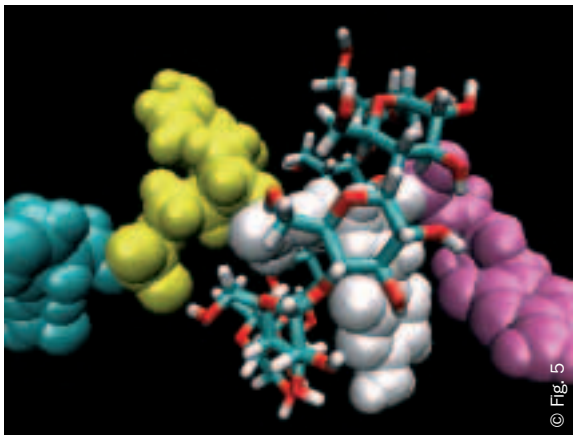
In vivo diagnostics refers in general to imaging techniques, but also covers implantable devices. Nano-imaging or molecular imaging includes techniques for the study of molecular events in vivo and for molecule manipulation. The main benefits of molecular imaging for in vivo diagnostics are the early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

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

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

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

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


© Fig. 5

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

2.1.4. Medical Devices

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

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

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

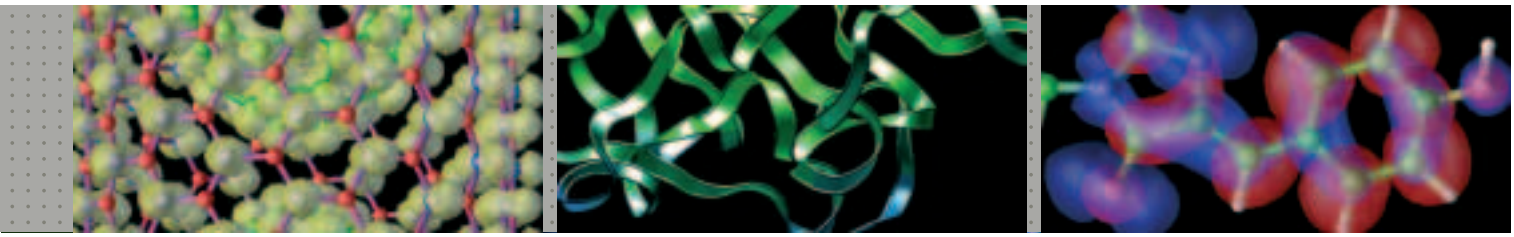
Nanotechnology also has many implications for in vivo diagnostic devices such as the swallowable imaging, diagnostic and therapeutic 'pill' and new endoscopic instruments. Monitoring of circulating molecules is also of great interest for some chronic diseases such as diabetes or HIV. Continuous, smart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

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

2.1.5. Strategic Research Priorities

In Vitro Diagnostics

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



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

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

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

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

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

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

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

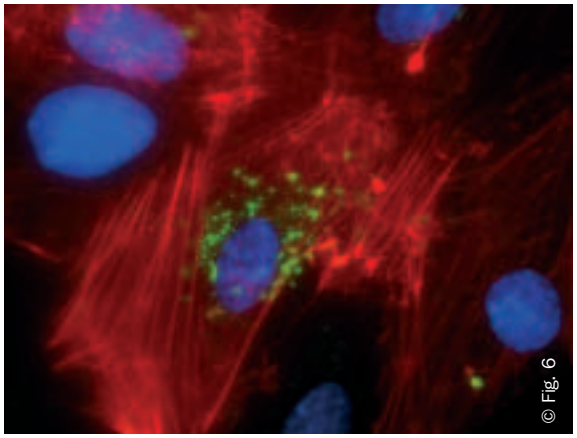
In Vitro Imaging

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

- Optical, electron or X-ray microscopies

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

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



© Fig. 6

In Vivo Imaging

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

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

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

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

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

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

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

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

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

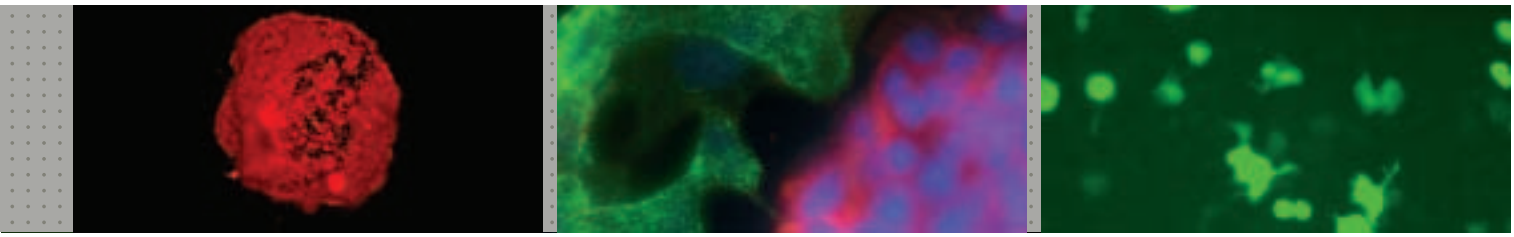
Therefore, ADME-Tox [1] studies of nano-probes will be most probably needed as for any new drug of this type. The development of multi-modal detectors requires specific multi-modal probes, which should be suitable for active drug release on the site of disease, and for reporting on the efficacy of the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

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

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

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

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



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

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

Medical Devices

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

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

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

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

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

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

2.2 Targeted Delivery-Multi-Tasking Medicines

2.2.1 Introduction

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

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

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

2.2.2 Strategic Research Priorities

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

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

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

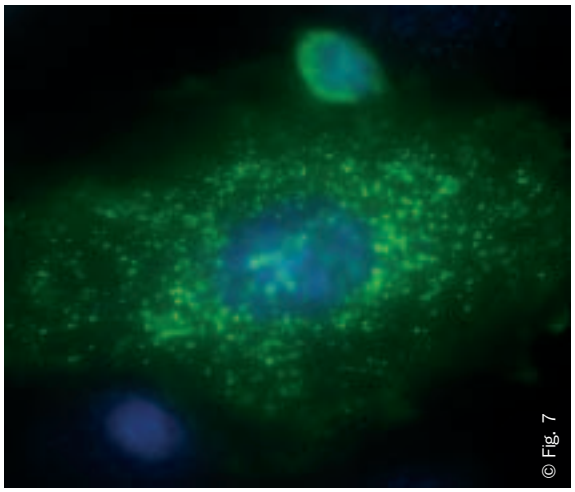
- Liposomes
- Micellular and micro-emulsion Systems
- Liquid crystal based formulations
- Nanocrystals
- Antibodies and conjugates
- Naturally occurring proteins as delivery systems
- Polymer conjugates and bio-conjugates based on the conjugation of polypeptides and polymers, which can be hierarchically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

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

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

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

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



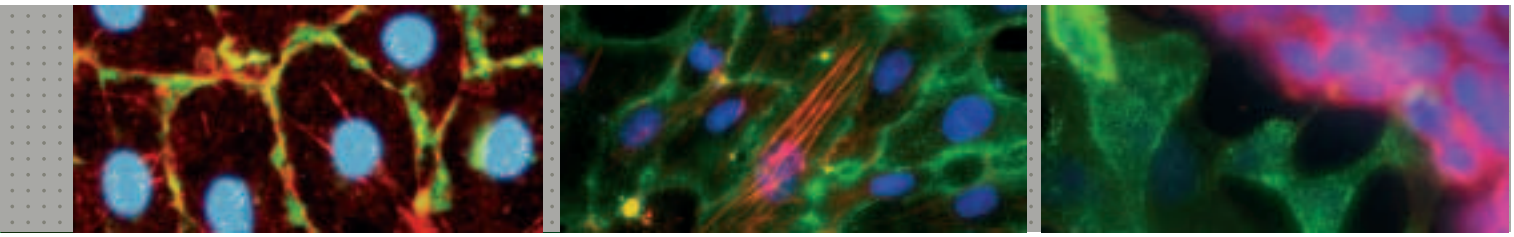
© Fig. 7

Improving Targeting Agents

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

Key research areas are:

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



Interactions between Biological Systems and Artificial Nanostructures

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

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

Pharmaceutics – Formulation and Stability

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

Easier Routes of Administration – Crossing Biological Barriers

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

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

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

The use of Nano-Devices for Targeted Delivery

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

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

- Controlled release mechanisms – sustained or pulsatile

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

© Fig. 8

Manufacturing Improvements

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

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

2.3. Regenerative Medicine

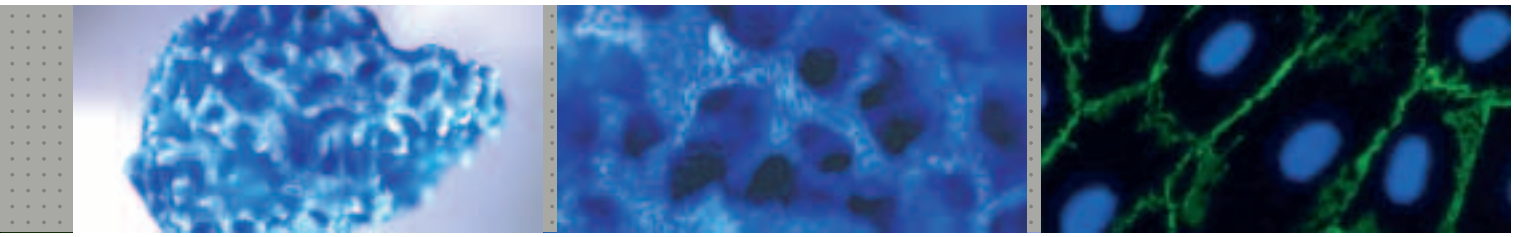
2.3.1. Introduction

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

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

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

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



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

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

2.3.2. Intelligent Biomaterials and Smart Implants

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

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

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

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

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

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

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

© Fig. 9

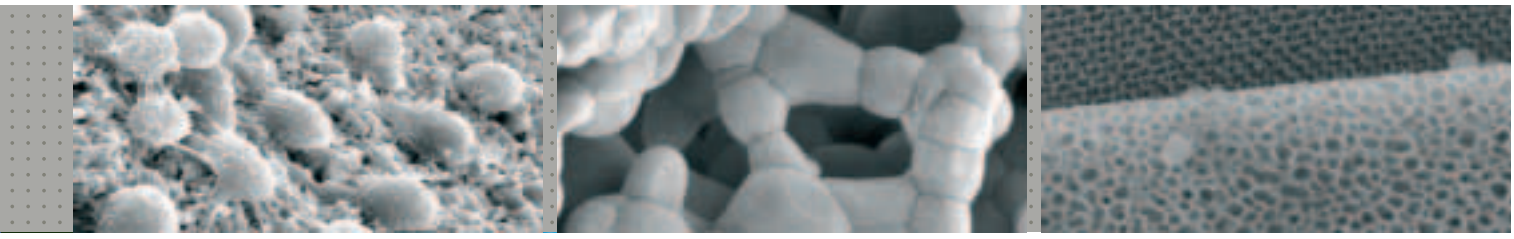
In conclusion, nanotechnology can assist in the development of biomimetic, intelligent biomaterials, which are designed to positively react to changes in their immediate environment and stimulate specific regenerative events at the molecular level. Advances in the areas of fundamental matrix biology,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

2.3.3. Bioactive Signalling Molecules

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

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

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



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

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

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

2.3.4. Cell Based Therapies

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

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

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

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

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

2.3.5. Strategic Research Priorities

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

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

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

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

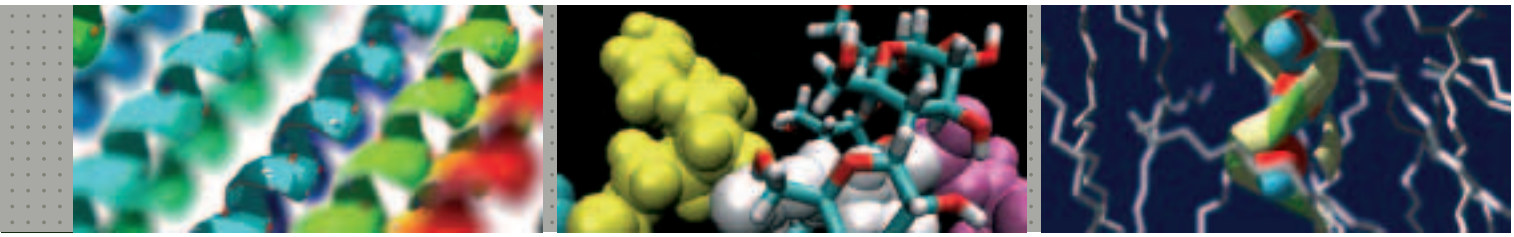
Projects will also need to be highly focused towards clearly identified clinical applications, not being confined to basic research on the optimisation of generic cell/artificial matrix constructs. They must be rooted in the specific characteristics of the tissue to be regenerated, and in the economic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

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

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

Intelligent Biomaterials and Smart Implants

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



Bioactive Signalling Molecules

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

Cell-Based Therapies

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

© Fig. 10

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

3. Providing the Environment to Facilitate Nanomedicine

3.1. Ethical and Social Aspects of Nanomedicine

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

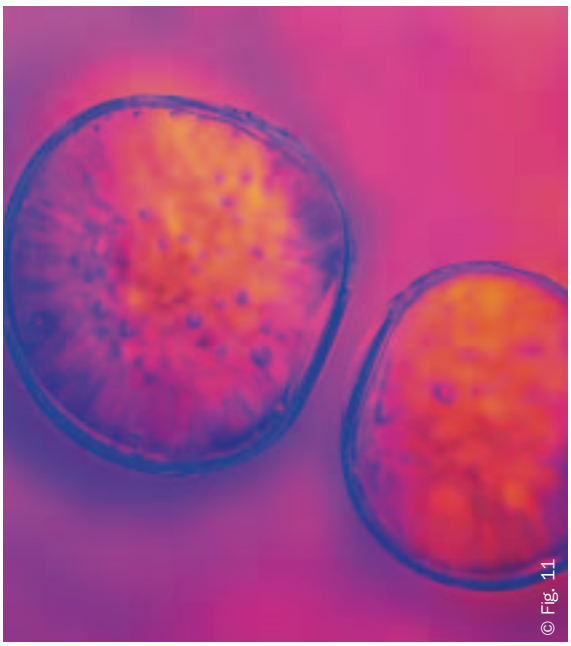
Nanotechnology may also add a new dimension to the bio (human) and non-bio (machine) interface such as retina implants due to improved biocompatibility, or nanoelectronics. This latter example shows that new inventions might add new horizons to ethical, legal, and social considerations. For example “where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

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

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

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

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



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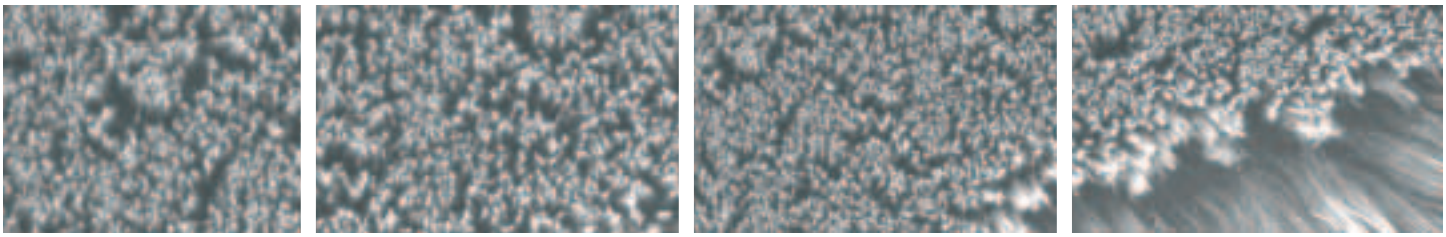


These issues call for a proactive round table approach involving scientists, experts in ethical, legal, and social aspects, patient groups, regulatory agencies, health insurances, national healthcare systems representatives, policy makers and company representatives to forecast the impact on healthcare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

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

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

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

3.2. Public Acceptance of Nanomedicine

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

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

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

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

3.3. Risk Assessment

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

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

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

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

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

© Fig. 12

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

Such scientific considerations lead on to specific research:

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

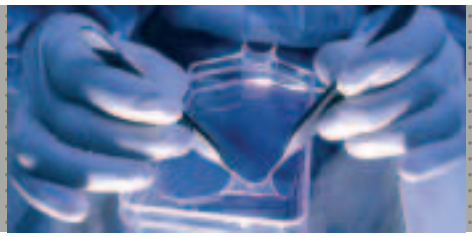
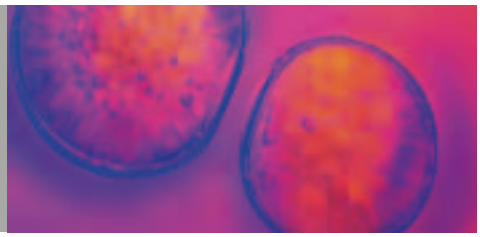
3.4. Regulatory Framework

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

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

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

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

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

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

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

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

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

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

3.5. Intellectual Property Rights

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

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

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

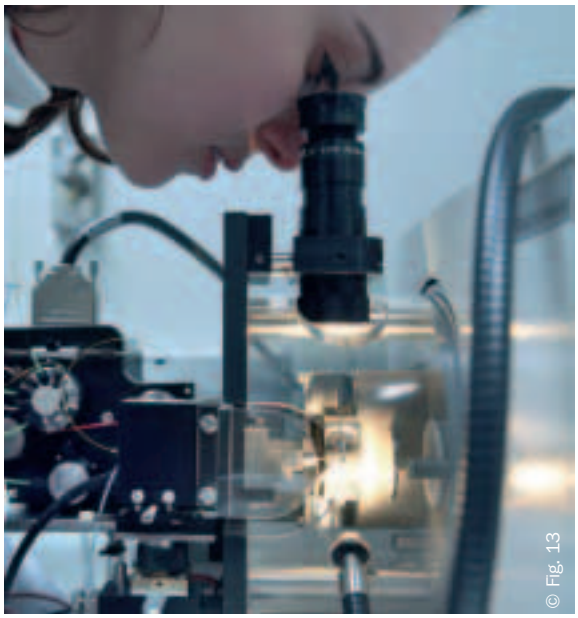
A working group composed of representatives from industry, academia, and public administration has been established to further elaborate the principles of the intellectual property policy of the European Technology Platform on NanoMedicine.

3.6. Required Research Infrastructure

Nanomedicine is a very special area of nanotechnology, because:

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

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



© Fig. 13



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

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

3.7. Education and Training Needs

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

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

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

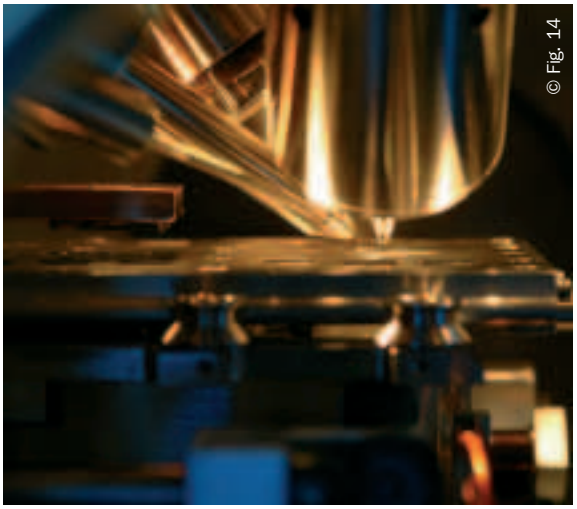
4. Making it Happen

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

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

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

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



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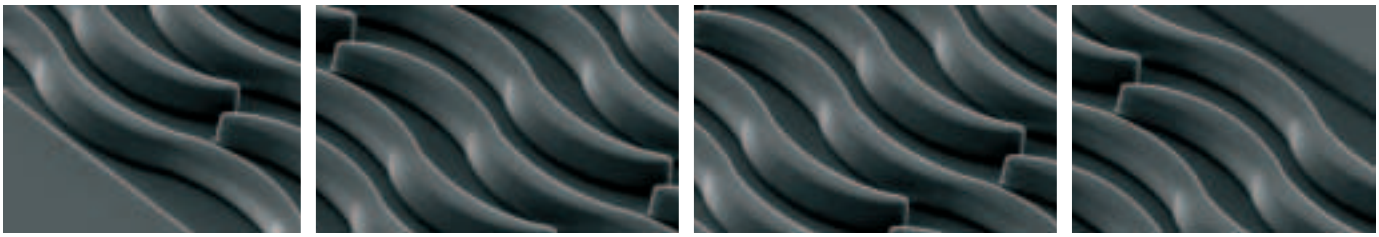
Due to the major importance of future healthcare, this issue is covered by various other European Technology Platforms. Besides the European Technology Platform on NanoMedicine, three other European Technology Platforms are addressing different facets of medical applications:
The scope of most European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

European Technology Platform on Innovative Medicines

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

European Technology Platform on Smart System Integration (EpoSS)

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



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

European Technology Platform on Photonics (Photonics 21)

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

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

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

Strategic Research Priorities

DIAGNOSTICS

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

TARGETED DELIVERY

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

REGENERATIVE MEDICINE

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

Strategic Research Agenda of the ETP NanoMedicine: Members & Contributors

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Appendix V:

Addendum requested by Professor Krzysztof Marczewski,

EGE Member:

"Having regard to insufficient risk evaluation, before this lack of knowledge will be overcome, the medical and health related application of nanotechnologies (e.g. cosmetics) should primarily be concentrated in to solving the problems in which a generally accepted traditionally alternative not exist".