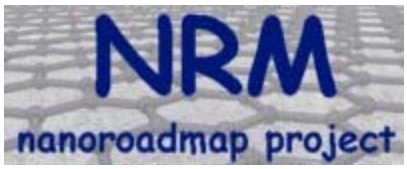

NanoRoadMap is a project co-funded by the 6th Framework Programme of the EC

Nanotechnology in Health and Medical Systems

Draft roadmap on drug encapsulation/ drug delivery/ drug targeting

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Date: July, 31 2005

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1 Introduction

1.1 Background

The NanoRoadMap (NRM) project, co-funded by the European Commission (EC), is aimed at roadmapping nanotechnology related applications in three different areas:

- Materials
- Health & Medical Systems
- Energy

Within the project, an international consortium consisting of eight partners covering eight European countries and Israel, has joined forces to cover the time-frame for technological development in this field up to 2014. The results of the NRM project are to be used by any European entity interested in planning an R&D strategy taking into account nanotechnology. An important potential user is of course the EC itself in the preparation of the 7th Framework Programme (FP7) for research and technology development. (For additional information on the NRM project, please refer to www.nanoroadmap.it)

1.2 Goals

The primary objective of NRM is to provide coherent scenarios and technology roadmaps that could help the European players to optimise the positive impact of nanotechnology on society, giving the necessary knowledge on its future development and when technologies and applications will come into full fruition.

The key users of the reports are mainly European SMEs, research organisations, public bodies in general and the EC in particular. Even though a special focus is put on SMEs, these roadmaps are also meant to be useful for larger corporations.

This report is one of the three final deliverables of the NRM project and it is aimed at providing a thorough overview of specific topics selected for roadmapping within the field.

1.3 Methodology

Collection and synthesis of relevant existing information

In October 2004 three sectoral reports were published, each covering one of the above mentioned areas. They were based on the collection and synthesis of existing public sources in 31 countries and were published as key input for the celebration of the First NRM International Conference held in Rome the 4th – 5th of November 2004. The full report can be downloaded for free on the project web site.

The report within the sector health and medical systems focused on reviewing the different aspects of nanotechnology in 11 topics, giving its definition, describing its most remarkable properties, current and future markets & applications, and leading countries & highlighted R&D activities in the field. A general review of non technological aspects (social, legal, ethical and health and safety aspects, but also economic aspects and infrastructures requirements) was also performed.

The 11 topics identified, even not being completely homogenous in terms of scope or classification, were intended to adequately cover the field of bionanotechnology.

The following list was agreed upon the different partners of the NRM project (similar classifications can be found in the existing bibliography):

- Tissue Engineering/Regenerative Medicine
- Bio Nano Structures
- Drug Encapsulation / Drug Delivery / Drug Targeting
- Molecular Imaging
- Biophotonics
- Biocompatible implants
- Biomimetic Membranes
- Biomolecular sensors
- Biochips/HighThroughputScreening
- Lab-on-a-chip
- Functional Molecules: Switches, pumps, means of transportation

Selection of topics

Another major goal of that report was to set the basis for discussion and selection for roadmapping of 4 out of the 11 topics identified above. A preliminary selection of topics was presented during the First International Conference in November, 2004.

Within a frame of criteria agreed upon with the European Commission and after a thorough discussion, which involved international experts in the field of nanotechnology, four topics were selected (and validated in dialogue with the European Commission). The subjects were partly combined with each other, leading to the four chosen topics:

- Drug encapsulation/ drug delivery/ drug targeting
- Molecular Imaging/ Biophotonics
- Biochips/ High-Throughput Screening/ Lab-on-a-chip technology
- Biomolecular Sensors

Roadmaps elaboration

One draft roadmap has been prepared for each of the four aforementioned topics. The result of these roadmaps will be presented in one international and eight national conferences in November and December 2005. Their preparation and execution is based upon a Delphi-like approach. The methodology consists of 2 cycles, which is the same for the four topics. The Delphi exercise consists in:

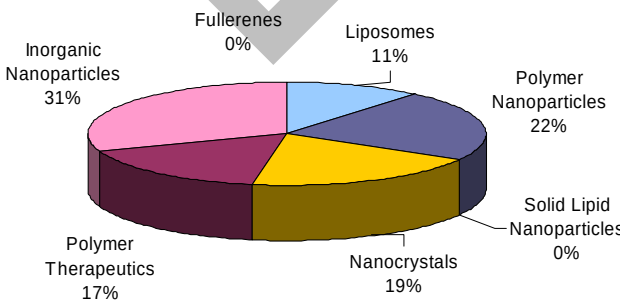
- Selecting top-international experts on the field
- Preparing a dedicated on-line questionnaire for each of the topics to be roadmapped
- Circulating the questionnaires and gathering experts' responses (1st cycle)
- Preparing a first summary of the given answers
- Circulating the summary and partly interpreted data, asking for feedback and reflection (2nd cycle). Interpretation was conducted in a way avoiding any prejudice
- Elaborating the roadmap taking into consideration aspects raised in the 2nd cycle

2 'Drug encapsulation/ drug delivery/ drug targeting' Roadmap

2.1 Introducing the subject

Despite outstanding achievements in the diagnostic and therapeutic medical sector, the pre-symptomatic detection and defence of diseases like for example cancer, cardiovascular problems, neurodegenerative diseases like Alzheimer and Parkinson or depression are still the most important challenges in modern medicine. Beyond the defence of these oftentimes mortal diseases, the annual number of fatal casualties as consequence of pharmaceutical side-effects is bigger than 10 000 people. Thus, the need for more specifically and efficiently acting drugs is very urgent. Research in pharmacogenetics is currently done. Due to this combination of personal compatibility with pharmaceutical effectiveness, it will be possible to harmonise the particular therapy with the patient's genetic makeup for drug metabolism, absorption, transport, and elimination. On the other hand nanotechnology will be increasingly used to creating systems that can deliver drugs to distinct areas within the body a better way. All participants of our Delphi panel are of the opinion that nanotechnology will provide pharmaceuticals with suitable properties which cannot be achieved using other concepts. By means of nanoparticles which act as "nanoscaled ferries", pharmaceuticals permeate through cell walls and are even able to pass the blood-brain-barrier. Research into the rational delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents is at the forefront of projects in nanomedicine. These involve the identification of precise targets (cells and receptors) related to specific clinical conditions and choice of the appropriate nanocarriers to achieve the required responses while minimizing the side effects. Mononuclear phagocytes, dendritic cells, endothelial cells, and cancers are key targets. "Smart Drug Delivery Systems" which are presently searched for, should protect the drug against decomposition during it's transport to their destination, accumulate actively or passively within target tissue and release the transported drugs in a controlled time-dose profile.

In terms of the most appropriate types of nanoparticles for their particular aims, the experts participating in our Delphi exercise named inorganic nanoparticles, polymer nanoparticles, polymer therapeutics and nanocrystals, followed by liposomes.



Inorganic Nanoparticles is the generic term for several nanoparticles including for example calcium phosphate, gold, silicate and magnetic nanoparticles. **Polymer nanoparticles** cover various natural or biocompatible synthetic polymers like polysaccharides, poly lactic acid, poly lactides, poly acrylates, poly alkyl cyano acrylates, poly alkyl vinyl pyrrolidones or acryl polymers. They include rationally designed macromolecular drugs, polymer-drug and polymer-protein conjugates, polymeric micelles containing covalently bound drug, and polyplexes for DNA delivery[1]. Polymer nanoparticles can be divided into *nanospheres* which build a continuous polymer matrix and can be referred as "drug

sponges" and *nanocapsules* which consist of a polymer layer enclosing a fluid-filled cavity and are mimicking liposomes. Nanospheres and nanocapsules differ in their drug delivery profile. Polymer therapeutics **Polymer therapeutics** differ from particle shaped drug delivery systems in their dimensions. They are molecular units with diameters of a few nanometres and can be subdivided into *polymer drugs*, *polymer drug conjugates*, *polymer micelles* and *dendrimers*. **Nanocrystals** are ground in special mills and thus nano-sized drugs which are applicable intravenously as nanosuspensions. This procedure enhances the surface/volume-ratio and bioavailability of almost insoluble pharmaceuticals. **Liposomes** are small phospholipid bilayer vesicles. Their basic modules are amphiphilic phospholipid molecules which spontaneously form liposomes in aqueous ambiance. Hydrophilic ends of the globular bilayers point to the water side, hydrophobic ends are oriented bilateral to the centre of the layer.

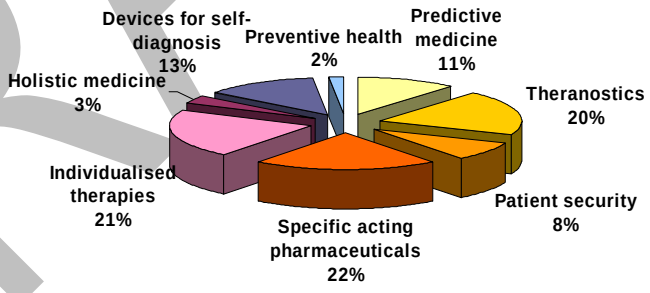
81% of the participating experts stated that the range of currently available nanoparticles is insufficient to solve existing drug distribution problems.

Small molecules, oligonucleotides and peptides are the most appropriate molecules that will be routinely encapsulated in therapeutically used nanoparticles which certainly does not exclude further molecules to be integrated and transported but to another degree.

2.2 Scientific and technological aspects

Trends & needs during the next decade

The progress in nanomedicine combined with a deepened understanding of the cellular architectures and biochemical processes give reason to hope for more effectively acting target drugs with less side-effects. This is mirrored in the estimations of the experts who were involved in the Delphi exercise within the pharmaceutical sector who anticipate an increasing need for specific acting pharmaceuticals which will enable more individualised therapies. Theranostics, which describes an integrated diagnose and therapy is estimated to play an important future role. This result coincides with the spectrum of answers of the experts within the molecular imaging topic which shows more or less the same distribution. Devices for self-diagnosis are estimated to should be developed for offering a wider product portfolio. More predictive medicine has a lower ranking and seams to be not as important as the mentioned aspects. More patient security is important in the opinion of only some experts, indicating that there is a broad contentment with the existing guidelines for patient security.

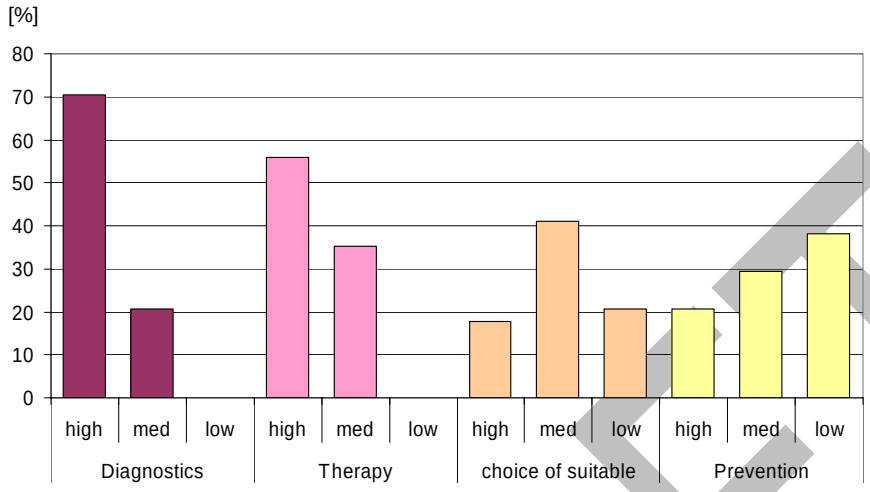


"Future medical practice will need more…. " Estimation of the experts within the drug sector.

Nanotechnology is expected to be critical in supplying the mentioned demands. All of the involved experts suppose nanotechnology to be unique in providing pharmaceuticals with the properties which are needed for their more efficient use. The enlargement of the surface/ volume ratio of the offered pharmaceuticals, resulting in an enhanced activity, is only one aspect that points this up. Nanomedical techniques will allow early diagnosis of diseases and are bound to provide a big impetus to prophylactic as well as preventive treatment. Technological advances in this field could mean that treatments are initiated even before the onset of initial symptoms which could lead to an entire healing or even prevention of diseases.

Impact of nanotechnology in the field considered

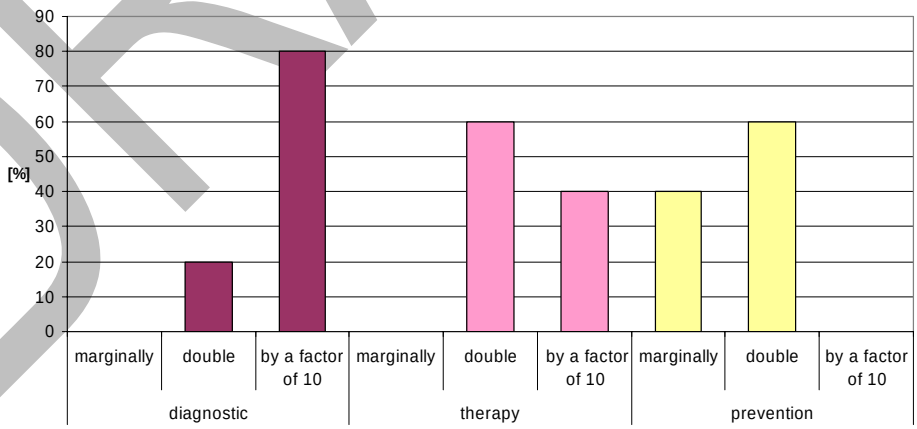
There is an ample accordance between the experts within the drug and medical imaging sector that the impact of nanotechnology in diagnostics will be high during the next decade. This applies to therapy as well, but to a lower degree. The impact on the choice of suitable therapies is expected to be rather medium whereas the estimation upon a nanotechnological impact in prevention ranges from high to medium with an emphasis on a low impact.



Impact of nanotechnology within a certain medical emphasis during the next decade
Estimation of experts within the drug and the medical imaging sector

The therapeutic sector is highly combined with the diagnostic one because a disease or the predisposition to fall ill has to be detected prior to be medicated. The expected quantum leap in diagnostics, leading to a far better pre-symptomatic detection of diseases, should improve the facilities to prevent them thus the shown tendency to state a rather low impact of nanotechnology in prevention is quite surprising.

The impact of nanotechnology within the three application areas diagnosis, therapy and prevention is hardly to define accurately. 20 % of the experts answered in total to this question, indicating the difficulty of such an estimation. Anyhow, the impact in diagnostic is supposed to increase to the biggest extend by a factor of ten. In therapy the impact is estimated to at least double within the next decade if not slightly raise to a higher degree whereas in prevention it is expected to develop rather measured and double at most.



The impact of nanotechnology in the three application areas within the next decade will increase...

Regarding the potential of nanoparticle based therapies to medicate special diseases there is a clear negation. The supposed impact of nanotechnology on certain diseases like adipositas, allergy, asthma, autoimmune diseases, cardiovascular diseases, chronic pain, dementia, depression, diabetes, inflammation, neuropathy, neurodegenerative diseases, rheumatism, vascular diseases or viral/bacterial infections was more or less equally distributed. The results emphasise that there is in fact

almost no simple medical indication which will take exclusive benefit from nanotechnology except cancer which is believed by almost 70 % of the experts to be highly affected. This means that nanotechnology is seen as a general platform to drug delivery.

Advantages of nanotechnology over existing/alternative technologies

The most revolutionary property of nanoparticles in the pharmaceutical sector compared to existing or alternative technologies is their ability to be specifically guided to targets due to their ability to interact with cell membranes or (guiding) proteins respectively peptides. There are a lot of drugs being principally able to affect the brain or spinal cord which either do not pass the blood brain barrier at all or do not pass in significantly large enough amounts. As a consequence, some drugs have undesirable peripheral side effects that pose a clinical problem. The above mentioned property regarding the specifically driven guidance combined with a suitable encapsulation in nanoparticulate form, the nanoparticles' ability to release drugs in a controlled manner and to overcome biological barriers will lead to a decrease in effective drug dosages and will improve the therapeutic index of drug reducing toxicity. The magnetic behaviour of certain types of nanoparticles combined with the other specific properties opens a wider spectrum of therapeutical methods such as nanoparticles based thermotherapy.

All the mentioned properties of nanoparticles are supposed to revolutionise the medical sector by offering new ways to deliver new classes of pharmaceuticals that cannot be effectively served by conventional means, by being supportive in individualized therapies and making them more efficient and thus enhancing patient acceptability and lowering healthcare costs.

Technology evolution

Nanotechnology provides a wide range of new technologies that optimize the delivery of pharmaceutical products. Since it is a technology at its very early stage with nanomedicine being a subdivision of the real broad field of nanotechnology, the technology evolution is hardly to characterise or to predict.

According to the experts there is a need for the investigation of further nanoparticles because the range of existing nanoparticles is not sufficient to fulfil presently needed therapeutic functions. Moreover there is a need for suitable new pharmaceuticals. The understanding of the limiting factors of drug release control and the ability to internally monitor the release system will increase and will improve the timing of drug delivery. The deepened knowledge of nanoparticle absorption, distribution, metabolism, defence mechanisms, interaction with other drugs, binding and interaction with receptors as well as the excretion of nanoencapsulated pharmaceuticals will certainly lead to a quantum leap in the therapy of diseases, especially if nanosystems and nanomaterials are discovered that match particular drugs.

Trends, challenges and discontinuities

Due to their unique properties, nanoparticles are expected to revolutionise the medical, especially the diagnostic and therapeutic sector. Nevertheless the technology is still at its early stage and there are huge challenges to meet.

One of the biggest technological challenges is the scalability of nanoparticle production. While large-scale production makes better economic sense, this is likely to be a complex task, especially when manufacturing three-dimensional nanostructures. Manufacturing standards for nanomaterials and components are yet to evolve. Furthermore, there is an urgent need for analytical methods that can provide both chemical and molecular characterisation at the nanoscale. These are essential for

the further investigation of nanoscaled matter and processes and an appropriate quality control measurement which is also needed in standardised manufacturing procedures.

The development of a broader scale of nanomaterials with specific properties is certainly a trend within the next decade. With a deepened knowledge of the nanoparticles' properties, e.g. their specific interaction with biomolecules, cellular structures or their degeneration and controlled drug release on the one hand and advanced know-how of disease genesis including the cellular metabolisms on the other hand, there will be much more specifically acting drugs and an increasing number of specific applications. For example it is assumable that one therapeutic substance will be able to be effective at different sites depending on its guidance and will be used in different applications. The discovery of further in vivo cellular uptake targets for drugs will improve existing therapy approaches, inter alia DNA delivery vehicles for gene therapy and the delivery of therapeutic proteins to their site of action.

Nanotechnologies in combination with other technologies and tools such as microtechnologies, combinatorial chemistry, computational biology, computer-aided drug design, data mining, and data processing tools will lead to increasing discovery and development of new drugs. Within the next 10 – 15 years the number of designer drugs, based on a person's genotype is supposed to rise.

Time- to- market

In the contrary to nanotechnological applications in other areas, its market share as well as its impact in the medical sector is rather low as can be seen in the following table. Due to the close interface between technology and human there is a special velocity of development which is reflected in long and preferably well defined admission procedures including several clinical trials and so on. Furthermore the variety of possible functionalisations is as manifold as the intracorporeal targets and the latter are still to be explored intensively to know the complex biological basic principles, making the nanotechnological impact very specific within the particular applications.

Application	Material/device	Estimated production rates (tonnes/annum)		
		Present	2005–2010	2011–2020
Structural applications	Ceramics, catalysts, composites, coatings, thin films, powders, metals	10	10^3	10^4–10^5
Skincare products	Metal oxides (titanium dioxide, zinc oxide, iron oxide)	10^3	10^3	10^3 or less
ICT	Single wall nanotubes, nano electronics, opto-electro materials (titanium dioxide, zinc oxide, iron oxide), organic light-emitting diodes (OLEDs)	10	10^2	10^3 or more
Biotechnology	Nanoencapsulates, targeted drug delivery, bio-compatible, quantum dots, composites, biosensors	less than 1	1	10
Instruments, sensors, characterisation	MEMS, NEMS, SPM, dip-pen lithography, direct write tools	10	10^2	10^2–10^3
Environmental	Nanofiltration, membranes	10	10^2	10^3–10^4

Source: The Royal Society & The Royal Academy of Engineering, July 2004

To learn more about the marketability of special nanotechnology driven applications and the expected time to market for such applications within the drug sector we asked the experts to evaluate the stage of maturity of specific technical challenges of nanoparticles in the pharmaceutical sector.

The results

which are shown in the following diagram reflect the relative importance of the particular nanoparticle properties and their implementation in applications within the next decade predicted in five years from now (2010) and in ten years from now (2015) and gives an integrated view of the different stage of development of the applications.

The generic distinctions in the graph chosen for the sequential phases in the innovation cycle have been taken as follows:

Basic Research & Development Phase (**basic**)

Applications in this phase have received the interest of at least one, or more researchers in the world. Some applications might still be in early development, while other are tough to develop and need a lot of basic research to be fully understood.

The object of basic R&D is to validate the original hypothesis. Many applications are currently in this phase as researchers are still struggling to understand basic properties of nano-material.

Applied Research & Development Phase (**applied**)

After the hypothesis is validated, research typically (but not necessarily) moves from pure research labs to more commercial labs and companies.

Applied R&D will eventually result in a proof of concept, a successful demonstration model. While the production issues might not have been solved yet, a successful prototype/model has been validated.

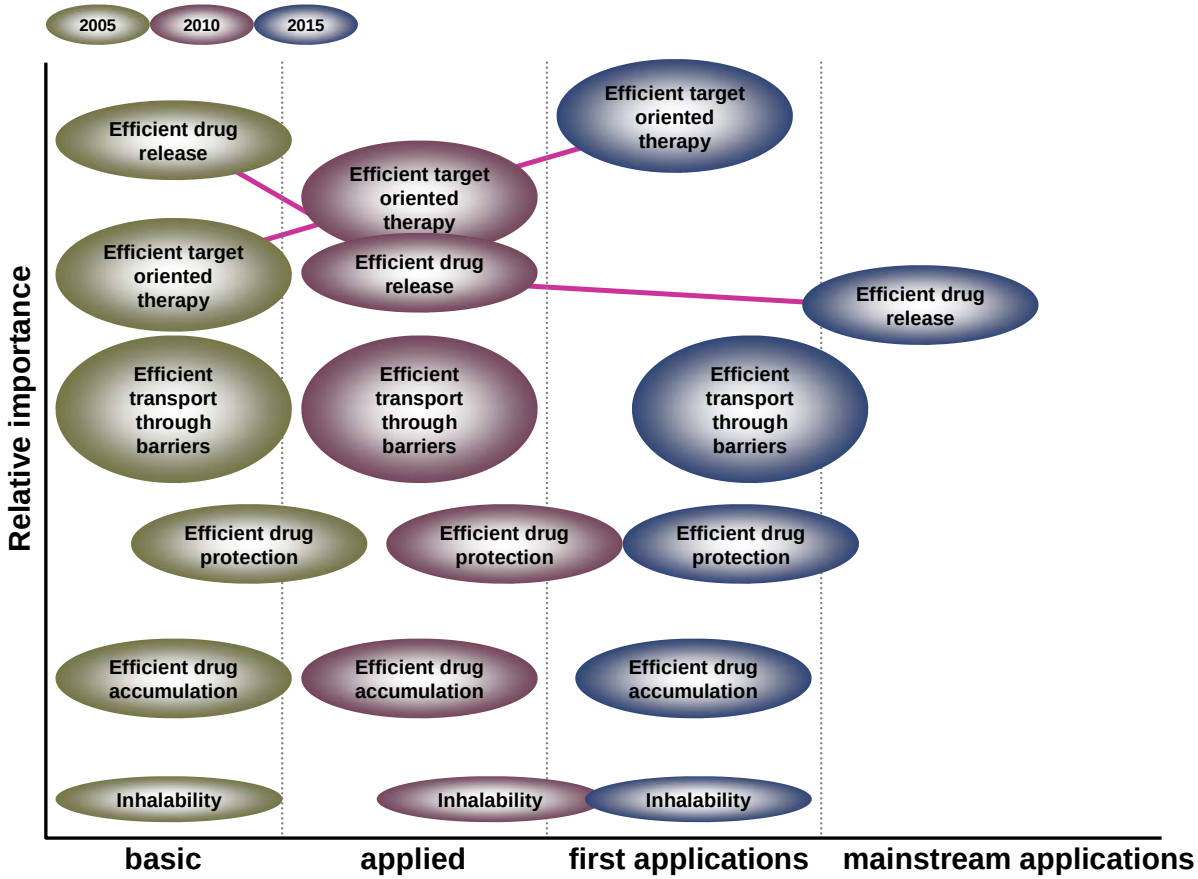
Product Research & Development Phase (**first applications**)

After first demonstrator models and prototypes, initial, usually prohibitively expensive, small numbers of products may be produced. At the same time, if these prove successful, companies will seek to enhance production to gain market share.

Generally at some point, demand increasing sufficiently to offset the investment needed to start production. This phase ends at a point when feasibility has been proven and production is to start.

Production level and incremental research (**mainstream applications**)

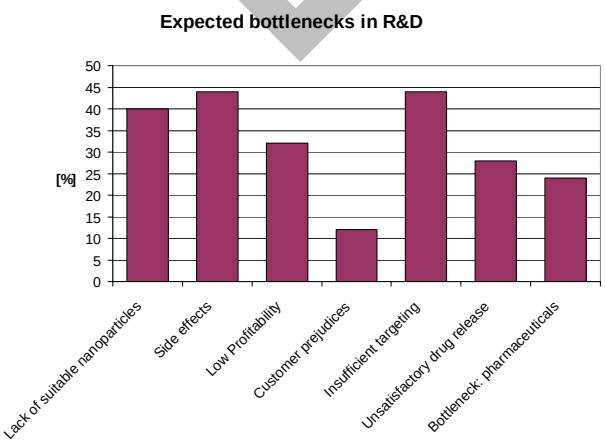
The final development phase, in this phase production has reached significant numbers and research focuses on incrementally improving the products.



According to this the only property which is supposed to be well established so that it is implemented in mainstream applications is an efficient drug release. Its importance, however, takes a back seat in comparison to an efficient target oriented therapy which of course implies the effective drug release. The inhalability of certain drugs which enlarges the range of pharmaceutical forms was stated to be of low importance because it is estimated to be not one of the central properties which makes the difference of nanobased compared to conventional therapies.

Gaps and barriers

Nanotechnology is a relatively young technology so that there are several gaps and barriers to deal with.



According to the answers given by the experts in the Delphi questionnaire the mostly expected bottlenecks are the insufficient targeting as well as consisting side effects of available nanoparticles (e.g. general cell toxic effects) which could prevail over medicative drug effects. These two are directly followed by a supposed lack of suitable nanoparticles. As a solution, a broader scale of materials with specific properties have to be developed. About 30 % of the experts state that a lot of research effort has to be put into the regulation of drug release which is expected to be a further future bottleneck. Any-

how, a quarter of participants suppose not the nanoparticles to be the constriction but the pharmaceuticals. Most of the basic things that will slow many developments will certainly be the lack of understanding of complex biological systems.

Regarding the barriers which are expected in connection with special kinds of nanoparticles they are mainly of technological and economic character. These are in general analytical methodes that can provide chemical (molecular) characterisation at the nanoscale which have to be urgently developed as well as the sensitivity and specifity of functionalised nanoparticles and a limited financial support for clinical evaluation, respectively. The barriers which are supposed to occur in various kinds of nanoparticles are listed in the following table:

	General	Liposomes	Polymer Nanoparticles	Nanocrystals	Polymer Therapeutics	Inorganic Nanoparticles	Chip-based technology
Technical	X	X	X	X	X	X	X
Economic	X	X	X	X	X	X	X
Medical			X				
Infrastructural			X	X	X	X	
environmental impact		X	X	X	X	X	

Expected barriers in the development of particular types of nanoparticles

The specifications of these barriers, given by the participants, are listed in the table below:

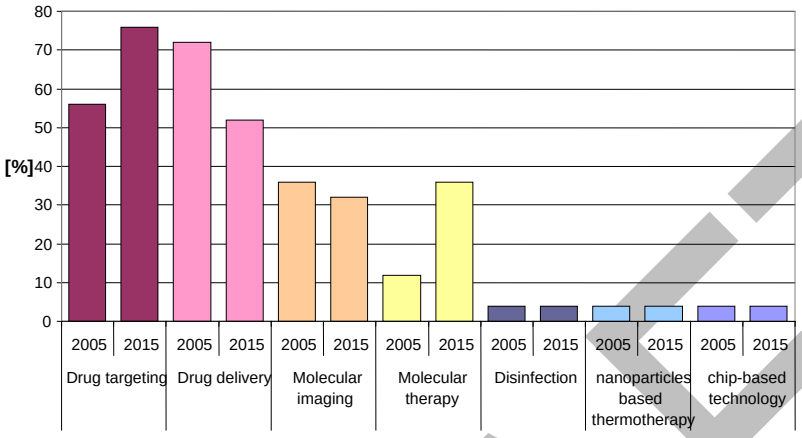
Barriers to success	**Technical**	**Economic**	**Medical**	**Infrastructural**	**Environmental impacts**
Liposomes	They are too large in size and biokinetics as well as cell- + protein interactions are not resolved	Their production is still too expensive			They are not yet analyzed
Polymer Therapeutics	A broader scale of materials with specific properties(e.g. biocompatible materials, which are very important) have to be developed	There is a need to identify cost effective systems in relation to applications			
Barriers to success	**Technical**	**Economic**	**Medical**	**Infrastructural**	**Environmental impacts**

		There are low financing opportunities for late stage (growth phase) start-up companies and limited financial support for clinical evaluation		regulation of IP, contracts, timeline of co-operation	
	Their biokinetics as well as cell- + protein interactions are still not resolved	Their production is still to expensive			They are not yet analyzed
Polymer Nanoparticles	There is a need for total biocompatibility, non-toxicity and biodegradability of the products,		They are too complex systems, close co-op. of many teams within an intern. project/network necessary	A close cooperation of nanoscience, medicine and physics is needed	
	A broader scale of materials with specific properties have to be developed	There is a limited financial support for clinical evaluation			
	There are stability problems in particles or liposomes to be solved	Moderate	Regulatory approval and safety testing are the most crucial points	Companies are not equipped for nanotech manufacturing	There are not forseeable problems
	Biokinetics and cell- + protein interactions are not resolved	The production is still too expensive			
Nanocrystals		High costs of production			Potential toxicity
Inorganic Nanoparticles	Biocompatibility	High costs of production			Potential toxicity
Chip based technology	Design of miniatuarised systems for in vivo sensing	Must be cost effective			

Most present and future relevant applications of nano-related products

Due to nanoparticles' unique properties, especially their high potential for targeting and overcoming barriers, the experts expect the probability that nanotechnology will play an important role in pharma-

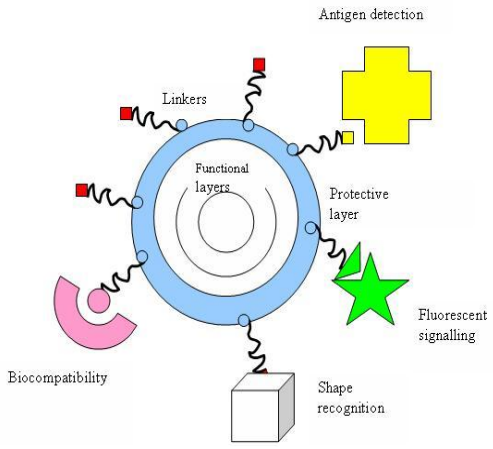
ceutical applications to be high (36%) respectively very high (32%). There is a progress made in drug delivery systems over the last two decades. In 2003 the FDA approved more biotech and drug delivery products than new small molecules. Recent approvals include polymeric drugs, polymer protein conjugates and liposomes and the first nanoparticle based anti cancer therapy has been approved in January 2005[2]. 12 % of the participants expect a rather medium role of nanotechnology in the pharmaceutical sector because "on the one hand drug metabolism and pharmacokinetics will reduce its broad entry" and on the other hand "the selectivity of future drugs query their ubiquitous use". Furthermore potent formulations are supposed to enlarge the extension of existing patents on drugs.



The most important applications of nanotechnology in the medical sector

Most of the relevant applications of nanoparticles in health are supposed to be in drug targeting. Drug delivery will be eclipsed by precisely targeted drugs. The development in drug delivery and drug targeting is supposed to be path-breaking by providing site-specific therapeutic action with fewer side effects. About one third of the experts expect molecular therapy to get more future importance than today. Molecular imaging is stated by one third of the participants to be presently important. The importance of nanotechnology in this technology is supposed by the experts to level off. Against the background of an expected annual growth rate of the medical devices market by 5 – 6% and medical imaging systems representing about 8 % of the total devices market[3], this is a surprising result because the segments imaging tools and imaging agents, including contrast media and radiopharmaceuticals, can certainly benefit from an advanced technology, based on a deeper understanding of materials and cellular activities.

Disinfecting properties of certain nanoparticles do not play any prominent present or future role. Nanoparticles based thermotherapy is one of several applications as well as chip-based technology. Further miniaturization and the ability to store and release chemicals on demand, offer new options even in the diagnostic field.



Typical configurations utilised in nanoparticles applied to medical or biological problems

Source: OV Salata, J Nanobiotechnology. 2004; 2: 3. Published online 2004 April 30.

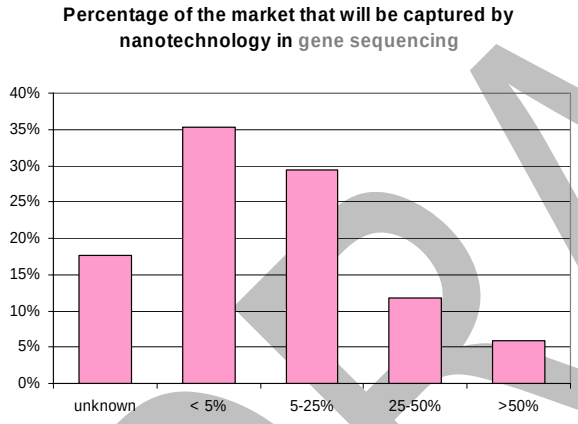
Within the drug encapsulation/ drug delivery/ drug targeting topic the range of applications is related to the function/ functionalisation of the nanoparticles. Since the size of nanoparticles is in the same range as proteins, they are suitable for bio tagging or labelling. In order to interact with biological target, a bioinorganic interface in form of a biological or molecular coating or layer should be attached to the nanoparticle. Examples of biological coatings may include antibodies, biopolymers like collagen, or monolayers of small molecules that make the nanoparticles biocompatible. In addition, as optical detection techniques are wide spread in biological research, nanoparticles should either fluoresce or change their optical properties.

2.3 Non technological aspects

Market trends for each application

The world pharmaceutical market in 2004 was about $ 506 billion[4]. The U.S. market for drug delivery systems in 2002 was $38.8 billion, and is expected to rise at an average annual growth rate of 11.3% and reach $74.5 billion by 2008[5]. Due to a study by BCC[6] the potential of such nanoscaled drug delivery systems is estimated at $ 50 million in 2007.

Worldwide government investment in nanotechnology research has increased more than ten-fold in the last six years from $ 432 million in 1997 to an estimated $4.6 billion in 2004. Most of this funding has been directed to very basic research that could be utilised in a variety of fields, including nanomedicine. In the U.S., the National Science Foundation is the leading funding source with $ 249 million granted in 2004. The National Institute of Health is a distant fourth with $ 70 million in funds granted in 2004. It is estimated that companies will invest $ 3.8 billion in nanotech R&D globally in 2004, and that this might be the last year that governments outspend the private sector[7].

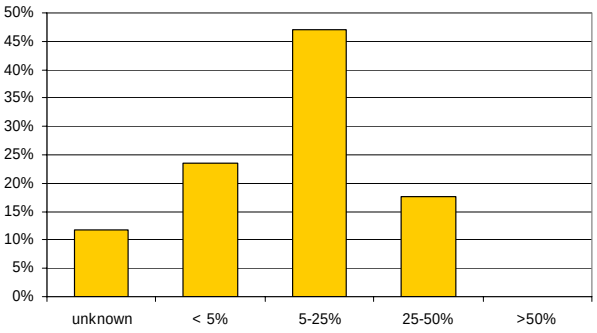


The market that will be captured by nanotechnology in five categories of the pharmaceutical value chain was asked to be estimated by the participating experts of the Delphi panel. 68 % of the participants answered to this question.

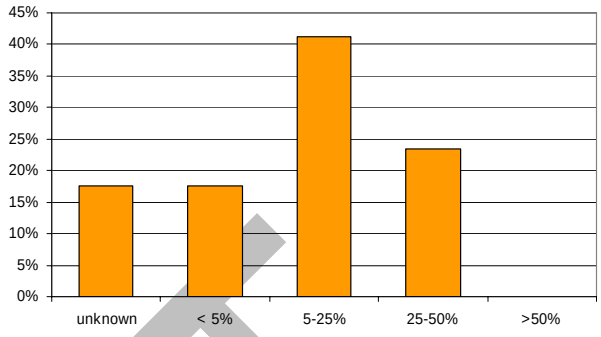
In gene sequencing one third estimates the market share to be lower than 5 %. Another 30 % rate it to be between 5 and 25 %. In fact, gene sequencing is a quite distinct market area. Nanotechnology is supposed to have an impact in improving the devices which are used for DNA exploration (e.g. Atomic Force Microscopy (AFM), which is customarily used to analyze the surface structure of materials at molecular resolution with the ultra-small tip of a sensitive probe[8]).

Most of the experts agree upon the market share of nanotechnology in target identification (5 – 25%) and in formulation (25 – 50%), indicating that these are the main categories which can be influenced by nanotechnology.

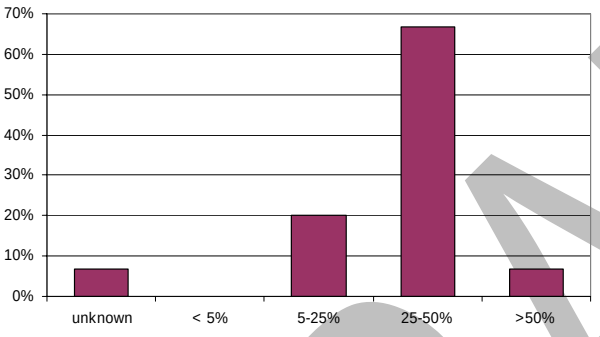
Percentage of the market that will be captured by nanotechnology in target identification



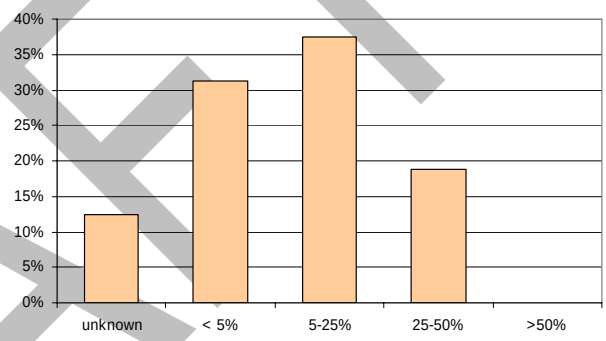
Percentage of the market that will be captured by nanotechnology in lead development



Percentage of the market that will be captured by nanotechnology in formulation



Percentage of the market that will be captured by nanotechnology in target validation



Infrastructure requirements

There is a heterogeneous opinion of the development of instrumentation costs for the manufacturing, characterisation and manipulation of nanotechnology in the particular areas.

Two thirds of the experts agreed upon the fact that the costs increase steadily, for the others this seamed not to be a crucial factor for their activities in this field.

Most of the experts emphasise the need for the creation of multidisciplinary centres with advanced knowledge on materials development and own pilot production facilities to be essential for supporting the European industry in taking its products to the final market.

However, while nanotechnology holds the promise of transforming the medical field, several challenges still remain. One of the most immediate issues is the need to develop inter-disciplinary expertise across a range of suitable technologies.

Educational requirements

According to the experts' estimations nanotechnology suffers from the problems that other interdisciplinary research areas face. Thus, most important for the growth and prosperity of European nanotechnology is a higher interaction between industry and academia facilitating an effective technology transfer and to turn nanoscience into nanotechnology. There is a need for focussing and multidisciplinary education. The notion that nanotechnology is completely new, divorcing from historical efforts in chemistry, biology and physics, is a mistake according to the experts estimation. The new "nano" requirements should be more clearly defined and then transferred into appropriate course design and curricula at the basic science medical and clinical interface.

HSE issues

The problem with all types of therapies is the interface between human beings and technology which is situated inside of the body. Thus, the benefits of such therapies have to prevail clearly over possible drawbacks which have, to render more precisely, to converge against zero. Each therapy has to run strict approval processes to eliminate any possibility of potential hazard.

There are obviously differences between unintentional and intentional anthropogenic nanoparticles which are the polydispersed and chemically complex nature of the former and the monodisperse and precise chemically engineered characteristics and solid form of the latter, generated in gas or liquid phase. However, the same toxicological principles are likely to apply for nanoparticles, because not only size but also a number of other particle parameters determine their biologic activity.

Nanoparticles, used as drug vehicle or drugs by themselves have an active and large surface that can interact potentially with many targets in the body. Due to their size and surface properties they are badly recognised by the immune system and even enhance response to antigens. They are in the size of proteins and can interfere with normal cellular signaling pathways. In several scientific experiments, it has been shown that nanoparticles can for example be uptaken by the brain, that they can cause acute inflammation with secondary effects such cancer or that combustion nanoparticles cause worsening of heart disease, atherosclerosis and asthma[9].

Although about two thirds (71%) of the participants negated a potentially HSE hazard raised by nanotechnological processes being involved in their products, all of them favour HSE impact studies on certain types of functionalised nanomaterials. In this aspect safety relates to the proposed chemistry and the proposed use. According to the experts opinion discussion of the safety of nanoparticles and nano tubes per se is not helpful without addressing the more specific points. Safety should relate to environmental exposure, manufacturing exposure, as well as any proposed clinical use.

European competitive position

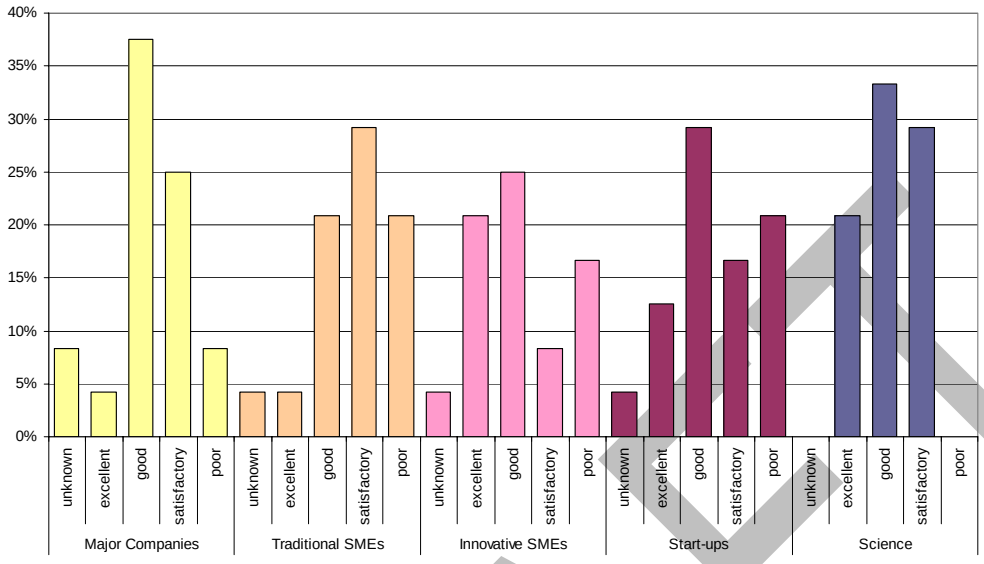
Only the European major industry is stated by the experts to have a good international standing. A larger spreading occurs in the estimation of innovative and traditional SME's, as well as start-ups, which may be due to different national governmental regimentation in the particular countries (see diagram below). According to the experts opinions not sufficient scientific technical experts are included in the discussion and strategic decision making process and many of the EU and National committees have failed to engage world leading European pharmaceutical scientists and committee members. However, this engagement of the academic and industrial technical expertise in the EU is crucial to lead the world in specific aspects of this sector.

In this respect a recently published report by the European Sience Foundation should be mentioned which gives a scientific look on nanomedicine and which raises the issue of international competitiveness[10].

"Turning to the organisation and funding of nanomedicine, however, the ESF analysis identifies potential weaknesses in the European system. While the rapidly growing investment in nanotechnology research at national and EU level is welcomed, it warns that the organisation and funding of nanomedicine in Europe is currently fragmented. 'This can inhibit attainment of the critical mass and the multidisciplinarity needed for effective research and development,' it adds.

To overcome this, the report proposes better coordination and networking of research activities, the establishment of European centres of excellence in nanomedicine, and the development of funding mechanisms with sufficient scale and scope and longer term budget cycles. The exploitation of research results is also an area that the ESF identifies as a potential weakness for Europe. 'To win and

maintain a leading position in nanomedicine it is essential that Europe improves technology transfer and shortens timelines from research to market,' it concludes. Finally, the report emphasises the importance of effective modes of communication: between scientists themselves, from the research community to political bodies, and to the general public at large."



Worldwide position of European industry and science if compared to other regions

Forming synergistic collaborations with drug and medical device companies represents one of the most obvious routes of achieving such multi-disciplinary proficiency. Initially, such partnerships could take the form of joint marketing efforts, paving the way for nanomedical companies to independently handle all stages from R&D to commercial exploitation, in the long run.

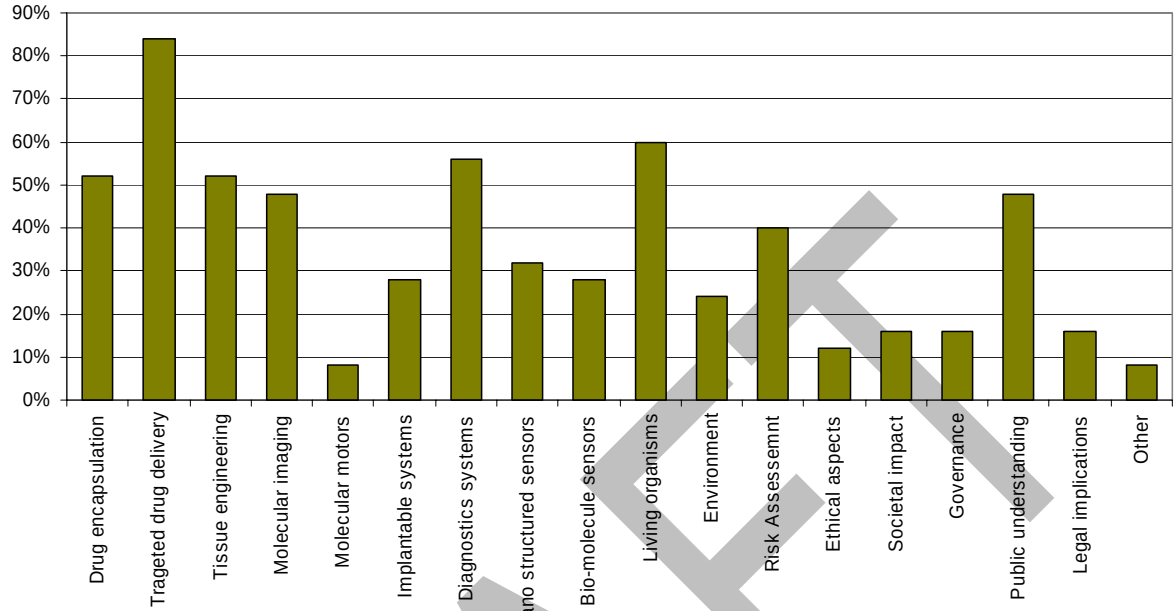
2.4 Recommendations by the Delphi panel

Trends, challenges and major gaps and barriers in the technological evolution which will lead to technological conclusions have been identified by the Delphi panel and described in this document.

Nanotechnology faces a strong challenge in the shape of negative public perceptions with growing reports about the possible toxic effects of exposure to nanoparticles. Non-technological conclusions towards the increasing concern about the potential ill effects of engineered nanomaterials such as carbon buckyballs and nanotubes through inhalation, ingestion, or absorption through the skin will have to be drawn.

The Delphi panel has expressed their opinion on reinforcing European endeavours in the field illustrated below.

Europe should reinforce its activities in health and medical applications in the following areas

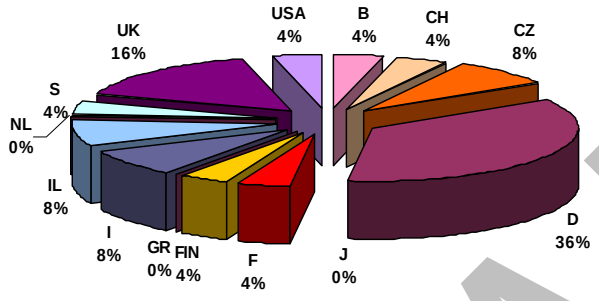


3 ANNEXES

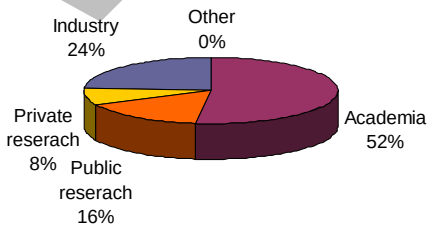
3.1 Statistics

In the drug encapsulation/ drug delivery/ drug targeting topic we asked 40 international experts from 14 different countries to give their input in this emerging field of nanotechnology. Moreover there were 32 experts pleased to participate without being related to a special topic in advance. Seven of them answered, three of them within the pharmaceutical topic. About 60 % of the invited experts answered in total to the two cycles of questionnaires. The experts which have been invited to participate were spread over universities, university research centres, public research organisations, private research organisations and industry. Nevertheless, almost half of the participants (52%) came from academia. 24% came from industry, 16% from public research organisations and 8% from private research organisations. Most of the participants (35%) are engaged in drug delivery, 23% deal with drug targeting and about 14% are busy in drug encapsulation. It has to be considered that the question wasn't answered by all experts. The R&D foci of the experts are likewise the investigation of pharmaceuticals, medical devices/ application systems as well as pure nanoparticles, including functionalisation and derivatisation as well as biokinetical aspects. Some experts deal with drug formulation or surface chemical characterisation at the nano- and microscale.

International spreading of the participants



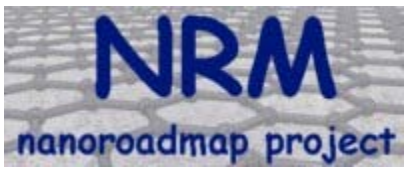
Organisation Type



3.2 List of participants

Robert Anderson Polymer Laboratories United Kingdom	**Udo Bakowsky** Philipps-University Marburg Germany	**John Daicic** Ytkemiska Institutet AB (YKI) Sweden
Ruth Duncan Welsh School of Pharmacy, Centre for Polymer Therapeutics United Kingdom	**Mike Eaton** Celltech Group United Kingdom	**Ben-Jacob Eshel** Tel-Aviv University Israel
Paolo Facci University of Modena and the Region of Emilia, Department of Physics Italy	**Monia Gentile** Center for Applied Research in Micro and Nano Eng.(CRIM) Italy	**Ian Gilmore** Surface and Nano-Analysis, National Physical Laboratory Teddington (NPL) United Kingdom
Heinrich Hofmann Section de Science et Génie des Matériaux - SMX, EPFL Switzerland	**Andreas Jordan** MagForce Applications GmbH Germany	**Elmar Keßenich** BASF AG Germany
Rafi Korenstein Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University Israel	**Wolfgang G. Kreyling** Focus Network Aerosols and Health Germany	**Claus Michael Lehr** Department of Biopharmaceutics and Pharmaceutical Technology, Saarland University Germany
Armin Leng Merck KgaA Germany	**Mauro Magnani** University Urbino, Institute of Biochemistry Italy	**Alexander Mullen** Bayer AG Germany
Edouard Panak Nanobiotix Prologue Biotech France	**Bernhard Sabel** NanoPharm AG Germany	**Ivo Šafařík** Department of Biochemistry and Microbiology Czech Republic
Jukka Seppälä Laboratory of Polymer Technology, Helsinki University Finnland	**Lucas Stéphane** University Notre-Dame de la Paix Belgium	**Karel Ulbrich** Department of biomedical polymers Academy of Science Czech Republic
Andreas Voigt Capsulution NanoScience AG Germany		

[1] Duncan R., *Nat Rev Drug Discov. 2003 May;2(5):347-60.*, The dawning era of polymer therapeutics.
[2] http://www.drugs.com/newdrugs.html
[3] IMS Health
[4] sources: Global Pharma Forecasts and IMS
[5] BCC, 2003: Advanced Drug Delivery Systems: New Developments, New Technologies
[6] BCC, 2003:Biomedical Applications of nanoscaled devices: Commercial Opportunities, Conference Proceedings, Nanotech and Biotech Convergence, Business Communication Corporation, 2003
[7] Kanellos, Michael. (2004, August 16) "Nanotech funding to grow to $8.6 billion," TechRepublic.com. Accessed online at: http://techrepublic.com.com/5100-22_11-5311278.html?part=rss&tag=feed&subj=tr
[8] News.Nano.Apex, Exploring revolutionary gene sequencing: Threading the molecular needle, Accessed online at: http://news.nanoapex.com/modules.php?name=News&file=article&sid=5191
[9] Reviewed in: Oberdorster et al.,*Environ Health Perspect*. 2005 Jul;113(7):823-39. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles.
[10] ESF Scientific Forward Look on Nanomedicine, February 2005



NanoRoadMap is a project co-funded by the 6th Framework Programme of the EC

Nanotechnology in Health and Medical Systems

Draft Roadmap on Molecular Imaging/ Biophotonics/ Medical Imaging

Partners:

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Willems & van den Wildenberg (ES/NL)

VDI/VDE (DE)

Institute of Nanotechnology (UK)

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Date: July 31 2005

Table of Contents

1 Introduction

1.1 Background

The NanoRoadMap (NRM) project, co-funded by the European Commission (EC), is aimed at road-mapping nanotechnology related application fields in three different areas:

- Materials
- Health & Medical Systems
- Energy

Within the project, an international consortium consisting of eight partners covering eight European countries and Israel, has joined forces to cover the time-frame for technological development in this field up to 2015. The results of the NRM project are to be used by any European entity interested in planning an R&D strategy taking into account nanotechnology. An important potential user is of course the EC itself in the preparation of the 7th Framework Programme (FP7) for research and technology development. (For additional information on the NRM project, please refer to www.nanoroadmap.it).

1.2 Goals

The primary objective of NRM is to provide coherent scenarios and technology roadmaps that help the European players to optimise the positive impact of nanotechnology on society, giving the necessary knowledge on its future development and when technologies and applications will come into full fruition.

The key users of the reports are mainly European SMEs, research organisations, public bodies in general and the EC in particular. Even though a special focus is put on SMEs, these roadmaps are also meant to be useful for larger corporations.

This report is one of the three final deliverables of the NRM project and it is aimed at providing a thorough overview of specific topics selected for roadmapping within the field.

1.3 Methodology

Collection and synthesis of relevant existing information

In October 2004 three sectoral reports were published, each covering one of the above mentioned areas. They were based on the collection and synthesis of existing public sources in 31 countries and were published as key input for the celebration of the First NRM International Conference held in Rome the 4–5 November 2004. The full report can be downloaded from the project web site.

The report within the sector health and medical systems focused on reviewing the different aspects of nanotechnology in 11 topics, giving its definition, describing its most remarkable properties, current and future markets & applications, and leading countries & highlighted R&D activities in the field. A

general review of non technological aspects (social, legal, ethical and health and safety aspects, but also economic aspects and infrastructure requirements) was also performed.

The 11 topics identified, even not being completely homogenous in terms of scope or classification, were intended to adequately cover the field of bionanotechnology.

The following list was agreed upon by the partners of the NRM project (similar classifications can be found in the bibliography):

- Tissue Engineering/Regenerative Medicine
- Bio Nano Structures
- Drug Encapsulation / Drug Delivery / Drug Targeting
- Molecular Imaging
- Biophotonics
- Biocompatible implants
- Biomimetic membranes
- Biomolecular sensors
- Biochips/HighThroughputScreening
- Lab-on-a-chip
- Functional Molecules: Switches, pumps, means of transportation

Selection of topics

Another major goal of that report was to set the basis for discussion and selection for roadmapping of 4 out of the 11 topics identified above. A preliminary selection of topics was presented during the First International Conference in November, 2004.

Within a frame of criteria agreed upon with the European Commission and after a thorough discussion, which involved international experts in the field of nanotechnology, four topics were selected (and validated in dialogue with the European Commission). The subjects were partly combined with each other, leading to the four chosen topics:

- Drug encapsulation/ drug delivery/ drug targeting
- Molecular Imaging/ Biophotonics
- Biochips/ High-Throughput Screening/ Lab-on-a-chip technology
- Biomolecular Sensors

Roadmap elaboration

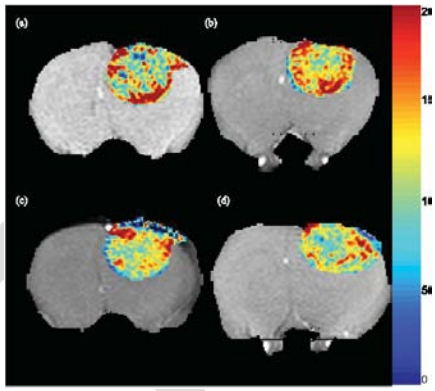
One draft roadmap has been prepared for each of the four aforementioned topics. The result of these roadmaps will be presented in one international and eight national conferences in November and December 2005. Their preparation and execution is based upon a Delphi-like approach. The methodology consists of 2 cycles, which is the same for the four topics. The Delphi exercise consists of:

- Selecting top-international experts on the field
- Preparing a dedicated on-line questionnaire for each of the topics to be roadmapped
- Circulating the questionnaires and gathering experts' responses (1st cycle)
- Preparing a first summary of the answers received

- Circulating the summary and partly interpreted data, asking for feedback and reflection (2nd cycle). Interpretation was conducted in a way avoiding bias.
- Elaborating the roadmap taking into consideration aspects raised in the 2nd cycle

2 Molecular Imaging/ Biophotonics/ Medical Imaging

2.1 Introducing the subject



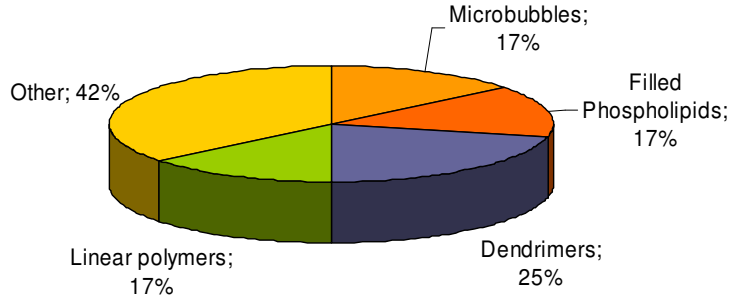
Source: Molecular Imaging, Vol. 2, No. 4, October 2003

Molecular Imaging is the visual representation, characterization, and quantification of biological processes at the cellular and subcellular levels within intact living organisms. It is a novel multidisciplinary field, in which the images produced reflect cellular and molecular pathways and in vivo mechanisms of disease present within the context of physiologically authentic environments. The term "molecular imaging" implies the convergence of multiple image-capture techniques, basic cell/molecular biology, chemistry, medicine, pharmacology, medical physics, biomathematics, and bioinformatics into a new imaging paradigm[1]. It is a newly emerging field in which the modern tools of molecular & cell biology are being married to state-of-the-art technology for non-invasive imaging. The goals of this field are to develop technologies and assays for imaging molecular/cellular events in living organisms. These approaches should help to lead to better methods for studying biological processes as well as diagnosing and managing diseases.

In molecular imaging, an imaging molecule is coupled to a transport molecule or particle, which possesses a targeting unit, e.g. special receptors, ligands or peptides. The target finding system should be a specific molecular marker of a certain disease thus the contrast medium accumulates within the sick tissue. Molecular imaging is developed for several diagnostic procedures such as magnetic resonance imaging, ultrasonic imaging, as well as nuclear and optical imaging technologies.

Photonics, the science of light, has a history of success in solving clinical and research problems in diverse applications through such products and techniques as spectroscopy, lasers, microscopy, imaging and fiber optics. **Biophotonics** is the technology of using light beams and other forms of energy to diagnose and monitor medical conditions. Nanotechnology in health and medical systems provides a slightly different definition to biophotonics.

If the above mentioned targeted drug delivery vehicles are equipped with light sensitive side groups, then Biophotonics could be used in disease defence, e.g. anti-cancer therapy. After vesicles have docked to their target, sick tissue (e.g. tumour cells) could be destroyed, by stimulation with light (e.g. laser), leading to an emission of photons which harm surrounding cells (tumour cells). Within Photodynamic Therapy, light sensitive drug is taken up by tumour cells. Laser light is applied to target area, thus destroying tumour cells while normal cells are spared.



In terms of the most appropriate types of nanoparticles for there are no clear preferences for certain nanoparticles. The experts participating in our Delphi exercise named dendrimers, linear polymers, filled phospholipids, microbubbles and “other”. These, were nano-caged compounds, multimeric (or unimeric) micellular assemblies

as well as inorganic nanoparticles with tuneable physical properties. **Dendrimers** are generally described as macromolecules, which are characterized by their highly branched 3D structure which provides a high degree of surface functionality and versatility. Dendrimers can be made out of virtually anything that can branch (metal atoms, organometallic groups, or purely organic materials) and they can have a variety of functionalities depending on the application[2]. Dendrimers and linear polymers, conjugated to metal chelates as well as liposomes containing paramagnetic ions are used as MR contrast agents, the first two have the potential to be used as diagnostic contrast agent. **Linear polymers** in this respect are tailored synthetic polymers as critical components in the development of nanoparticles with defined architecture and function. **Microbubbles** are used as contrast media as well. They can evolve for example by the means of contrast-enhanced ultrasound as gas-filled microbubbles. To survive in the circulation, the gas bubbles have to be encapsulated with surfactant or proteins or polymers or some other material. Once they have been created they do not need to be filled with gas, but with something else, such as a drug, creating a very appealing potential for targeted drug delivery. The microbubbles are about the same size as red blood cells. Coupled targeting molecules act as vectors guiding the vesicles to their destination. Microbubbles are used preliminary to visualise targets within blood vessels so that target molecules should be located at the inner surface of the vessel. Much smaller particles are needed for the use outside vascular regions. Only particles of a size < 0,5 µm are able to pass endothelial cells, lining the blood vessels. Microbubbles with a special targeting region actually are applied in two application fields: the diagnose of blood vessel diseases and detection of new built blood vessels which is called angiogenesis and which is associated with tumour creation.

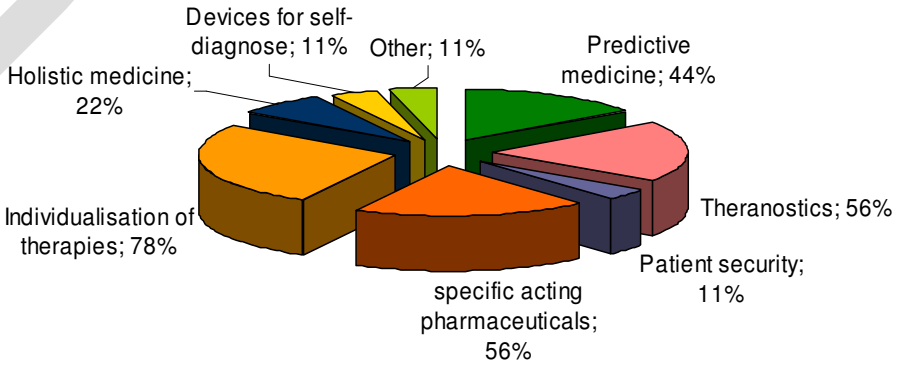
The contrast enhancing media which are mainly used by the participating experts are gadolinium and supermagnetic iron oxides. Perfluorocarbon nanoparticles, fluorescent quantum dots, chromophore-coupled target molecules as well as near infrared fluorophores, radionuclides and proteins are more rarely used for this purpose. Chemical exchange saturation transfer (CEST)-agents are not used at all.

2.2 Scientific and Technological Aspects

Trends & needs during the next decade

Advances in cell biology, biochemical agents, and computer analysis have enhanced interest in and use of molecular imaging in recent years. By using magnetic, nuclear, and optical imaging techniques the molecular interactions that underlie biological processes can increasingly be studied. .

Molecular imaging promises new insights into disease processes in the laboratory and since the imaging modalities employed are applicable clinically, they can be used to translate this knowledge into new diagnostics and treatments in the clinic.



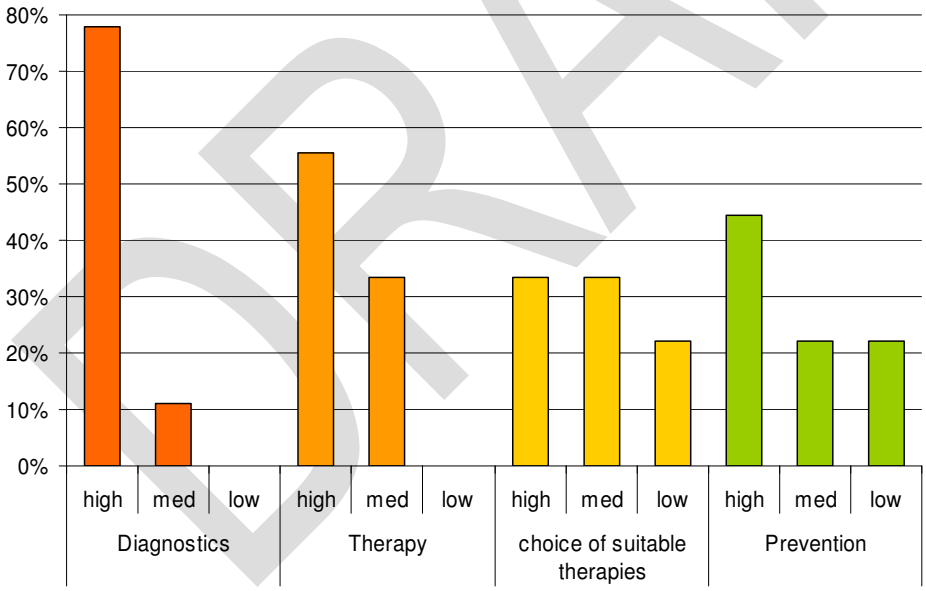
"Future medical practice will need more..." Estimations of the experts withi the Molecular Imaging field

Molecular imaging usually exploits specific molecular probes as the source of image contrast. This change in emphasis from a non-specific to a specific approach represents a significant paradigm shift, the impact of which is, that imaging can now provide the potential for understanding of integrative biology, earlier detection and characterization of disease, and evaluation of treatment. This is reflected in the experts' estimations according to which more future emphasis has to be put in individualisation of therapies (78%), followed by specific acting pharmaceuticals and theranostics (56% each). More holistic medicine, being a contrast to modern drug based medicine, is demanded to be emphasised by two out of nine persons. More patient security is important in the opinion of only one expert, perhaps indicating that there is a broad contentment with the existing guidelines for patient security. Devices for self-diagnosis are estimated by one expert to be of future need. According to one expert, another focus should be set on activities in health sustainment, i.e. nutrition, sports, etc.

Nanotechnology is expected to be critical in supplying the mentioned demands. Two thirds of the involved experts suppose nanotechnology to be unique in providing contrast enhancing media with the properties which are needed for their more efficient use.

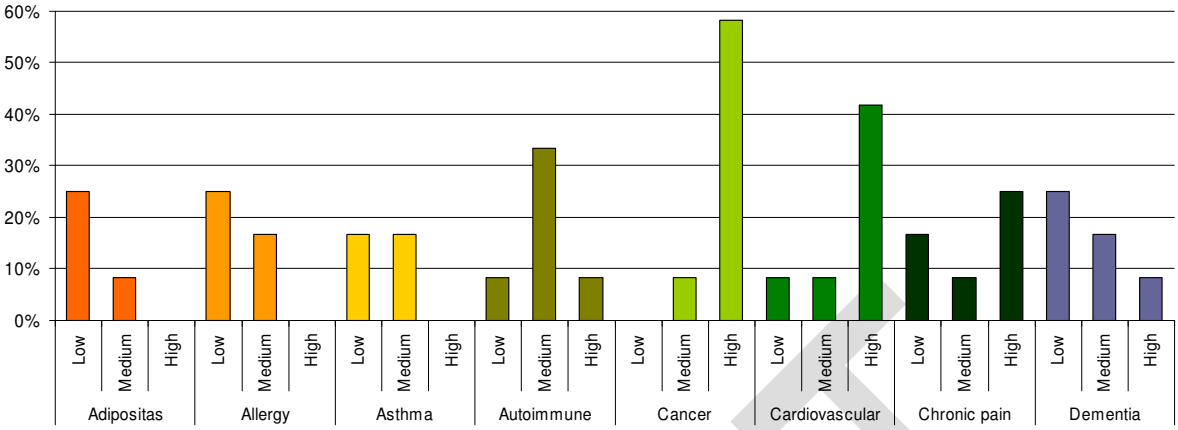
Impact of nanotechnology in the field considered

There is an ample accordance between the experts within the drug and medical imaging sector that the impact of nanotechnology in diagnostics will be high during the next decade. This applies to therapy as well, but to a lower degree. The impact on the choice of suitable therapies is expected to be rather medium whereas the estimation upon a nanotechnological impact in prevention ranges from high to medium with an emphasis on a low impact.

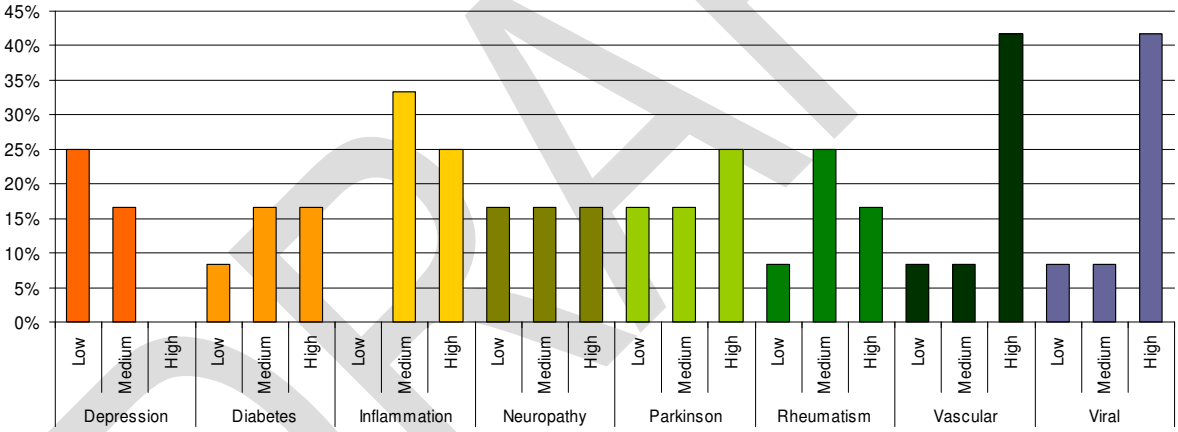


The therapeutic sector is highly combined with the diagnostic one because a disease or the predisposition to fall ill has to be detected prior to be medicated. The expected quantum leap in diagnostics, leading to a far better pre-symptomatic detection of diseases, should improve the facilities to prevent them.

Regarding the potential of nanotechnological based molecular imaging and biophotonics to detect and medicate special diseases there is a clear negation with a few exceptions, i.e. cancer, vascular and cardiovascular diseases as well as viral infections. The supposed impact of nanotechnology on certain diseases like adipositas, allergy, asthma, chronic pain, dementia, depression, diabetes, inflammation, neuropathy, neurodegenerative diseases or rheumatism, was more or less equally distributed. The results emphasise that there are at least only a few medical indications which will take exclusive bene-



fit from nanotechnology. Nanotechnology will revolutionise the molecular imaging/ biophotonics/ medical imaging field generally through targeted transportation of drugs or contrast enhancing media by which means various diseases can be specifically diagnosed and treated. Thus, nanotechnology is a general platform for drug targeting, drug delivery and medical imaging.



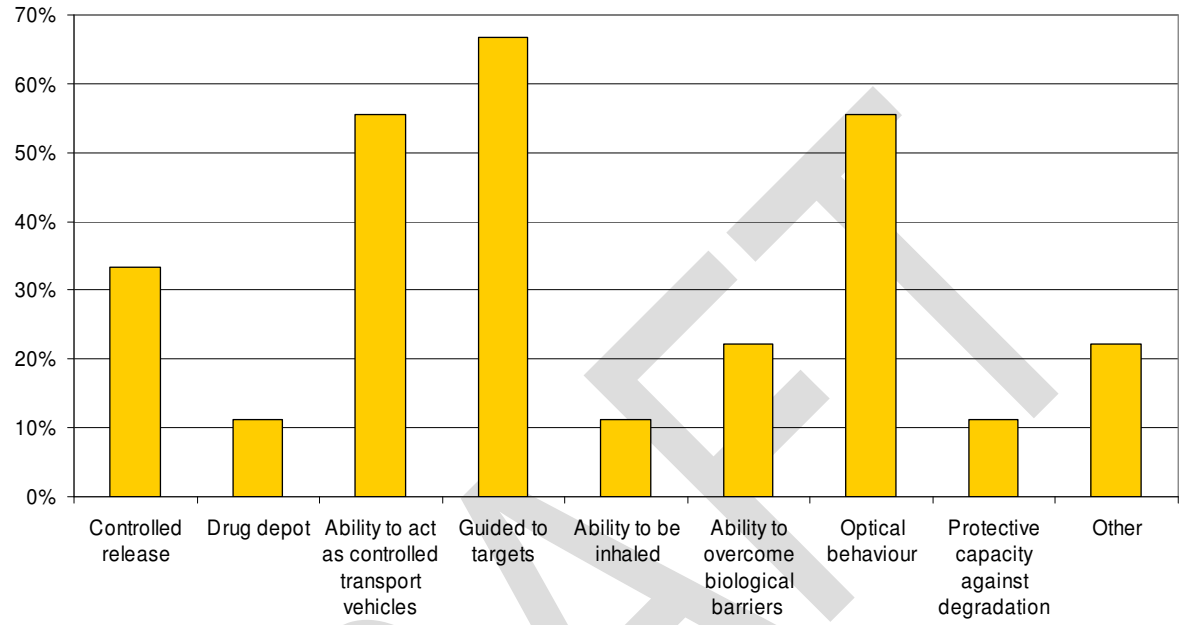
Advantages of nanotechnology over existing/ alternative technologies

Molecular imaging permits both the temporal and the spatial biodistribution of a molecular probe and related biological processes to be determined in a more meaningful manner throughout an intact living subject. Visualization of functions and interactions of a particular gene becomes easier in a more realistic manner that respects the dynamics of complex biological networks and of complete and holistic biological systems in the entire living subject.

The most revolutionary property of nanoparticles in the pharmaceutical sector compared to existing or alternative technologies is their ability to be specifically guided to targets.

The abilities to release drugs in a controlled way, to be used as transport vehicles (which is implied in the specific target guidance) and their optical behaviour which makes the targeting observable, are estimated to be also revolutionary in comparison to existing technologies.

The implementation of molecular imaging approaches in drug discovery processes offers the advantage of being able to study a potential drug labeled for imaging in an animal model, before phenotypic changes become obvious, and then move into human studies. It is likely that preclinical trials can be accelerated to rule out drugs with unfavourable bio distribution and/or pharmacokinetics prior to human studies.



Most revolutionary properties of nanotechnology in molecular imaging compared to existing/alternative technologies

The abilities to being used as drug depot, to be inhaled or to protect drugs against degradation are evaluated only by few experts to be revolutionary enough to compete against existing/ alternative technologies. Further revolutionary properties were mentioned to be protective capacity against degradation, environmental (disease specific) activation and the ability to act as drugs with controlled effects.

Technology evolution

Biological discovery has moved at an accelerated pace in recent years, with considerable focus on the transition from in vitro to in vivo models. As such, there has been a greater need to adapt clinical imaging methods for noninvasive assays of biochemical processes. Considerable efforts have been directed in recent years toward the development of noninvasive, high-resolution *in vivo* imaging technologies.

Nanotechnology provides a wide range of new technologies that optimise the targeting and delivery of pharmaceutical and imaging products, i.e. contrast enhancing media. Since it is a technology at its very early stage with nanomedicine being a subdivision of the real broad field of nanotechnology, the technology evolution is hardly to characterise or to predict.

According to two-thirds of the experts there is a need for more research and development to enlarge the range of existing nanoparticles and thus the possibilities that are provided by molecular imaging / biophotonics

The experts within the drug delivery field stated that in addition there is a need for suitable new pharmaceuticals. The understanding of the limiting factors of drug release control and the ability to internally monitor the release system will increase and will improve the timing of drug delivery. The deepened knowledge of nanoparticle absorption, distribution, metabolism, defence mechanisms, interaction with other drugs, binding and interaction with receptors as well as the excretion of nanoencapsulated pharmaceuticals will certainly lead to a quantum leap in the therapy of diseases, especially if nanosystems and nanomaterials are discovered that match particular drugs. This is certainly also valid for molecular imaging.

Trends, challenges and discontinuities

Due to their unique properties, nanoparticles are expected to revolutionise the medical, especially the diagnostic and therapeutic sector. Nevertheless the technology is still at its early stage and there are huge challenges to meet.

Molecular imaging in living subjects presents more theoretical and practical challenges than in vitro or cell culture detection, primarily because of the need for probes to be biocompatible, the presence of additional delivery barriers, and the necessity for developing special in vivo amplification strategies. Future research efforts will be necessary to perform in vivo molecular imaging. First of all there has to be a selection of sophisticated appropriate cellular and subcellular targets to image. Secondly, suitable *in vivo* affinity ligands, i.e. molecular imaging probes, should be developed to clarify what biocompatible chemical/biochemical/molecular entity can be used *in vivo* to distinguish a particular biological process and help to generate specific images of the specific target. Furthermore, specific acting probes, transporting drugs and contrast enhancing media, must be able efficiently to overcome biological barriers. The sensitivity of measuring and thus imaging has to be enhanced to detect minimal target concentrations, usually in the pico- to nanomolar range and to minimise the signal/ noise ratio.

Time-to-market

To learn more about the marketability of special nanotechnology driven applications and the expected time to market for such applications within the medical sector the experts were asked to evaluate the stage of maturity of specific technical challenges of biochips in the diagnostic area.

The results which are shown in the following diagram reflect the relative importance of the particular nanoparticle properties and their implementation in applications within the next decade predicted in five years from now (2010) and in ten years from now (2015) and give an integrated view of the various stage of development of the applications.

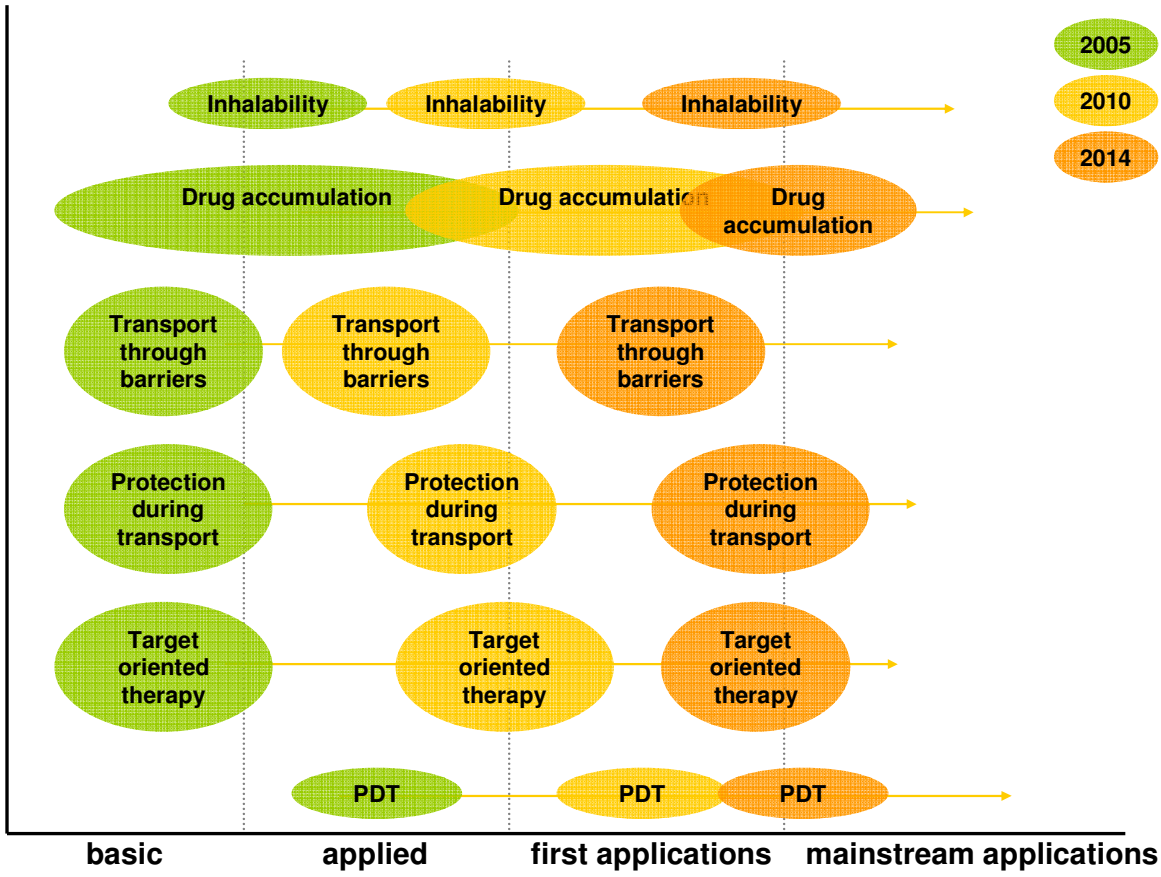
The generic distinctions in the graph chosen for the sequential phases in the innovation cycle have been taken as follows:

Basic Research & Development Phase (**basic**): Applications in this phase have received the interest of one or more researchers in the world. Some applications might still be in early development, while other are tough to develop and need a lot of basic research to be fully understood. The object of basic R&D is to validate the original hypothesis. Many applications are currently in this phase as researchers are still struggling to understand basic properties of nano-material.

Applied Research & Development Phase (**applied**): After the hypothesis is validated, research typically (but not necessarily) moves from pure research labs to more commercial labs and companies. Applied R&D will eventually result in a proof of concept, a successful demonstration model. While the production issues might not have been solved yet, a successful prototype/model has been validated.

Product Research & Development Phase (**first applications**): After first demonstrator models and prototypes, initial, usually prohibitively expensive, small numbers of products may be produced. If these prove successful, companies will seek to enhance production to gain market share. Generally at some point, demand increases sufficiently to offset the investment needed to start production. This phase ends at a point when feasibility has been proven and production is to start.

Production level and incremental research (**mainstream applications**): The final development phase, when production has reached significant numbers and research focuses on incrementally improving the products.



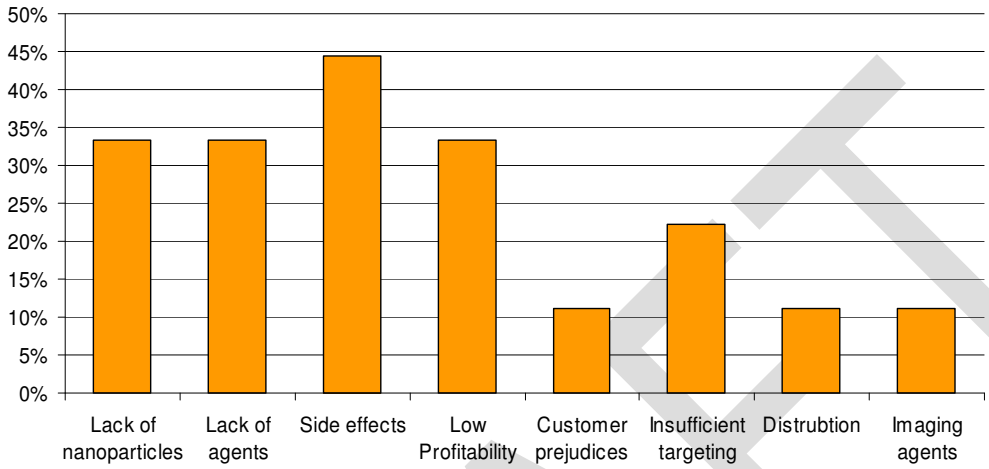
Gaps and barriers

Nanotechnology is a relatively young technology so that there are several gaps and barriers to deal with.

Several challenges have to be met in the next decade. The participants within the molecular imaging field stated too much negative side effects of available nanoparticles (e.g. general cell toxic effects) to be the most important barrier, followed by the lack of suitable nanoparticles to solve existing contrast media distribution problems, a lack of suitable imaging agents and low profitability of molecular imaging and subsequent therapy due to expensive and extended R&D. An insufficient targeting, i.e. coupling of specific particle-linked side-groups to their correspondent target molecule, were regarded by two of nine experts to be future bottleneck. Too much customer prejudices against nanoparticles and

unsatisfactorily target oriented distribution of imaging agent containing nanoparticles were not regarded to be major bottlenecks.

Interestingly there was a slightly different evaluation regarding the sufficiency of targeting by the experts in the drug encapsulation / drug targeting/ drug delivery field. They considered an insufficient targeting as well as consisting side effects of available nanoparticles (e.g. general cell toxic effects) which could prevail over medicative drug effects, to be the main bottlenecks occurring.



Most of the basic things that will slow many developments will certainly be the lack of understanding of complex biological systems.

Regarding the barriers which are expected in connection with special kinds of nanoparticles they are mainly of technological and economic character.

	General	Filled phospholipids	Microbubbles	Dendrimers	Inorganic nanoparticles with tunable-physical properties	Linear polymers	Multimeric or "unimeric" micellular assemblies
Technical	X		X	X	X	X	X
Economic	X	X	X	X		X	
Medical							
Infrastructural		X					
Environmental impact	X						
Other			X				

The specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in the table below:

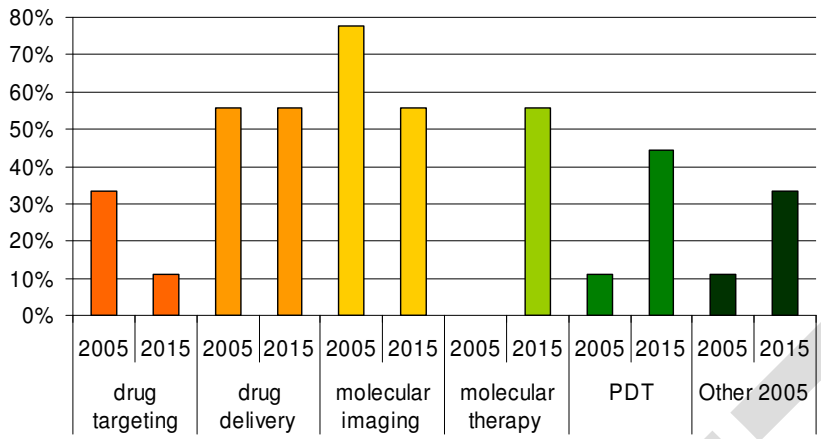
Barriers to success	**Technical**	**Economic**	**Infrastruc-tural**	**Environ-mental im-pact**	**Other**
General	Patient safety; stability	Costs of product develop-ment		Toxicity concerns and disposal routes	
	Analytical technique de-velopment for nano-scaled chemical surface analysis				
Filled phos-pholipids		Investments for instru-ments are mandatory for success-ful work	Bottom up interdisciplin-ary work is important		
Microbub-bles		Close col-laboration between industry, academia and regula-tory bodies			Integration of European medicines evaluation agency (EMEA) to change ap-proval proc-ess
Dendrimers	Breakthroughs on re-search (e.g. coating)	The rela-tively high cost of "pure" den-drimers could be overcome by the use of hyper-branched linear poly-mer systems			
Inorganic nanoparti-cles with tunable physical prop.	Suitable manufacturing process & quality control with industrial level				

Linear polymers	Many of the responsive polymer systems and even the non re-sponsive "simple" hydrophilic carriers are non degradable & may result in significant bioaccumulation; therefore: developing fully/ partially degradable systems but not at the expense of scalability & economic viability of the products				
Mutimeric (or unimeric) micellular assemblies	Stable micellular assemblies & polymersomes, plasma half life & targeting efficiency of certain therapeutics but are often limited by in-tercellular compartmentalisation into non productive vesicles & thus lowers efficiency; current ef-forts towards responsive micellular systems for triggered release are addressing such issues & may lead to clinical trials of improved delivery systems in the next few years				

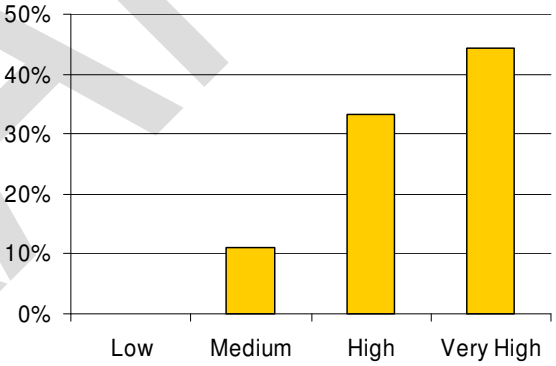
Most present and future relevant applications of nano-related products

Nanoparticles can serve as modular platforms, from which a wide variety of highly sensitive and specific imaging agents can be created. For example, many hundreds or thousands of atoms that provide imaging signals, such as radioisotopes, lanthanides, or fluorophores, can be attached to each nanoparticle, to form imaging agents that would provide higher sensitivity that can be obtained from agents based on small molecules. Similarly, many copies of targeted ligands can be attached to nanoparticles to markedly increase specific binding. Drugs or therapeutic isotopes can be added to create multifunctional nanoparticles. Appropriately labeled and targeted nanoparticles could lead to a paradigm change in which cancer detection, diagnosis, and therapy are combined in a single molecular complex.

According to the experts the main impact of nanotechnology within the pharmaceutical sector will occur in molecular therapy. Pure drug targeting will take a future back seat being eclipsed by precisely targeted drugs. The Photo Dynamic Therapy is expected to increase in the next decade. A further present and future application was mentioned to be the generation of pure starting material for all kind of downstream analysis and therapeutical aspects. Moreover diagnostics, combined diagnostic and therapeutic imaging capabilities as well as specific nontoxic and triggered therapeutic nanotools will gain increasingly more importance.



The experts expect the probability that nanotechnology will play an important role in biochip applications to be high (33%) or very high (44%). One out of nine experts rated the probability to be rather medium. He mentioned high costs in individual therapy. One of those who estimated the probability of nanotechnology to play an important role in molecular imaging expects the drug/ agent delivery to become a platform. Between those experts who are of the opinion that nanotechnology will play a very high role in molecular imaging /biophotonics one stated that the rate of new drug development is failing and the pharmaceutical industry will look to increase product lifetimes and profitability through reformulation. Furthermore he states nanotechnology to have the potential to offer improved pharmacokinetics and pharmacodynamics thus generic companies could leverage considerable value by combining off patent products with improved delivery technologies. Consequently the financial return from such applications will outstrip the potential improvement offered by specifically developed nanotherapeutics. Another opinion is, that nanotechnologies will solve some of the problems of current pharmaceutical approaches and will increase the ratio benefit over risk.



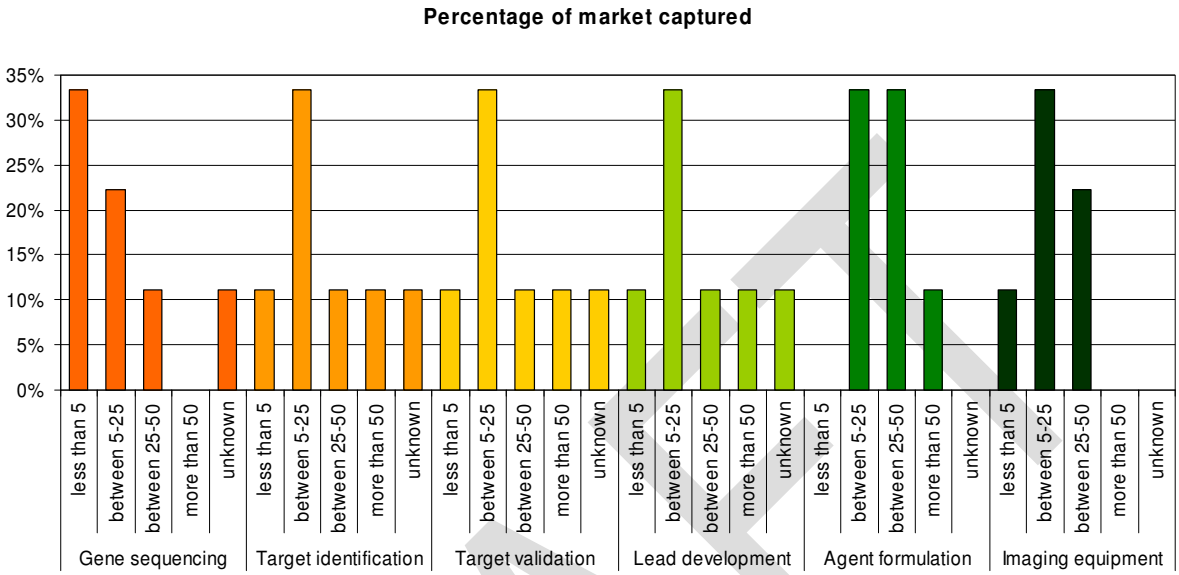
2.3 Non-technological aspects

Market trends for each application

Conventional contrast media for ultrasonic, nuclear or magnetic resonance imaging meet a considerable but decreasing market due to a fading progress. The new equipment needs less contrast media or goes without it. Nevertheless, the top players within this field posted increasing revenues over the last years. For example Schering could enhance its revenue with contrast media for magnetic resonance tomography about 8% in 2003. Due to a market study by Frost & Sullivan of 2002, the consid-

erable world market volume of about 684 million US$ in 2003 increases up to more than 914 million US$ in 2008.

U.S. sales of medical imaging contrast media reached $1.41 billion in 2003 and are expected to rise to $2.58 billion by 2009. Contrast media sales grew 7% in 2003; however, this annual growth rate is ex-



pected to increase to 9-10% per year between 2004-2006 and rise to 11-12% per year from 2006-2009. Iodine sales were $964 million in 2003 and have been under competitive pressure for the last several years, but should resume growth in the range of 6-8% between 2004-2006, increasing to 8-9% per year from 2006-2009. This will be driven by continued growth of CT procedure volume and increases in the proportion of enhanced studies. Sales of MR contrast media grew 13.5% in 2003 to $342 million, stimulated by rapid growth in the proportion of enhanced studies. In 2003, 46% of MR studies were enhanced. This proportion should rise to about 60% by 2009. Growth of MR procedure volume should continue at 10-11% for the next several years. However, the growth of enhanced studies will be in the range of 14-17% per year in the near term. Therefore, MR contrast media sales should rise to $700 million by 2009. Ultrasound contrast media sales were still on the threshold in 2003, with sales of $35 million. However, this should accelerate, as new indications are approved and new products introduced. Based on these assumptions, ultrasound contrast media sales should increase to $262 million by 2009. Market growth should also benefit from higher prices for new products in all modalities. In addition, more products will incorporate targeting capabilities, expanding the range of imaging procedures. This technical influx will help all segments of the contrast media field as imaging and therapy move closer together. One effect is that clinicians will have more options as alternatives to higher risk and more costly invasive procedures. This will stimulate more research and investment, adding strength and stability to newer venture companies as well as those more established in the field[3].

There is a relatively distinct estimation of the market share which will be captured by nanotechnology in the particular chain links of the medical imaging value chain. According to this nanotechnology will sum up less than 5% of gene sequencing and between 5 to 25% in target identification as well as in validation and in lead development. In agent formulation and imaging equipment the estimated percentage ranges between 5 to 50%.

Infrastructure requirements

There is a heterogeneous opinion of the development of instrumentation costs for the manufacturing, characterisation and manipulation of nanotechnology in the particular areas. For most of the experts this seams to be of no importance.

According to the experts most important for the growth and prosperity of European nanotechnology is a higher interaction between industry and academia facilitating an effective technology transfer as well as higher governmental support.

Furthermore the establishment of an European health institute (comparable to NIH) was demanded to bundle and streamline biomedical research, reduce bureaucracy of EU-funding and to learn from best practice.

More pro-activity, reducing the level of self-criticism as well as recruitment of highly-skilled professionals from other regions in the world, i.e. USA or Japan, were stated to benefit also the molecular imagig field.

Educational requirements

Regarding the educational offer in nanotechnology the opinions are nonuniform. Half of the experts regard it being adequate, the others are indifferent whether the offer is sufficient to manage the raising knowledge demand in the field or not.

A few experts within the category drug encapsulation/ drug delivery/ drug targeting suggested that there is a “need for focussing and multi-disciplinary education” and that “the notion that nanotechnology is completely new divorcing from historical efforts in Chemistry, Biology and Physics is a mistake. The new "nano" requirements should be more clearly defined and then transferred into appropriate course design at the basic science medical (clinical) interface”. This applies also for the molecular imaging field, since all experts agree upon the need for multidisciplinary centres with advanced knowledge on materials development and own pilot production facilities to be essential for supporting the European industry in taking its products to the final market.

HSE issues

Regarding a potentially HSE hazard raised by nanotechnological processes being involved in the products the experts are developing/ working with, most of them (87%) negated. Interestingly, most of the experts think that HSE impact studies on certain types of functionalised nanoparticles are needed.

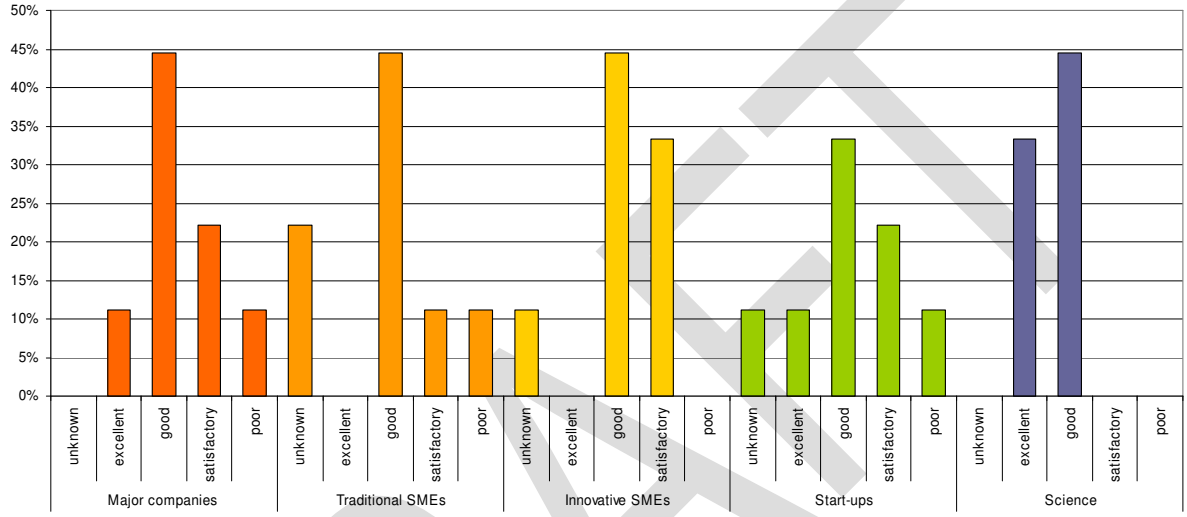
Some experts gave an explanation. According to them, HSE studies are needed on a continuous basis. The development needs to be evaluated with high regulatory control. Any pharmaceutical product and specific aspect due to utilization of nanoparticles should be added to general guidelines and safety rules. One participant proposed that the HSE impact has to be fully tested prior to use to avoid technological drawbacks. According to one expert from the category drug encapsulation/ drug delivery/ drug targeting, which is close to and partly overlapping the molecular imaging field, “there are certainly issues to be carefully addressed but the fact that regulatory authorities have already been devising new strategies for the approval of "safe" nanomedicines has almost been totally disregarded. It must be emphasised that safety relates to the proposed chemistry and the proposed use - discussion of the safety of nanoparticles and nano tubes per se is not helpful without addressing the more specific points. Safety must relate to environmental exposure, manufacturing exposure, as well as any proposed clinical use.”

European competitive position

The Delphi panel on molecular imaging has a relatively high proportion of industrial participants. The graph illustrates the quite consistent experts view on the competitive position of Europe in comparison to the global situation. It is stated as being mainly good to satisfactory in all size categories of industry.

Major companies are rated between excellent and poor showing an emphasis on good not claiming an excellent position of European enterprises for this size category in the main.

Within the traditional SMEs the position is predominantly estimated to be good with some statements of unknown positions.



Innovative SMEs are rated good to satisfactory with a lack of excellent positioning, despite their expected proximity of their core-business to scientific excellence.

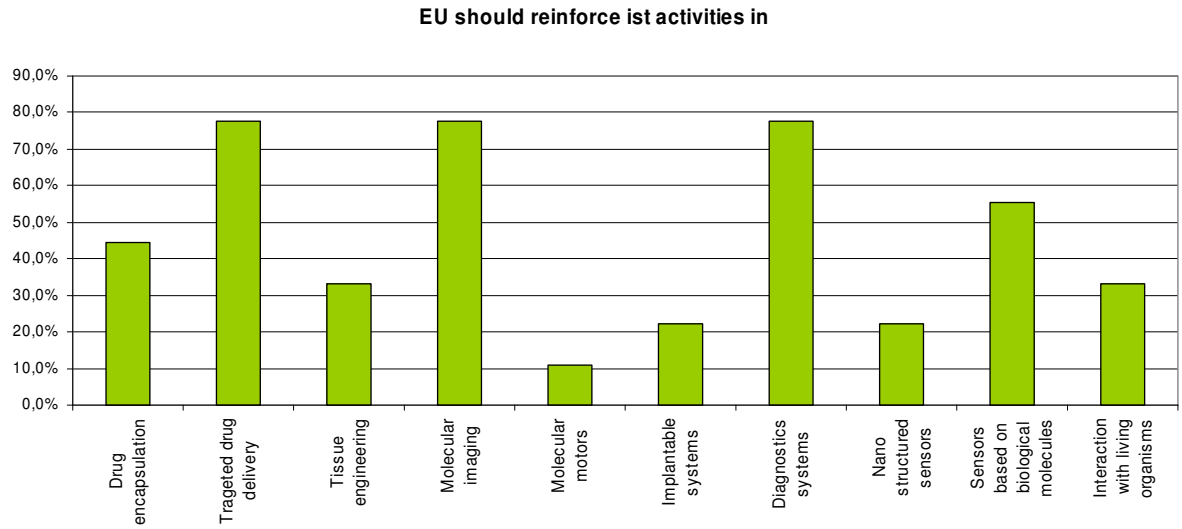
Start-up companies do gain a firmer rating in good and satisfactory alike the innovative SMEs with a slight move to excellent according to the experts.

Apart from the specific ratings in the various size categories of industry a stronghold in a good to excellent worldwide position is claimed in science.

2.4 Recommendations by the Delphi panel

Trends, challenges and major gaps and barriers in the technological evolution which will lead to technological conclusions, have been identified by the Delphi panel and described in this document.

The Delphi panel for the field of Molecular Imaging/ Biophotonics/ Medical Imaging has expressed their opinion on reinforcing European endeavours in the field with regard to technological aspects are illustrated below.



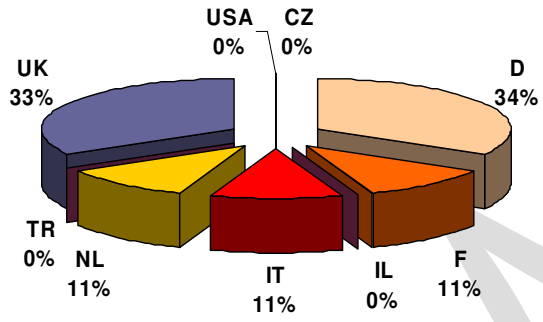
In addition the Delphi panel has expressed their opinion on the need to reinforce European endeavours in non-technological aspects.

3 ANNEXES

3.1 Statistics

Within the topic *molecular imaging/biophotonics* we asked 20 international experts from 9 countries. Moreover there were 32 experts pleased to participate without being related to a special topic in advance. Seven of them answered to our questionnaires, one of them within the topic *molecular imaging/ biophotonics.*

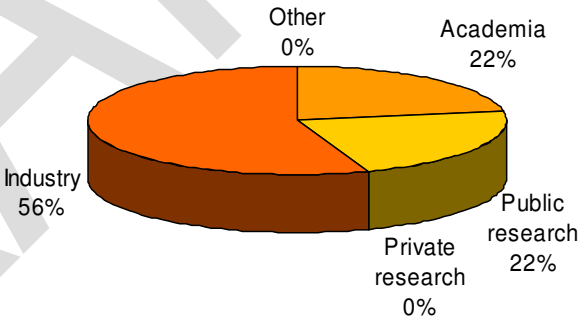
International spreading of the participants



Nine experts answered in total, the international distribution is shown in the following diagram:

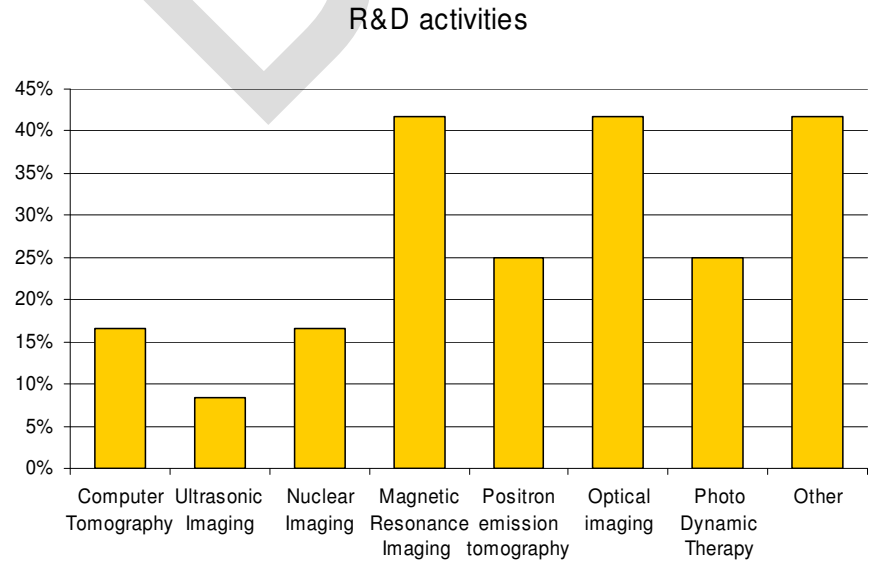
56.3 % of the invited experts responded to the two cycles of questionnaires. Of course, a statistical interpretation of the data of such a few participants is hardly to do. Nevertheless we tried to generalise some answers. The small amount of answering experts has yet to be kept in one's mind.

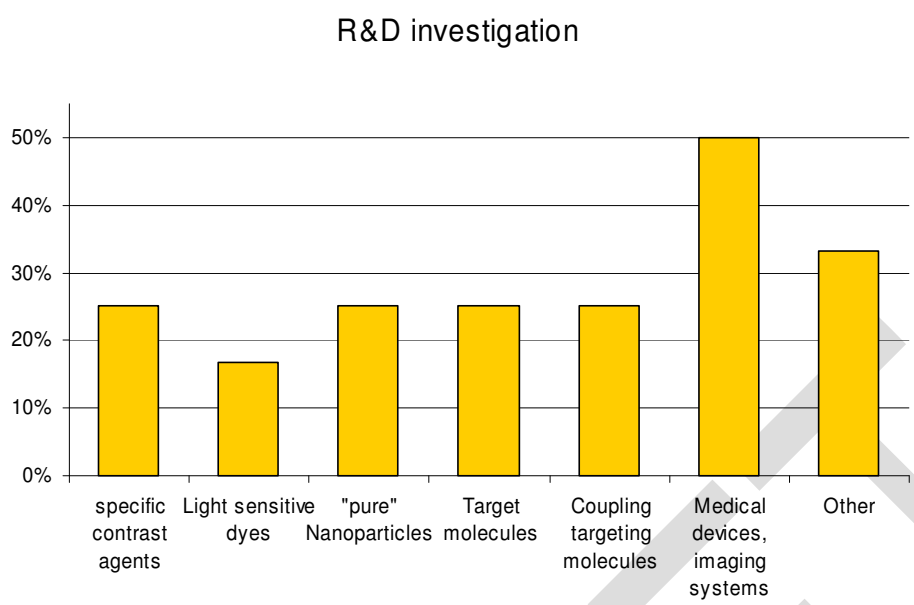
Organisation Type



The experts invited to participate were spread over universities, university research centres, public research organisations, private research organisations and industry. Nevertheless, more than half of the participants (56%) came from industry. 22% came from academia and another 22% from public research organisations.

The main focus of the experts who answered is in magnetic resonance imaging and optical imaging. Most of the experts are involved in several activities. In addition to the available topics these are fluorescence imaging; bio spectroscopy; single molecule fluorescence non-contact laser capture microdissection and downstream applications, drug delivery, activated nanoparticles by external field, optical coherence tomography; bioendo-



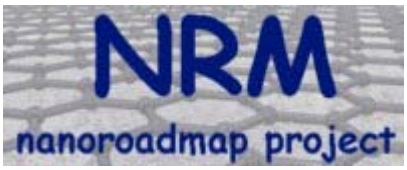


scopy, surface and nanoscale chemical characterisation. The investigation foci of the participants are more or less equally distributed among the available categories. Beneath those listed sectors there are further areas of investigation which are diagnostics, biopharmaceutical quality control, research activities in life sciences, environmentally responsive delivery platforms for imaging/ therapeutic delivery, surface chemical analysis at the nanoscale (either spatially or with depth); development of chemical characterisation of nanostructures inclusive nanoparticles and fibres as well as development of spectroscopic methods that do not require the use of molecular tagging.

3.2 List of participants

Fabio Beltram National Enterprise for NanoScience and Nanotech-nology Italy	**Mark Eccleston** University of Cambridge, New Museums Site, Department of Chemical Engineering United Kingdom	**Ian Gilmore** National Physical Laboratory Teddington (NPL) United Kingdom
Alex Knight National Physical Laboratory (NPL) United Kingdom	**Ruth Knüchel-Clarke** Medizinische Fakultät der RWTH-Aachen Germany	**Laurent Levy** Nanobiotix Prologue Biotech France
Ralf Raue Philips Medical Systems The Netherlands	**Tobias Schäffter** Philips Medical Systems Germany	**Karin Schütze** PALM Microlaser Technologies AG Germany

[1] Molecular imaging in living subjects: seeing fundamental biological processes in a new light, T.F. Massoud, S.S. Gambhir, Genes & Development, Vol. 17, No. 5, pp. 545-580, March 1, 2003
[2] Roadmap Report on Dendrimers, author W&W, July 2005
[3] The U.S. market for medical imaging contrast media, Report by BIO-TECH SYSTEMS, INC. Market Research in the Health Care Field, released July 2004.



NanoRoadMap is a project co-funded by the 6th Framework Programme of the EC

Nanotechnology in Health and Medical Systems

Draft Roadmap on

Biochips/ High Throughput Screening/Lab-on-a-chip devices

Partners:

AIRI/Nanotec IT

Willems & van den Wildenberg (ES/NL)

VDI/VDE (DE)

Institute of Nanotechnology (UK)

MATIMOP (IL)

Technology Centre (CZ)

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Date: July, 31 2005

Table of contents

1 Introduction

1.1 Background

The NanoRoadMap (NRM) project, co-funded by the European Commission (EC), is aimed at roadmapping nanotechnology related application fields in three different areas:

- Materials
- Health & Medical Systems
- Energy

Within the project, an international consortium consisting of eight partners covering eight European countries and Israel, has joined forces to cover the time-frame for technological development in this field up to 2015. The results of the NRM project are to be used by any European entity interested in planning an R&D strategy taking into account nanotechnology. An important potential user is of course the EC itself in the preparation of the 7th Framework Programme (FP7) for research and technology development. (For additional information on the NRM project, please refer to www.nanoroadmap.it).

1.2 Goals

The primary objective of NRM is to provide coherent scenarios and technology roadmaps that help the European players to optimise the positive impact of nanotechnology on society, giving the necessary knowledge on its future development and when technologies and applications will come into full fruition.

The key users of the reports are mainly European SMEs, research organisations, public bodies in general and the EC in particular. Even though a special focus is put on SMEs, these roadmaps are also meant to be useful for larger corporations.

This report is one of the three final deliverables of the NRM project and it is aimed at providing a thorough overview of specific topics selected for roadmapping within the field.

1.3 Methodology

Collection and synthesis of relevant existing information

In October 2004 three sectoral reports were published, each covering one of the above mentioned areas. They were based on the collection and synthesis of existing public sources in 31 countries and were published as key input for the celebration of the First NRM International Conference held in Rome the 4–5 November 2004. The full report can be downloaded from the project web site.

The report within the sector health and medical systems focused on reviewing the different aspects of nanotechnology in 11 topics, giving its definition, describing its most remarkable properties, current and future markets & applications, and leading countries & highlighted R&D activities in the field. A general review of non technological aspects (social, legal, ethical and health and safety aspects, but also economic aspects and infrastructure requirements) was also performed.

The 11 topics identified, even not being completely homogenous in terms of scope or classification, were intended to adequately cover the field of bionanotechnology.

The following list was agreed upon by the partners of the NRM project (similar classifications can be found in the bibliography):

- Tissue Engineering/Regenerative Medicine
- Bio Nano Structures
- Drug Encapsulation / Drug Delivery / Drug Targeting
- Molecular Imaging
- Biophotonics
- Biocompatible implants
- Biomimetic membranes
- Biomolecular sensors
- Biochips/HighThroughputScreening
- Lab-on-a-chip
- Functional Molecules: Switches, pumps, means of transportation

Selection of topics

Another major goal of that report was to set the basis for discussion and selection for roadmapping of 4 out of the 11 topics identified above. A preliminary selection of topics was presented during the First International Conference in November, 2004.

Within a frame of criteria agreed upon with the European Commission and after a thorough discussion, which involved international experts in the field of nanotechnology, four topics were selected (and validated in dialogue with the European Commission). The subjects were partly combined with each other, leading to the four chosen topics:

- Drug encapsulation/ drug delivery/ drug targeting
- Molecular Imaging/ Biophotonics
- Biochips/ High-Throughput Screening/ Lab-on-a-chip technology
- Biomolecular Sensors

Roadmap elaboration

One draft roadmap has been prepared for each of the four aforementioned topics. The result of these roadmaps will be presented in one international and eight national conferences in November and December 2005. Their preparation and execution is based upon a Delphi-like approach. The methodology consists of 2 cycles, which is the same for the four topics. The Delphi exercise consists of:

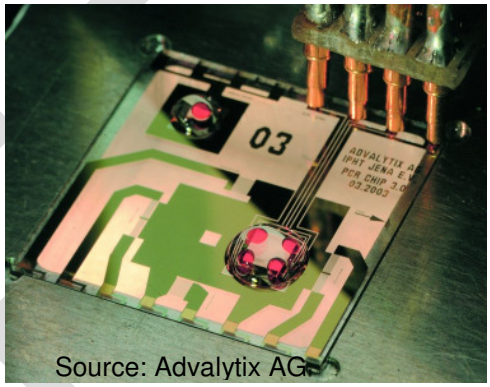
- Selecting top-international experts on the field
- Preparing a dedicated on-line questionnaire for each of the topics to be roadmapped
- Circulating the questionnaires and gathering experts' responses (1st cycle)
- Preparing a first summary of the answers received
- Circulating the summary and partly interpreted data, asking for feedback and reflection (2nd cycle). Interpretation was conducted in a way avoiding bias.
- Elaborating the roadmap taking into consideration aspects raised in the 2nd cycle

2 Biochips/ High Throughput Screening/ Lab-on-a-chip devices Roadmap

2.1 Introducing the subject

Biochips, broadly defined, are measurement devices, combining electronics and biology for research and diagnosis. They can hold and analyze very small amounts of biological material which are incorporated as biological recognition components. The preparations use both traditional techniques of microlithography and new microarraying (spotting and *in situ* synthesis) technologies.

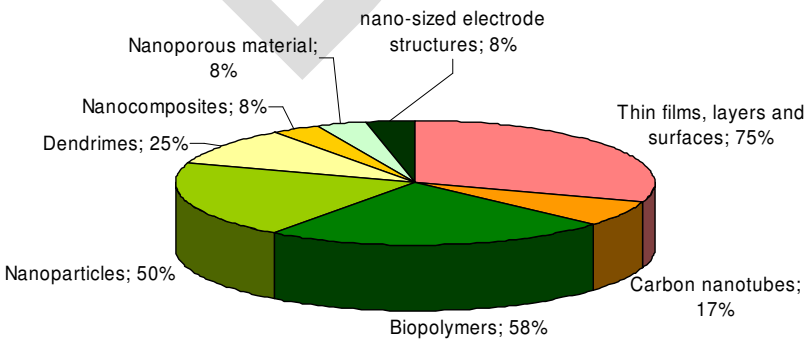
Chip technology has developed to a wide-spread method in biological and biomedical fundamental research and in pharmaceutical drug screening. By means of miniaturisation, automation and parallelisation an increase of performance of simultaneously measurable parameters is attainable which cannot be achieved by conventional serial biotechnological methods. New technical and methodical developments enable continuously advanced analyses, raise the reproducibility and permit the required quality assurances. Thus, chip based analysis systems are increasingly applied in clinical and diagnostic use like genotyping for mutational analysis or diagnostic of infectional diseases.



Source: Advalytix AG

The wide range of possible detection methods gives the biochip its tremendous diversity. Among these are electronic devices (such as field effect transistors), microelectromechanical systems (MEMS) devices such as cantilevers, simple metallic and semiconductor electrodes for electrochemical (amperometric, voltametric and impedimetric) detection, optical devices including fibres and fibre bundles (for absorption, fluorescence, luminescence and chemiluminescence), mass sensitive oscillating crystal devices, thermal detection methods that measure heats of recognition reactions, radio labelling and mass spectrometry.

Microarrays, principally DNA and proteins (although organelle, cellular and tissue microarrays are emerging), exploit an ordered, two-dimensional presentation of biorecognition entities, fluorescence or radio tagging of targets and scanning confocal or radio imaging of the recognition–target complex or product. The array of nucleic acids or proteins on solid surfaces of various platforms allow automated, rapid and parallel analyses of genes and gene products and thus make possible a whole new experimental approach in molecular biology.



Most of the presently used systems in biomedical research are not classified as nanobiotechnological devices since they neither have a nanoscaled structure nor is nanotechnology applied in their detection systems. However, there are several approaches to improve present chip platforms or to supplement distinct functions via nanotechnology.

In terms of the most appropriate types of nanotechnologies for their particular aims, the experts participating in our Delphi exercise named thin films, layers and surfaces, followed by biopolymers and nanoparticles to be the nanotechnologies mostly used in their devices. Dendrimers, carbon nanotubes, nanocomposites, nanoporous materials as well as nano-sized electrode structures are applied to a lesser degree.

Thin films, are deposited as one or more materials' layers with thicknesses below the order of 100 nm onto surfaces. The main advantage of thin films or of any other coating is that material properties can be transferred to the surface (thus enabling the use of not specialised substrates).

The most remarkable properties are of

- optical (light trapping, transmission, opaqueness, fluorescence, waveguides, "light valves", anti reflection, etc.),
- mechanical (wear/ abrasion resistance, hardness, scratch resistance, dry lubrication, reduced strain-to-failure, etc.),
- electrical (energy potentials, binding energies, conductivity, insulation, etc.),
- chemical (water repellence, anti-fogging, chemical barriers and chemical inertness, oxygen or moisture barriers over polymers, antimicrobial surfaces, etc.),
- magnetic (data storage) and
- thermal characters (application of multi-layered thin films allows, for instance, blocking the travel of atomic vibrations that produces heat flow whilst still letting the electrons flow as a current application in thermoelectric devices)[1].

Biopolymers are naturally occurring polymers that are formed during the growth cycles of all organisms; they are also referred to as natural polymers. Their synthesis generally involves enzyme-catalyzed, chain growth polymerization reactions, typically performed within cells by metabolic processes. They represent the most abundant organic compounds in the biosphere and constitute the largest fraction of cells. This diverse and versatile class of materials has potential applications in many sectors of the economy.

Nanoparticles are particles with a size up to 100 nm. They exhibit completely new or improved properties based on specific characteristics (size, distribution, morphology, phase, etc.), if compared with larger particles of the bulk material they are made of. Nanoparticles can be made of a wide range of materials, the most common being metal oxide ceramics, metals, silicates and non-oxide ceramics. Even though nanoparticles of other materials exist, e.g. those based on polymer materials or compound semiconductors, the former categories count for the most part of current applications[2].

Dendrimers are generally described as macromolecules, which are characterized by their highly branched 3D structure which provides a high degree of surface functionality and versatility. Dendrimers can be made out of virtually anything that can branch (metal atoms, organometallic groups, or purely organic materials) and they can have a variety of functionalities depending on the application[3].

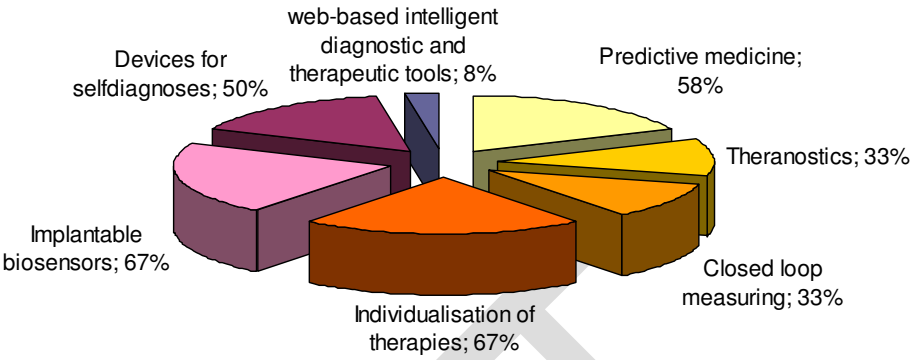
Nanocomposites enclose a large variety of systems such as one-dimensional, two-dimensional, three-dimensional and amorphous materials, made of dissimilar components and mixed at the nanometer scale which results in e.g. improved mechanical, electrical and optical properties which can be applied in various products.

2.2 Scientific and Technological Aspects

Trends & needs during the next decade

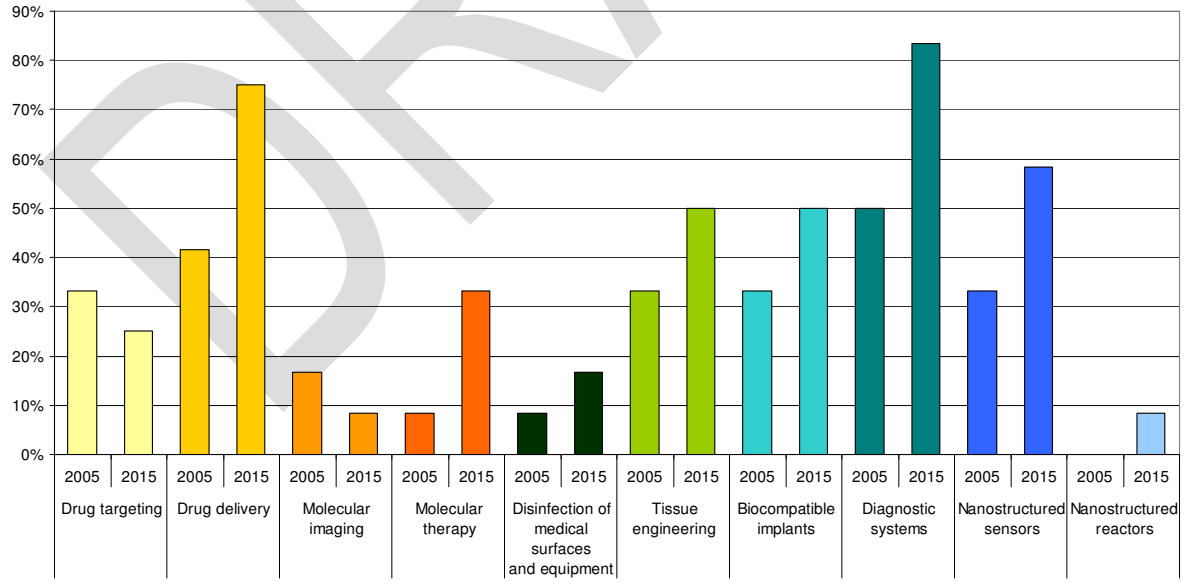
Up to now, microarray technology has been most valued in the basic research arena as a hypothesis generating technique. Studies using microarrays have served to advance understanding of the disease process. With the evolving technology, it will become a tool for clinical medicine, providing a

rich source of information on disease susceptibility, diagnosis and prognosis. This is reflected in the experts' estimations according to which more future emphasis has to be put in implantable biosensors and the individualisation of therapies, followed by a more predictive medicine. 16 % of the participants demand more devices for self diagnoses which will increasingly put the patients in charge of their own health and which probably will relieve health care systems. Only 11 % of the experts are of the opinion that theranostics, as an integrated diagnose and therapy, will be of added future benefit. These results differ slighty from those for the drug delivery and molecular imaging sectors which participants (20 %) expect a further emphasis in theranostics, whereas only 11 % expect a future stress on predictive medicine.



"Future medical practice will need more...." Estimations of the experts within the biochips field

Nanotechnology is expected to be critical in supplying the mentioned demands. 83 % of the involved experts suppose nanotechnology to be unique in providing biochips with the properties which are needed for their more efficient use. This influence is stated to be obvious for example in nanostructuration, which will offer novel ways to structure and coat surfaces, and produce building blocks for small devices as well as nanoscale optics to allow the study of individual and collective properties of luminescent particles (e.g. molecules, quantum particles). Furthermore, nanomaterials hold promises



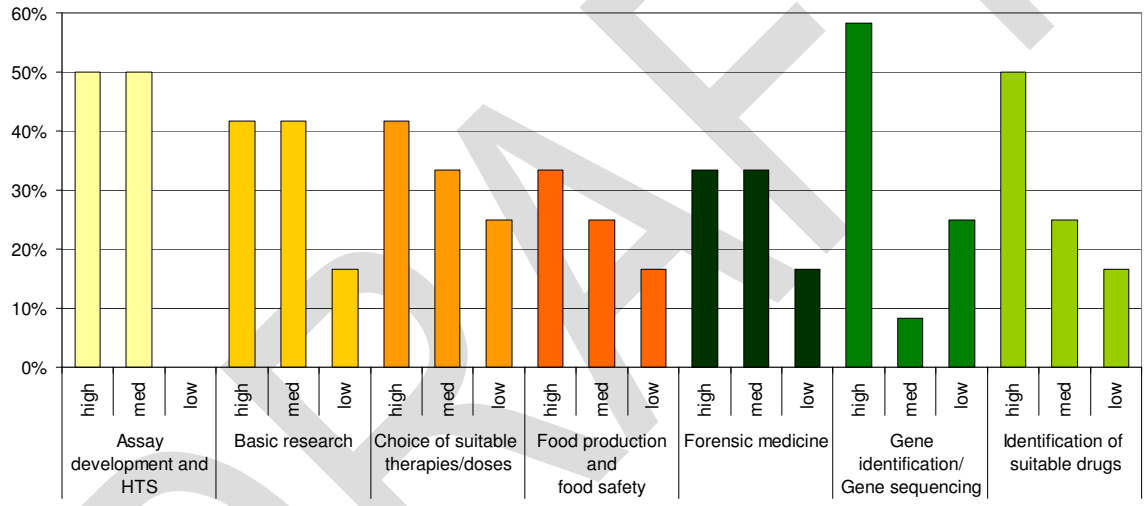
The most important applications of nanotechnology in the medical sector

for improving the use of materials by tailoring them to desired mechanical, electrical, magnetic or optical properties. This leads to novel applications, with a positive environmental impact and cost-reduced processes.

In general, the experts within the biochip sector state the main nanotechnological applications within the next decade to be in drug delivery and in diagnostic systems. Nanostructured sensors, which should be included in diagnostic systems are also expected to offer benefits of nanotechnology within the next 10 years as well as biocompatible implants, tissue engineering, molecular therapy and the disinfection of medical surfaces and equipment, but to different degrees. Interestingly molecular imaging is expected to be of less importance in 2015, probably taking a back seat compared to molecular therapy, which includes the maturity of molecular imaging. Nanostructured reactors are further nanotechnological application areas, stated by few experts which could be understood as reflection of the increasing complexity of lab-on-a-chip devices, improved by nanotechnology.

Impact of nanotechnology in the field considered

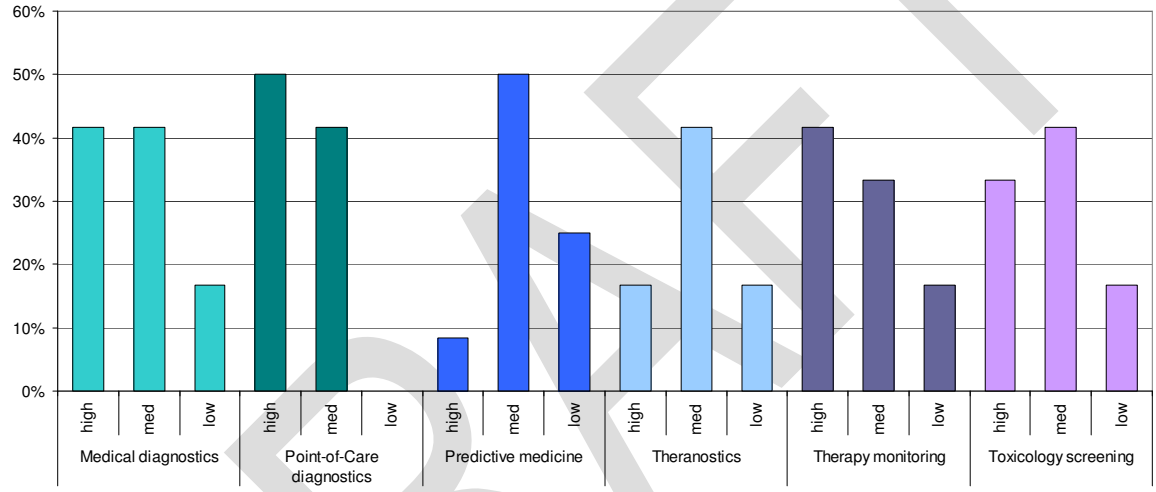
The experts' ranking regarding the impact of nanotechnology in several subjects within the diagnostic and partly the therapeutic sector is rather heterogeneous, probably due to the complexity of the particular applications and the various possibilities for nanotechnological tools to affect on them or to the "youth" of nanotechnology which makes it difficult to identify the various impact opportunities.



A high impact is expected in **gene identification** and **gene sequencing** on the one hand with both DNA microarrays and better imaging tools and on the other hand through miniaturization and more sensitive, selective and accurate sensors. Furthermore it is expected that new nanoenabled devices will eliminate the need for PCR in DNA analysis and will decrease cost and errors. In the **identification of suitable drugs** the expected nanotechnological impact is also rather high and is expected to enable the development of new sensor arrays. Nanotechnology is supposed to affect the **assay development** and **High-Throughput Screening** through further miniaturisation. In this way new assays will be generated for disease profiling and discovery. With wide spread DNA Microarrays, the miniaturization of invasive diagnostics and coating of the invasive agents as well as new methodologies, nanotechnology will benefit basic research to a high to medium degree. In the **choice of suitable therapies and doses** nanotechnology will both provide and help to evaluate insights into disease profiles and characteristics. The nanotechnological impact on **food production and safety** will depend on the applications, according to the experts. Smart food is expected to be investigated (e.g. with nanosensors for the quality and freshness). Food production is expected to become highly effective and functional. Also in forensic medicine an impact is assumed which will happen through miniaturisation. In addition, more sensitive, selective and accurate sensors will be obtainable.

In **medical diagnostics** the impact is expected to be high to medium sized which will be of basic benefit especially for cancer and genetic diseases. Nanotechnology will improve quality and yield of biochips and smart biosensor arrays will be integrated into ambient systems.

The same properties are needed in **Point-of-Care diagnostics** which will benefit as well from nanotechnology. This is supposed to affect this application in a high to medium manner. Low cost DNA screening, enabled through nanotechnology to a great extend, is supposed to be possible soon and will enlarge and enhance **predictive medicine**. **Theranostics** will benefit from nanotechnology by the increasing possibility to link smart biosensors with decision assisting and drug delivery therapy. Miniaturization of invasive diagnostics and coating of the invasive agent will affect therapy monitoring. **Toxicology screening** will profit by nanotechnology because sensor devices will be much better than today. Another application which will benefit by nanotechnology was mentioned to be **Chemical reactor technology.**

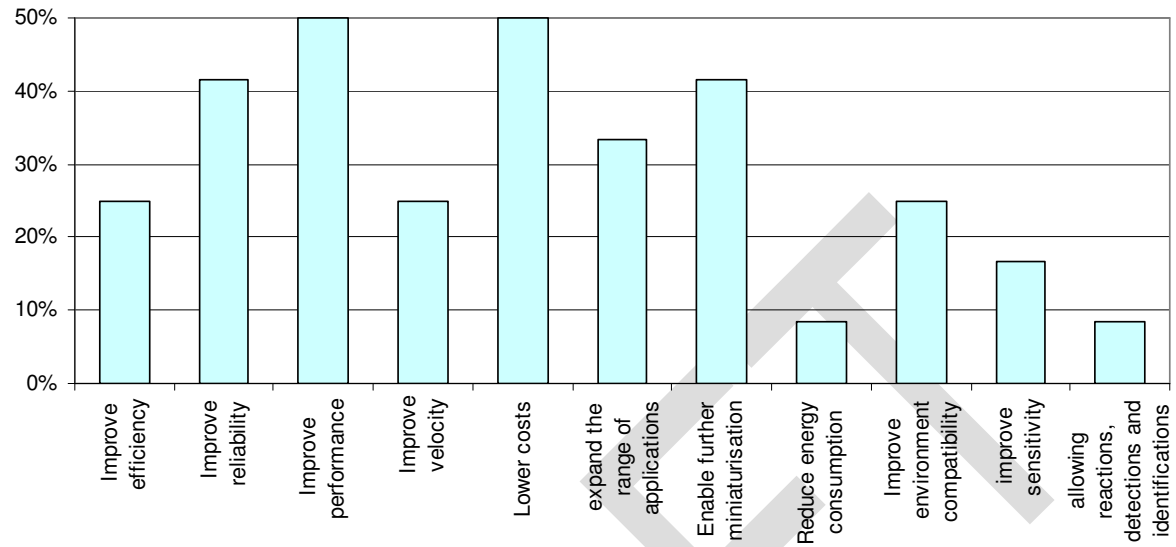


Advantages of nanotechnology over existing/alternative technologies

The most exciting prospect of nanotechnology in biochips compared to existing or alternative technologies is its ability to lower costs, according to the experts. The ability to improve device performance, efficiency and reliability as well as to enable further miniaturisation and to expand the range of applications are further important properties. Other properties mentioned include the ability to enhance sensitivity, improve equipment compatibility, reduce energy consumption and allow reactions, detections and identifications not otherwise available.

These qualities will lead to improved biochip devices, such as lab-on-a-chip, i.e. bio-smart molecular scale devices with built-in nano-optical, mechanical and electronic intelligence. New nanomaterials, among them programmable adaptive protein-based materials, will form the base for new forms of catalysis, energy storage, energy conversion and biomolecule detection which will be integrated into highly miniaturised diagnostic systems. The use of nanotechnology will enable totally new production processes for chip devices with integrated bottom-up assembly of structures at a molecular level.

The most revolutionary property of nanotechnology in biochips/ lab-on-a-chip devices compared to existing/alternative technologies is its ability to



Technology evolution

Nanotechnology provides a wide range of new technologies that will optimize biochip devices. Since it is a technology in its very early stage, the technological evolution is hard to characterise or to predict.

Biochips began as high-end, expensive products aimed exclusively at genetic research and pharmaceutical development. Until now they are typically glass slides with biological material printed on them and they cost upwards of US $1.000. The equipment, reading such slides are expensive too. One slide can hold tens of thousands of DNA test strands, and some even contain the entire human genome or the entire genome of showcase organisms (like the rat). The high costs of existing devices due to the predominant oversupply of chip content and cost intensive production result in the need for cheaper chips with broader applications. The implementation of this goal is furthered by the steadily proceeded technology evolution which allows e.g. for new materials, new detection devices, new production processes, and which increases the knowledge about biological and technical cohesions.

Beneath the genetic research and pharmaceutical development market, two other areas in the health secor are evolving, one of them being the point-of-care market, in which companies are developing simple, low-cost blood screening tests e.g. for certain toxins or even for specific proteins that indicate acute diseases. They can be used in hospitals and perhaps later in local medical centres. The second is the clinical diagnostics market. Chips for this market also speed up diagnosis of disease, but the testing is done in a clinical lab rather than in a hospital emergency room. Those chips can speed up the diagnosis and make them more specific with a lot of added values for the patient, beginning with a greater individualisation and ending with more specificity, efficiency and the shortened stay in hospital.

A third market is just beginning to emerge as well: the "point of need" market, in which biochips could be used for an easy and rapid detection of toxins or diseases, such as the bird flu, in shipments arriving at a country's borders.

Trends, challenges and discontinuities

A key challenge to the biochip industry is standardisation of the assays themselves and also of the ancillary instrumentation, so that they can be used and their data interpreted in the same way by all users. This is particularly important when genetic diagnostic applications are at stake, because important clinical decisions are to be based on the interpretation of gene chip readouts, and these results need to be independent of the biochip manufacturer.

Due to its unique properties, nanotechnology is expected to revolutionise the medical, especially the diagnostic and therapeutic sector. Nevertheless the technology is still at its early stage and there are huge challenges to meet.

We asked the experts to identify the major nanotechnological challenges in biochip development which are listed in the following table:

The major challenges of biochip technologies within the next 10 years	**How is nanotechnology to help realising those trends?**
The hardware technological background is sound but the biological components need further studies to improve stability, reproducibility and performance related to the specific needs.	Funding on fundamental aspects of nanotechnology without a clear commercial target, is vital.
The handling and delivery of the samples and the interfacing of the nano sensor with the macroworld	Nanofluidics is being pursued but with little hope; better hope offers in situ diagnostics but it will require longer times; the whole field of nanoanalytical chemistry has to go through a progress towards maturity phase similar to that that followed the move towards microanalysis that happened in the sixties
Finding a cheap way of producing them and at the same time improving their quality, in terms of density and chip to chip reproducibility	Novel production methods, better density, better characterisation tools, chip-to-chip reproducibility, better characterisation and imaging tools
Solving standardisation and reproducibility problems impeding medical diagnostic applications	Providing inexpensive high throughput solutions
1) To ensure a quality control technology as required by the regulatory bodies for diagnostics, 2) To bring down costs and increase throughput to reach the status quo of today's analyzers	1) Production technologies for spotted arrays that give yields close to 100%, 2) Miniaturization and parallel processing
Long term stability of the biologic components	Chemically well defined surfaces, interdisciplinary work of material scientists and biologists
Reliable and cost-effective large scale production of robust devices utilization of self-assembly techniques in fabrication reimbursement through health care systems	Self-assembly techniques will help to lower the fabrication costs, particularly of nano-structured devices, which would otherwise require expensive equipment and labours assembly. Cost is particularly critical where diagnostics applications are concerned. Nanotechnology can bring about potential advantages with respect to sensitivity and selectivity of detection.

The major challenges of biochip technologies within the next 10 years	How is nanotechnology to help realising those trends?
Will be driven by applications	
Highly sensitive, selective biosensors, systems integration: how to integrate the different enabling components, Costs: lower the manufacture cost solutions that then become affordable to the wider community.	Mainly from the sensor point of view with regards to improvement in sensitivity and selectivity via new functionalised nano-bio interfaces.
Development of cell-based biochips	Realisation of cell compatible surfaces and realisation of tools for cell manipulation and characterization

Time-to-market

To learn more about the marketability of special nanotechnology driven applications and the expected time to market for such applications within the medical sector the experts were asked to evaluate the stage of maturity of specific technical challenges of biochips in the diagnostic area.

The results which are shown in the following diagram reflect the relative importance of the particular nanoparticle properties and their implementation in applications within the next decade predicted in five years from now (2010) and in ten years from now (2015) and give an integrated view of the various stage of development of the applications.

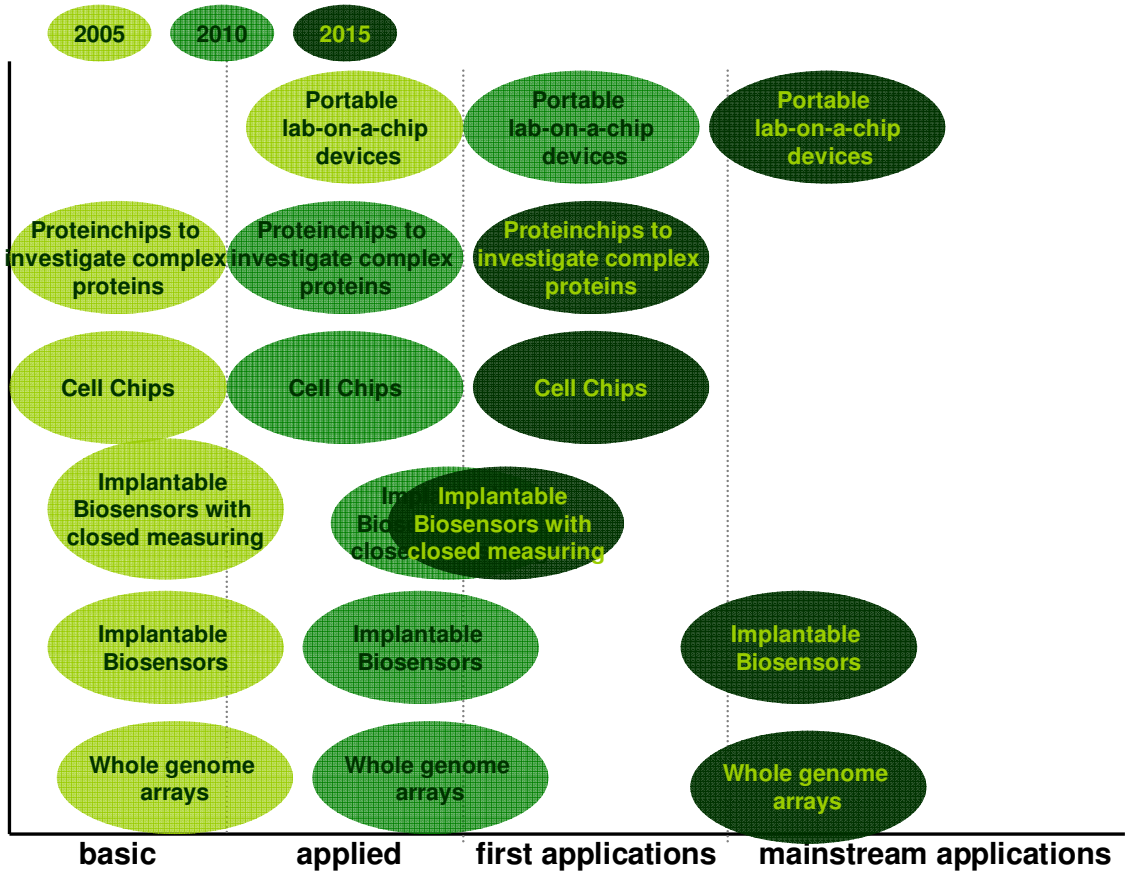
The generic distinctions in the graph chosen for the sequential phases in the innovation cycle have been taken as follows:

Basic Research & Development Phase (**basic**): Applications in this phase have received the interest of one or more researchers in the world. Some applications might still be in early development, while other are tough to develop and need a lot of basic research to be fully understood. The object of basic R&D is to validate the original hypothesis. Many applications are currently in this phase as researchers are still struggling to understand basic properties of nano-material.

Applied Research & Development Phase (**applied**): After the hypothesis is validated, research typically (but not necessarily) moves from pure research labs to more commercial labs and companies. Applied R&D will eventually result in a proof of concept, a successful demonstration model. While the production issues might not have been solved yet, a successful prototype/model has been validated.

Product Research & Development Phase (**first applications**): After first demonstrator models and prototypes, initial, usually prohibitively expensive, small numbers of products may be produced. If these prove successful, companies will seek to enhance production to gain market share. Generally at some point, demand increases sufficiently to offset the investment needed to start production. This phase ends at a point when feasibility has been proven and production is to start.

Production level and incremental research (**mainstream applications**): The final development phase, when production has reached significant numbers and research focuses on incrementally improving the products.



According to this there are three mainstream applications in 2015, being sophisticated portable lab-on-a-chip devices, implantable biosensors and effective and cheap whole genome arrays. Whereas the development of portable lab-on-a-chip devices is expected to proceed in a linear manner, the progression in implantable sensors and whole genome arrays is supposed to take discontinuous courses which were not explained further. This result indicates the huge estimations which are coupled to nanotechnology in the particular applications.

On the other hand implantable biosensors with close-loop measuring are assumed to remain in a medium state of development after 2010.

Gaps and barriers

Biochips are applied in several research areas like cytology, evolutionary biology, pharmacology, toxicology or molecular diagnostics. Accuracy and reliability are crucial for the analysis of biological parameters. These depend to a critical degree on the chip platform design. Thus, technical barriers have to be overcome.

	Thin films, layers and surfaces	Carbon nanotubes	Nanoparticles	Biopolymers	Dendrimers
Technical	X	X	X	X	X
Economic	X	X	X	X	X
Infrastructural	X		X	X	X
Environmental impact			X	X	X
Ethical concerns			X	X	X

The barriers which are expected in connection with special kinds of nanotechnologies are predominantly of technological and economic character. The experts who answered within the drug encapsulation sector stated general barriers, which apply to the biochip field, especially in thin films, layers, and surfaces. These are analytical methods that can provide chemical (molecular) characterisation at the nanoscale which have to be urgently developed. The barriers specified by the experts within the biochip sector to occur in various kinds of nanotechnologies are listed in the table shown to the left.

The specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in the table below:

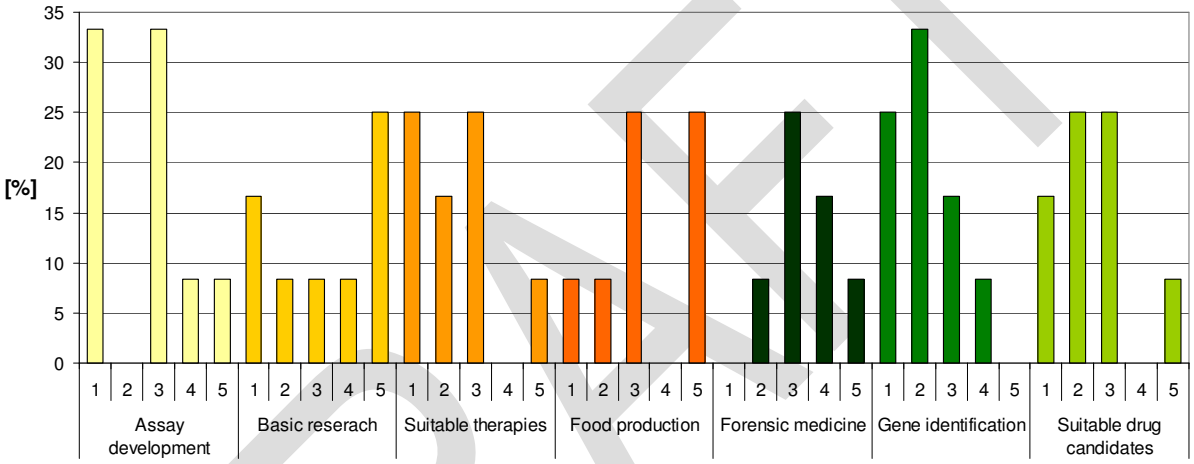
Barriers to success	**Technical**	**Economic**	**Infrastructural**	**Environmental impact**
Thin films, layers and surfaces	By nanofabrication within five years	Lower cost and improve quality of thin films	Education of interdisciplinary researchers, in many years	
	Durability, and reproducibility. These barriers will be overcome when more reliable characterisation tools will be in place.			
	Lack of adequate physical description			
	Lateral resolution of analytics on nanoscale have to be developed			

	Compatibility to application must be improved			
	Expensive equipment	Embryonic market, urgent need for appropriate applications		
Biopolymers	Design and synthesis of functionalised nanoparticles	Cost effective production	Facilities and procedures required for volume manufacturing	Toxicity and biodegradability issues must be investigated
	Compatibility to application must be improved		Interdisciplinary education is needed but it may take many years	
	Identify biopolymers for coating compatible with the desired assay			
	Biocompatibility	Relatively expensive, pure material is often not available in EU		
Carbon nanotubes	Lack of proper reproducibility for industrial production			
Nanoparticles	Quantity production will take more than 10 years			
	Compatibility to application must be improved			Data for the effects on environment is required
	Limited knowledge on reaction kinetics at production			
Dendrimers	Not further specified			

Most present and future relevant applications of nano-related products

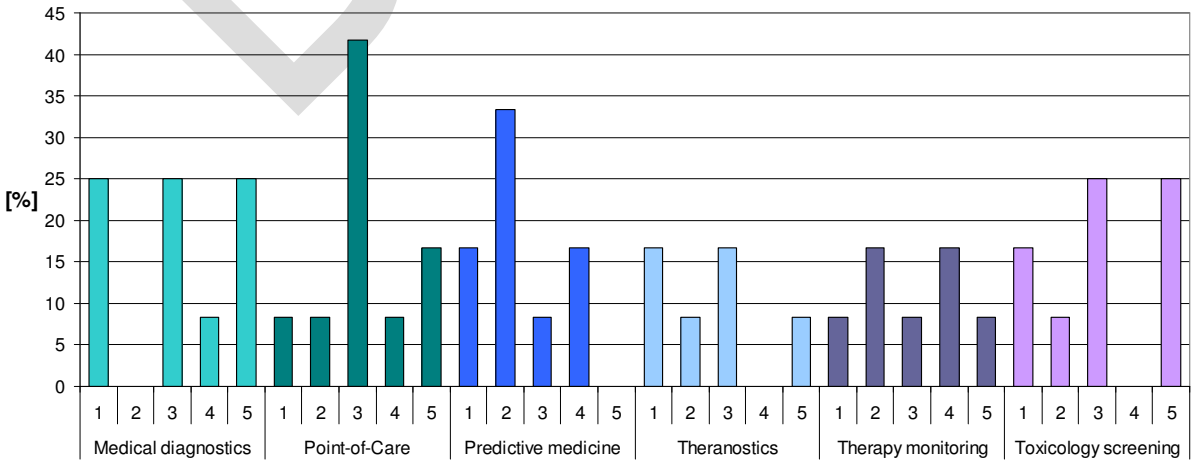
Due to the unique properties that can be achieved by the combination of nanotechnology and biochip technology, especially the high potential for lowering costs and improve the device performances, the experts assume the probability that nanotechnology will play an important role in biochip applications to be high (33%) or very high (50%). Some of the experts stated that nanotechnology is the most appropriate and promising enabling technology. Defined surface functions are essential for biochip applications which can be achieved by nanotechnology.

Regarding the expected impact of nanotechnology the experts were asked to give a ranking upon the impact of nanotechnology in distinct diagnostic topics in which biochip devices also will play a more or less important role with "1" mapping a huge and "5" a rather negligible impact.



Ranking of nanotechnologies in distinct diagnostic topics

The results are rather heterogeneous, possibly due to the low total number of participants whose expertise did not reflect the whole range of shown applications in detail or to the fact that most of the experts were not familiar with this type of "ranking". Thus, they should be interpreted with caution. The nanotechnological impact is supposed to be medium to high in assay development, the search for



Ranking of nanotechnologies in distinct diagnostic topics

suitable therapies, gene identification, the choice of suitable drug candidates and predictive medicine. It is assumed to be rather medium to low in basic research, which is probably a too expanded field, in food production and in toxicology screening.

Among the topics mentioned there are several products including **nanobiosensors** which will couple nanostructures with biomaterials such as enzymes, DNA, receptors and antibodies. Another example for definite applications are **nanoelectrodes** for sensitive measurements of very small amounts of important molecules such as neurotransmitters, carbohydrates, pollutants, and proteins which will be incorporated into "lab-on-chip devices", capable of performing reactions, separation and detection.

2.3 Non-technological aspects

Market trends for each application

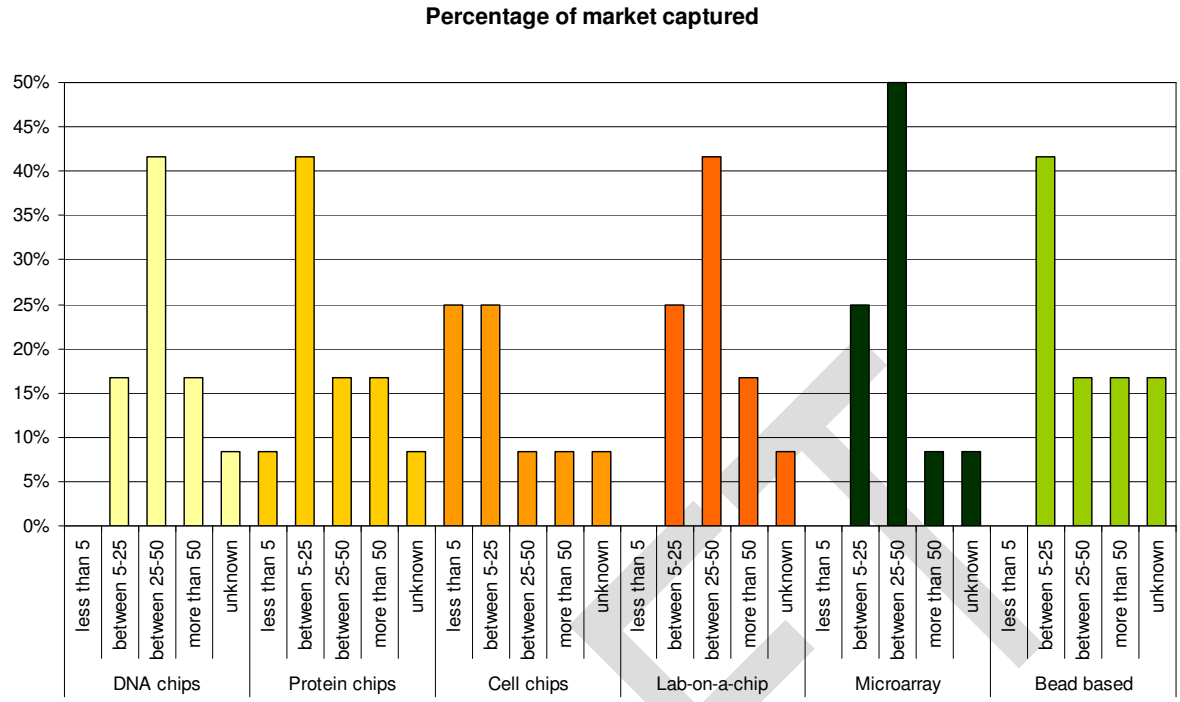
Although the biochip development may have started as a high-end market for elite researchers, most of the biochip companies are concentrating on the faster-growing point-of-care, clinical diagnostics and the above mentioned point-of-need markets. The potential for increased efficiency, lower cost and faster response time is driving the growth in these markets.

The biochip market is very fluid, making it difficult to put companies into neat categories and to give long lasting estimates about the growth rate. Thus, several ratings of the expected market development can be found. They all have one thing in common: the need for biochips certainly leading to an increase of the market size in the following decade. Only the magnitude differs between the particular forecasts. Not only do different companies define the market differently but they also use a variety of manufacturing and technology approaches in their products.

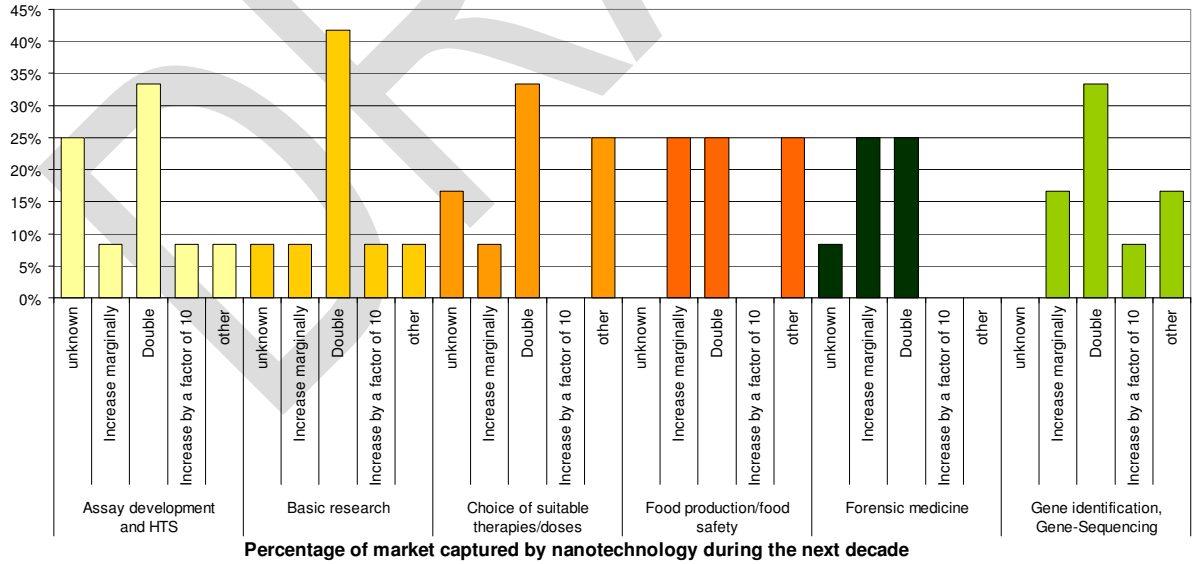
According to BCC, the total market for DNA microarrays and materials is rising at an average annual growth rate of 13.4% and is expected to just exceed $1 billion in 2007. By 2007, the total revenues of protein array technologies will approach $336 million[4].

There are several studies on market potentials of DNA chips. They range in the same order of magnitude, exhibiting quite similar future growth rates. Due to a study by BCC, the world market for DNA chips amounted to $ 150 million in 1999 and is forecasted to attain total revenues of $ 745 million[5]. This data is approved by a study by Freedonia [2002]. Revenues, achieved with peripheral equipment are much higher, in 2006 they are expected to amount to about $ 1 billion. Due to their importance in drug research, protein chips are expected to become tools of outstanding impact for the pharmaceutical industry. The market for protein chips was expected in 2002 to amount $ 700 million by 2006[6], the same group corrected the expectations in 2003 down to a total annual revenue of $ 400 million after depressed revenues within this sector in recent years. In the long run protein chips are expected to attain much higher total revenues than DNA-chips. Due to a market analysis of the Freedonia group [2002] total revenues, achieved by Lab-on-a-chip devices will amount to around $ 160 million in 2006.

To get a more specific view of the market, the experts were asked to appoint their estimation about which percentage of the market will be captured by nanotechnology in several categories in 2015. In microarray technology there were main accordances between the experts who suppose it to be 5 to 25 %. Lab-on-a-chip devices and DNA-chips are expected to be affected to the same degree, whereas the assumed proportion in proteinchips and bead based chips is 5 to 25% and in cell chips less than 5 up to 25 %.

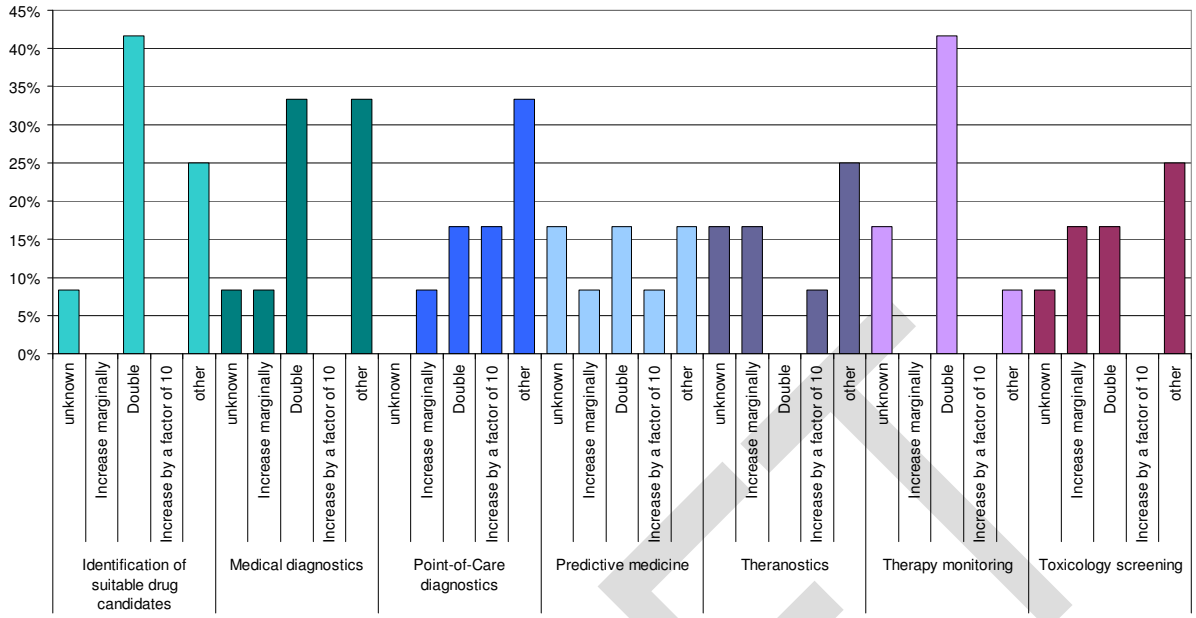


Most of the experts estimated the percentage of market which will be captured by nanotechnology to double in assay development, basic research, choice of suitable therapies and doses, gene identification, identification of suitable drug candidates, and therapy monitoring during the next decade. Not all of the experts responded to this question, several participants assumed the nanotechnological market in the particular fields to develop to an "other" degree. Unfortunately they did not quantify their votes rendering them without usable conclusion.



Percentage of market captured by nanotechnology during the next decade

In fact, the data reflect the difficulty to size the market, especially for distinct applications and the results show that the nanotechnological impact is expected to increase.



Percentage of market captured by nanotechnology during the next decade

Infrastructure requirements

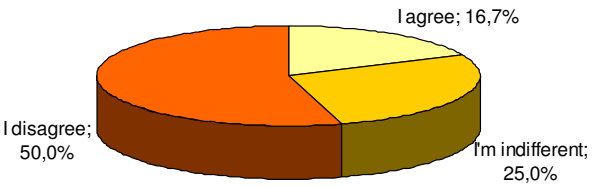
Half of the experts state that the instrumentation costs for the manufacturing, characterisation and manipulation of nanotechnologies in their application areas in biochip (HTS/ Lab-on-a-chip technologies) increase steadily, whereas 25 % deny this. About 17 % seem not to be affected by this because they were indifferent on that subject. About 92 % of the participants state that they do not have any problems in finding nanotechnological solutions to satisfy their R&D and/or manufacturing needs in biochips/ lab-on-a-chip devices.

According to the experts most important for growth and prosperity of European nanotechnology is a higher governmental support followed by a higher interaction between industry and academia facilitating an effective technology transfer. Proper taxation is needed to promote venture capital and private equity investments. Some experts from the other sections (drug encapsulation and molecular imaging) gave explanations to their choice. According to this, “not enough scientific technical experts are included in the discussion and strategic decision making process in their topics and many of the EU and National committees have failed to engage world leading European scientists and committee members. If the hype and over marketing of this field progresses without engaging the academic and industrial technical expertise in the EU (which in many sectors is high) an opportunity will be missed to world lead in specific aspects of this sector”. Furthermore support for late development (prototyping) and cross laboratory trials is needed.

Educational requirements

According to the experts, the educational system is poorly adapted and has to be changed. Furthermore more and real interdisciplinary is needed. Up to them the issue needs more public dissemination and debate. One expert made demands on less bookish learning and more lab teaching as well as more applied interdisciplinary.

"Nanotechnology suffers from the problems that other interdisciplinary research areas face. Thus, most important for the growth and prosperity of European nanotechnology is a higher interaction between industry and academia facilitating an effective technology transfer and to turn nanoscience into nanotechnology. There is a need for focussing and multidisciplinary education. The notion that nanotechnology is completely new, divorcing from historical efforts in chemistry, biology and physics, is a mistake according to the experts. The new "nano" requirements should be more clearly defined and then transferred into appropriate course design and curricula at the basic science medical and clinical interface"[7].



Educational offer is adequate

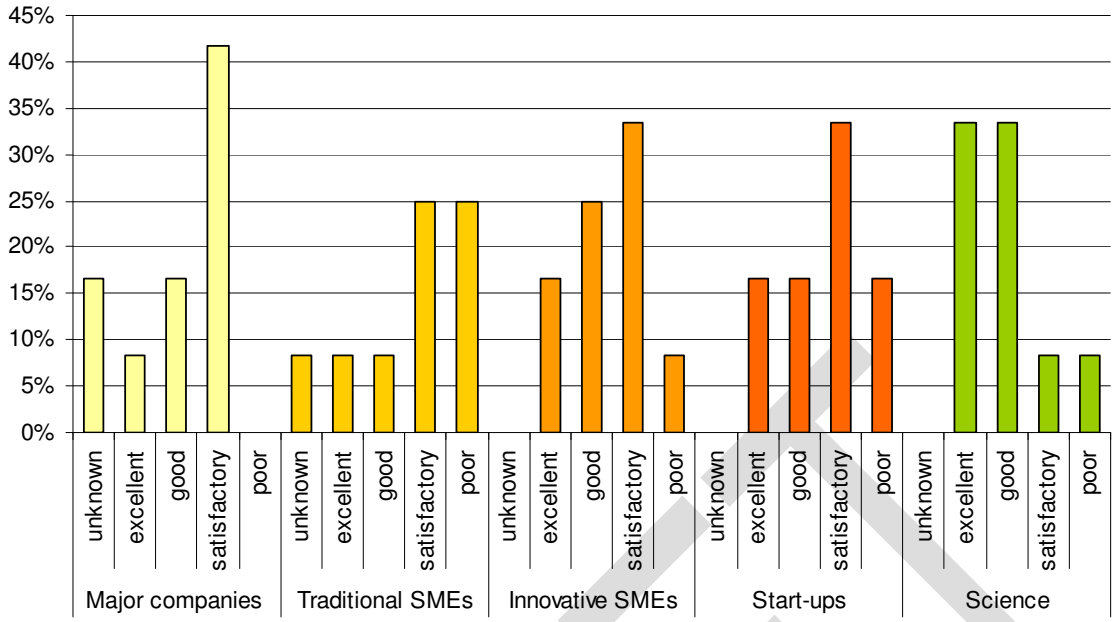
HSE issues

Although about 60 % of the participants negated a potentially HSE hazard raised by nanotechnological processes being involved in their products, 83 % of them favour HSE impact studies on certain types of functionalised nanomaterials. In this aspect safety relates to the proposed chemistry and the proposed use. According to the experts from drug delivery discussion of the safety of nanoparticles and nano tubes per se is not helpful without addressing the more specific points. Safety should relate to environmental exposure, manufacturing exposure, as well as any proposed clinical use.

European competitive position

Biochips are a broad technology platform that consists of the miniaturization of a variety of biological processes and their deposition onto computer chip-like substrates for automated, high throughput analysis. They promise to revolutionize genetic diagnostics, because of their reproducibility, low cost and speed. They also promise to open new areas of drug screening development once proteins and other non-DNA molecules are successfully deposited, and their reactions read by detectors, onto chips. The field already attains actual sales of products, and it represents a robust technology with a significant business future.

The graph illustrates the experts view on this business future and in particular of the competitive position of Europe in comparison to the global situation. It is stated as being mainly satisfactory in all size categories of industry. Within the traditional SMEs the position is stated as being equally poor and satisfactory. Innovative SMEs are rated excellent to a higher degree and poor to a lesser degree. Start-up companies do gain a firmer rating in excellent and good compared to traditional SMEs according to the experts.

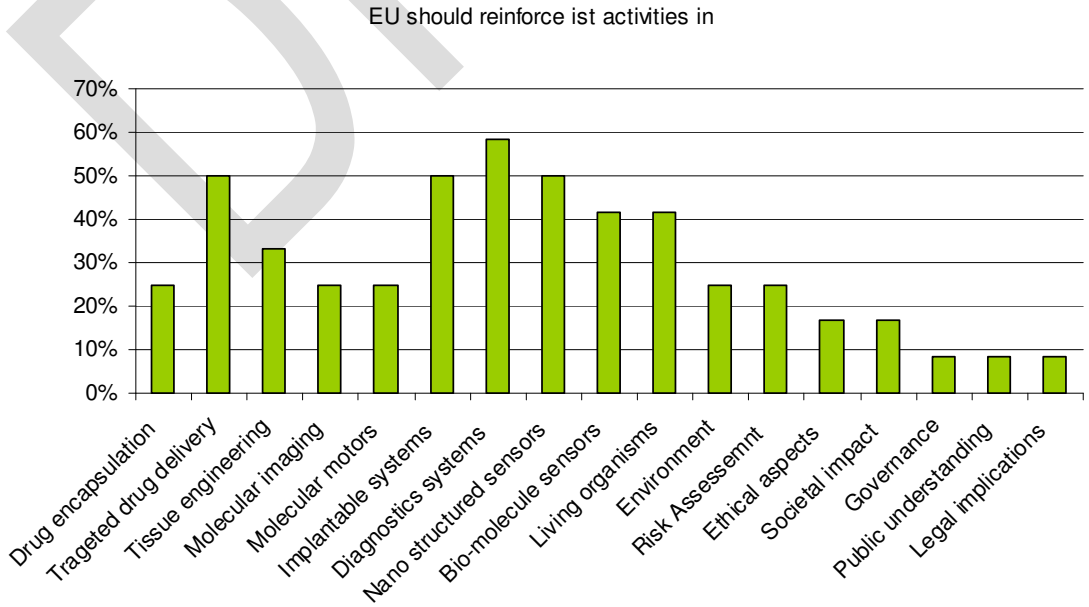


Apart from the specific ratings in the various size categories of industry a stronghold in an *excellent* and *good* worldwide position is claimed in science.

2.4 Recommendations by the Delphi panel

Trends, challenges and major gaps and barriers in the technological evolution which will lead to technological conclusions, have been identified by the Delphi panel and described in this document.

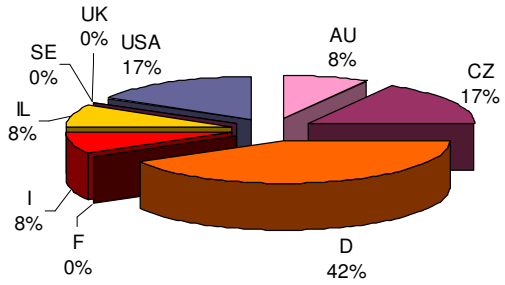
The Delphi panel for the field of Biochips/ High Throughput Screening/ Lab-on-a-chip devices has expressed their opinion on reinforcing European endeavours in the field illustrated below.



3 ANNEXES

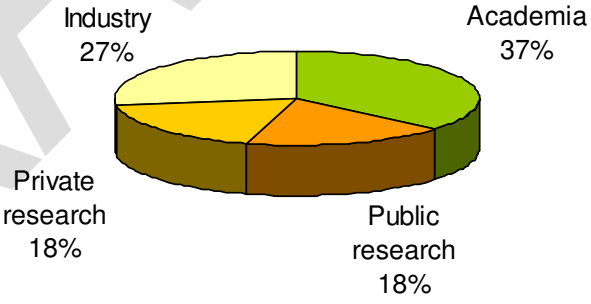
3.1 Statistics

In the biochips/ HTS/ lab-on-a chip topic we asked 24 international experts from 8 different countries to give their input in this emerging field of nanotechnology. Moreover there were 32 experts pleased to participate without being related to a special topic in advance. Seven of them answered, one of them within the biochips topic. 56.3 % of the invited experts responded to the two cycles of questionnaires. The experts invited to participate were spread over universities, university research centres, public research organisations, private research organisations and industry. Nevertheless, almost half of the participants (52%) came from academia. 24% came from industry, 16% from public research organisations and 8% from private research organisations. Most of the participants (83%) are engaged in biochips, about 50% deal with sensors. (Multiple choices were allowed in this question). The R&D foci of the experts are the investigation of biochip technology platforms (83.3%), as well as likewise the peripheral biochip devices (detection etc.), nanotechnology to improve biochip properties and surface modification / functionalising (50 % each). Nanoparticles as biochip tools (42 %) and the biochip content is in the responsibility of about one third of the experts. Some experts deal with “pure” biochips and with bioinformatics, as well as nanoparticles as catalysators for chemical reactions.

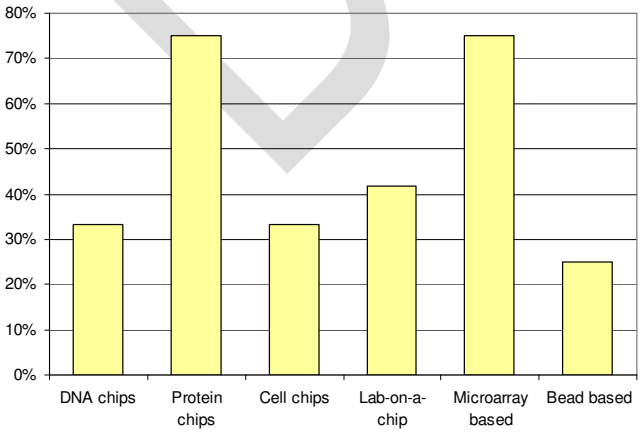


International spreading of the participants within the biochip sector

Organisation type



Kind of biochips the participants are working with?

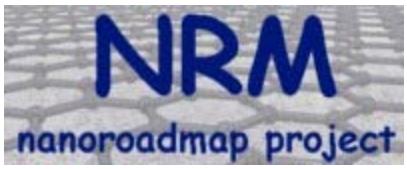


Most of the experts work with protein chips in a microarray based form (about 75% each). 40 % deal with Lab-on-a chip devices, about 30% are familiar with cell chips and DNA chips and about 25% with beat based devices.

3.2 List of participants

Andrew Campitelli MiniFAB, Pty Ltd, Bio Micro Nano Technology Austria	**Darvas Ferenc** THALES Nanotechnology Ltd. Czech Republic	**Christoph Gauer** Advalytix AG Germany
Gianfranco Gilardi Dipartimento Biologia Animale e dell'Uomo Italy	**Thomas Joos** NMI Natural and Medical Sciences Institute at the University of Tuebingen Germany	**Christian Oehr** FhG IGB Germany
Giacinto Scoles Princeton University USA	**Francesco Stellacci** Department of Materials Science and Engineering, MIT USA	**Martin Stelzle** NMI Natural and Medical Sciences Institute at the University of Tuebingen Germany
Dalibor Štys Academic&University Centre, University of South Bohemia Czech Republic	**Hagen Thielecke** IBMT - Fraunhofer Institute for Biomedical Engineering Germany	

[1] Work document on Nanomaterials, State of the art overview and forecasts based on existing information of nanotechnology in the field of nanomaterials, published October 2004, Willems& van den Wildenberg (W&W) within the NRM project
[2] Roadmap Report on Nanoparticles, author W&W, July 2005
[3] Roadmap Report on Dendrimers, author W&W, July 2005
[4] BCC, 2003: Protein Chips: Where To?
[5] DZ-Bank, Technology Trends: Biochips, 2001
[6] BioPerspectives, 2002
[7] Roadmap on Drug encapsulation/ drug delivery/ drug targeting, July 2005, VDI/VDE-IT GmbH



NanoRoadMap is a project co-funded by the 6th Framework Programme of the EC

Nanotechnology in Health and Medical Systems

Draft Roadmap on Biomolecular Sensors

Partners:

AIRI/Nanotec IT

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Date: July, 31 2005

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1 Introduction

1.1 Methodology

The NanoRoadMap (NRM) project, co-funded by the European Commission (EC), is aimed at road-mapping nanotechnology related application fields in three different areas:

- Materials
- Health & Medical Systems
- Energy

Within the project, an international consortium consisting of eight partners covering eight European countries and Israel, has joined forces to cover the time-frame for technological development in this field up to 2015. The results of the NRM project are to be used by any European entity interested in planning an R&D strategy taking into account nanotechnology. An important potential user is of course the EC itself in the preparation of the 7th Framework Programme (FP7) for research and technology development. (For additional information on the NRM project, please refer to www.nanoroadmap.it).

1.2 Goals

The primary objective of NRM is to provide coherent scenarios and technology roadmaps that help the European players to optimise the positive impact of nanotechnology on society, giving the necessary knowledge on its future development and when technologies and applications will come into full fruition.

The key users of the reports are mainly European SMEs, research organisations, public bodies in general and the EC in particular. Even though a special focus is put on SMEs, these roadmaps are also meant to be useful for larger corporations.

This report is one of the three final deliverables of the NRM project and it is aimed at providing a thorough overview of specific topics selected for roadmapping within the field.

1.3 Methodology

Collection and synthesis of relevant existing information

In October 2004 three sectoral reports were published, each covering one of the above mentioned areas. They were based on the collection and synthesis of existing public sources in 31 countries and were published as key input for the celebration of the First NRM International Conference held in Rome the 4–5 November 2004. The full report can be downloaded from the project web site.

The report within the sector health and medical systems focused on reviewing the different aspects of nanotechnology in 11 topics, giving its definition, describing its most remarkable properties, current and future markets & applications, and leading countries & highlighted R&D activities in the field. A

general review of non technological aspects (social, legal, ethical and health and safety aspects, but also economic aspects and infrastructure requirements) was also performed.

The 11 topics identified, even not being completely homogenous in terms of scope or classification, were intended to adequately cover the field of bionanotechnology.

The following list was agreed upon by the partners of the NRM project (similar classifications can be found in the bibliography):

- Tissue Engineering/Regenerative Medicine
- Bio Nano Structures
- Drug Encapsulation / Drug Delivery / Drug Targeting
- Molecular Imaging
- Biophotonics
- Biocompatible implants
- Biomimetic membranes
- Biomolecular sensors
- Biochips/HighThroughputScreening
- Lab-on-a-chip
- Functional Molecules: Switches, pumps, means of transportation

Selection of topics

Another major goal of that report was to set the basis for discussion and selection for roadmapping of 4 out of the 11 topics identified above. A preliminary selection of topics was presented during the First International Conference in November, 2004.

Within a frame of criteria agreed upon with the European Commission and after a thorough dscussion, which involved international experts in the field of nanotechnology, four topics were selected (and validated in dialogue with the European Commission). The subjects were partly combined with each other, leading to the four chosen topics:

- Drug encapsulation/ drug delivery/ drug targeting
- Molecular Imaging/ Biophotonics
- Biochips/ High-Throughput Screening/ Lab-on-a-chip technology
- Biomolecular Sensors

Roadmap elaboration

One draft roadmap has been prepared for each of the four aforementioned topics. The result of these roadmaps will be presented in one international and eight national conferences in November and December 2005. Their preparation and execution is based upon a Delphi-like approach. The methodology consists of 2 cycles, which is the same for the four topics.

The Delphi exercise consists of:

- Selecting top-international experts on the field
- Preparing a dedicated on-line questionnaire for each of the topics to be roadmapped
- Circulating the questionnaires and gathering experts' responses (1st cycle)
- Preparing a first summary of the answers received
- Circulating the summary and partly interpreted data, asking for feedback and reflection
- (2nd cycle). Interpretation was conducted in a way avoiding bias.
- Elaborating the roadmap taking into consideration aspects raised in the 2nd cycle

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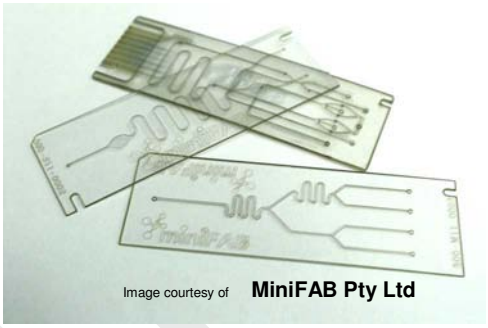
2 Biomolecular Sensors Roadmap

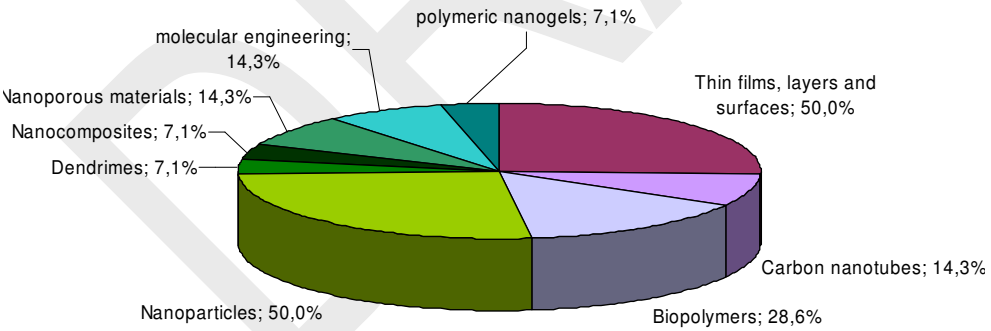
2.1 Introducing the subject



Biosensors are analytical devices which convert biological responses into electrical signals. In a way they act like noses by specifically detecting certain molecules with recognition units that are based on biological components. Thereupon physically measurable signals are built which are enhanced through suitable adjacent circuits or which are further processed. The biologically responsive material is either built of proteins, i.e. enzymes, or nucleic acids, but even other biological systems, like cells, cell structures or complex receptors may be used. As example for the detecting mechanism by bio-components specific antibody-antigen complexes or cell membrane-coupled receptors may serve. These bonding reactions induce detectable changes in mass, temperature, optical properties or electro-chemical parameters (i.e. potential, current or conductivity). As detector elements for this signals and therefore the electronic components of biosensors gravimetric, thermal, optical or electro-chemical sensors Ion-sensitive field effect transistors are deployed. Biosensors are able to detect chemicals e.g. explosives and drugs, as well as bacteria or other cells.

The properties of nanotechnology which permit the operation on the scale of atoms and molecules, have a dramatic impact on sensor design and capabilities. The small size of these sensors will lead to reduced weight, low power requirements and greater sensitivity.

In terms of the most appropriate types of nanotechnologies for their particular aims, the experts participating in our Delphi exercise named thin films, layers and surfaces and nanoparticles, followed by biopolymers, carbon nanotubes, nanoporous materials and molecular imaging being mostly used in their devices. Dendrimers, nanocomposites and polymeric nanogels are applied to a lesser degree.



Thin films, are deposited as one or more materials' layers with thicknesses below the order of 100 nm onto surfaces. The main advantage of thin films or of any other coating is that material properties can be transferred to the surface (thus enabling the use of not specialised substrates).

The most remarkable properties are of

- optical (light trapping, transmission, opaqueness, fluorescence, waveguides, "light valves", anti reflection, etc.),
- mechanical (wear/ abrasion resistance, hardness, scratch resistance, dry lubrication, reduced strain-to-failure, etc.),
- electrical (energy potentials, binding energies, conductivity, insulation, etc.),

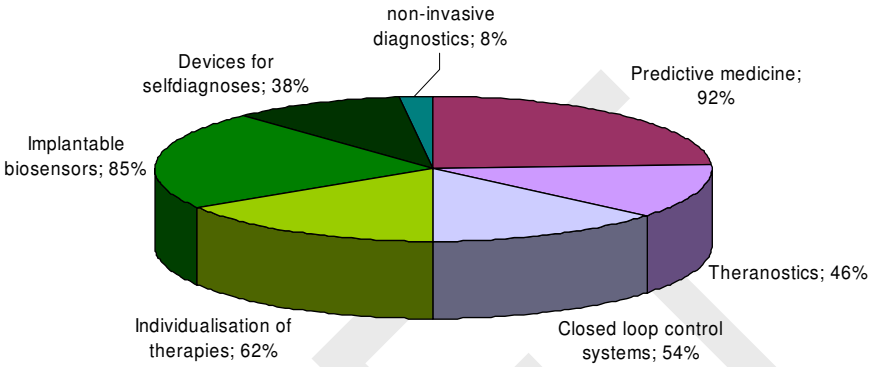
- chemical (water repellence, anti-fogging, chemical barriers and chemical inertness, oxygen or moisture barriers over polymers, antimicrobial surfaces, etc.),
- magnetic (data storage) and
- thermal characters (application of multi-layered thin films allows, for instance, blocking the travel of atomic vibrations that produces heat flow whilst still letting the electrons flow as a current application in thermoelectric devices)[1].

Nanoparticles are particles with a size up to 100 nm. They exhibit completely new or improved properties based on specific characteristics (size, distribution, morphology, phase, etc.), if compared with larger particles of the bulk material they are made of. Nanoparticles can be made of a wide range of materials, the most common being metal oxide ceramics, metals, silicates and non-oxide ceramics. Even though nanoparticles of other materials exist, e.g. those based on polymer materials or compound semiconductors, the former categories count for the most part of current applications[2]. **Biopolymers** are naturally occurring polymers that are formed during the growth cycles of all organisms; they are also referred to as natural polymers. Their synthesis generally involves enzyme-catalyzed, chain growth polymerization reactions, typically performed within cells by metabolic processes. They represent the most abundant organic compounds in the biosphere and constitute the largest fraction of cells. This diverse and versatile class of materials has potential applications in many sectors of the economy. **Nanoporous materials** are materials with holes less than 100 nm in diameter. They can be bulk nanoporous materials or membranes. The pores can be open (interconnected) or closed and can have amorphous, semi-crystalline or crystalline (e.g. lamellar, cubic, hexagonal) frameworks. These two characteristics influence the applications a specific nanoporous material is suitable for. Nanoporous materials could be natural or synthetic, organic or inorganic or hybrid materials. Examples of materials are carbon, silicon, silicates, polymers, metal oxides, organic/metals, organic/silicon, etc. Materials specifically considered for membranes include materials such as the widely used zeolites or the so-called schwartzites[3]. **Molecular engineering** can be described as the manufacturing and control of the structure of matter at the molecular level. It may be used to create, on an extremely small scale, most typically one at a time, new molecules which may not exist in nature, or be stable beyond a very narrow range of conditions. The field can be seen as a precision form of chemical engineering that includes protein engineering, the creation of protein molecules, a process that occurs naturally in biochemistry. Molecular engineering is an important part of pharmaceutical research and materials science[4]. **Dendrimers** are generally described as macromolecules, which are characterized by their highly branched 3D structure which provides a high degree of surface functionality and versatility. Dendrimers can be made out of virtually anything that can branch (metal atoms, organometallic groups, or purely organic materials) and they can have a variety of functionalities depending on the application[5]. **Nanocomposites** enclose a large variety of systems such as one-dimensional, two-dimensional, three-dimensional and amorphous materials, made of dissimilar components and mixed at the nanometer scale which results in e.g. improved mechanical, electrical and optical properties which can be applied in various products. There are at least two ways of defining **polymeric nanogels** and microgels. One of them originates from the definition of polymer gels. A polymer gel is a two-component system consisting of a permanent three-dimensional network of linked polymer chains, and molecules of a solvent filing the pores of this network. Nanogels and microgels are particles of polymer gels having the dimensions in the order of nano- and micrometers, respectively. The other definition says that a nanogel or a microgel is an internally crosslinked macromolecule[6].

2.2 Scientific and Technological Aspects

Trends & needs during the next decade

Biosensors are increasingly seen as medically desirable for the control and effective treatment of a range of chronic conditions. Easing the patient experience, and improving the functionality and reducing the cost of these devices are critical to ensuring their widespread success[7]. Like biochips, biosensors will with the evolving technology become a tool for clinical medicine, providing a rich source of information on disease susceptibility, diagnosis and prognosis. This is reflected in the estimations of the experts upon the future medical emphases. 92 % of the experts demand a stress on predictive medicine followed by the need for implantable biosensors (85%), individualisation of therapies (62%), closed loop control systems (54 %) and theranostics (46%). Only 8 % demand an emphasis on non-invasive diagnostics, which is due to the fact that this item was mentioned by one expert in the second round of the Delphi questioning after which no further feedback of the experts was given.



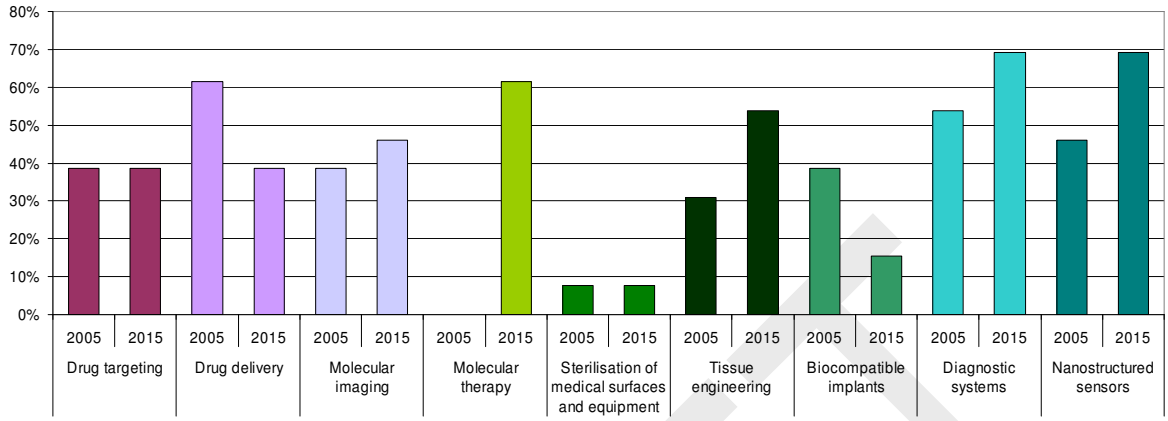
"Future medical practice will need more" Estimations of the experts within the biosensors field

The results of the biomolecular sensor field differ from those of the biochip and drug delivery area, in which only 58 % or 11 % of the experts, respectively, state that a stress on predictive medicine should be made.

Nanotechnology is expected to be critical in supplying the mentioned demands. All of the involved experts predict nanotechnology to be unique in providing biochips with the properties which are needed for their more efficient use. Like in biochips, this influence can be seen for example in nanostructuring, which will offer novel ways to structure and coat surfaces. The potential to tailor nanomaterials to desired mechanical, electrical, magnetic or optical properties will lead to novel applications, with a positive environmental impact and cost-reduced processes.

In general, the experts within the biosensor field state the main nanotechnological applications within the next decade to be in diagnostic systems and nanostructured sensors, which are included in the first ones. Diagnostic systems as well as nanostructured sensors are estimated to play already presently important roles which will be enhanced in the next decade. Molecular therapy is predicted by more than 60 % of the experts to be one of the most important applications of nanotechnology in 2015, whereas they stated that there is no present one. The number of important applications in drug targeting remain on the same level as today, which indicates that there is a scepticism upon the nanotechnological impact on pharmaceutical issues. This is stressed by the results for drug delivery. Less than 40 % of the biosensor experts predict important future nanotechnological applications in drug delivery, whereas more than 60 % do this in 2015. Molecular imaging is expected to be increasingly influenced by nanotechnology, but taking a back seat against molecular therapy in 2015which includes the maturity of molecular imaging. Interestingly biocompatible implants are expected to be influenced by nanotechnology less in 2015 than today. This is hardly to understand, keeping in mind that implantable biosensors were chosen by 85 % of the experts to need more future attention and can probably be interpreted that nanotechnological impact will automatically decrease on this issue once a biocompatibility is achieved. Probably that is expected to happen before 2015.

Sterilisation of medical surfaces and equipment due to properties of certain nanoparticles do not play any prominent current or future role according to the experts within the biomolecular sensor field.

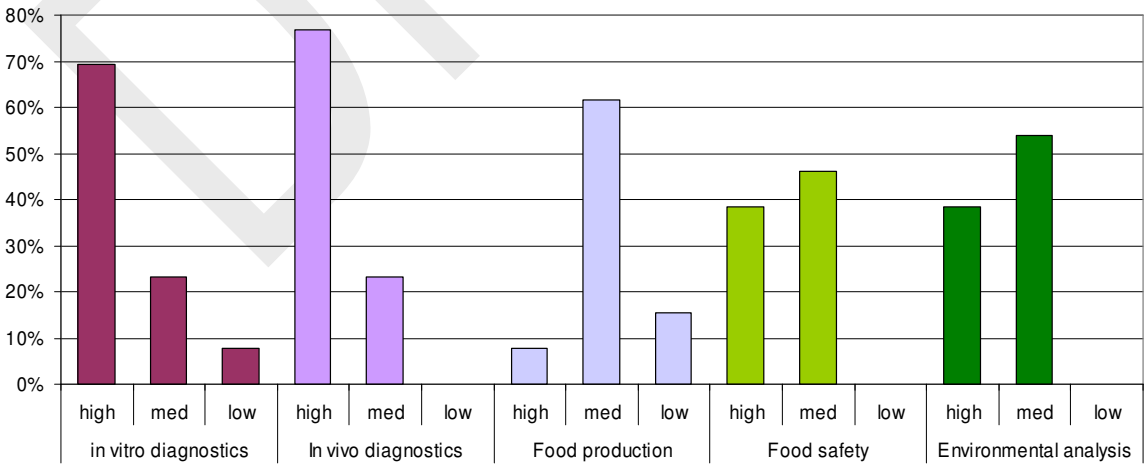


The most important applications of nanotechnology in the medical sector

Impact of nanotechnology in the field considered

The experts' ranking regarding the impact of nanotechnology in several subjects within the diagnostic and partly the therapeutic sector is relatively clear. A high impact is expected to occur both in *in vitro* and *in vivo* diagnostics. A medium impact is stated to proceed in food production, whereas it is expected to be high to medium in food safety and environmental analysis.

In ***in vitro* diagnostics** the impact is predicted to occur via miniaturisation, new products, more reliable, new targets, new highly sensitive and selective biosensor arrays, which will be integrated highly



Impact of biomolecular sensors in different fields

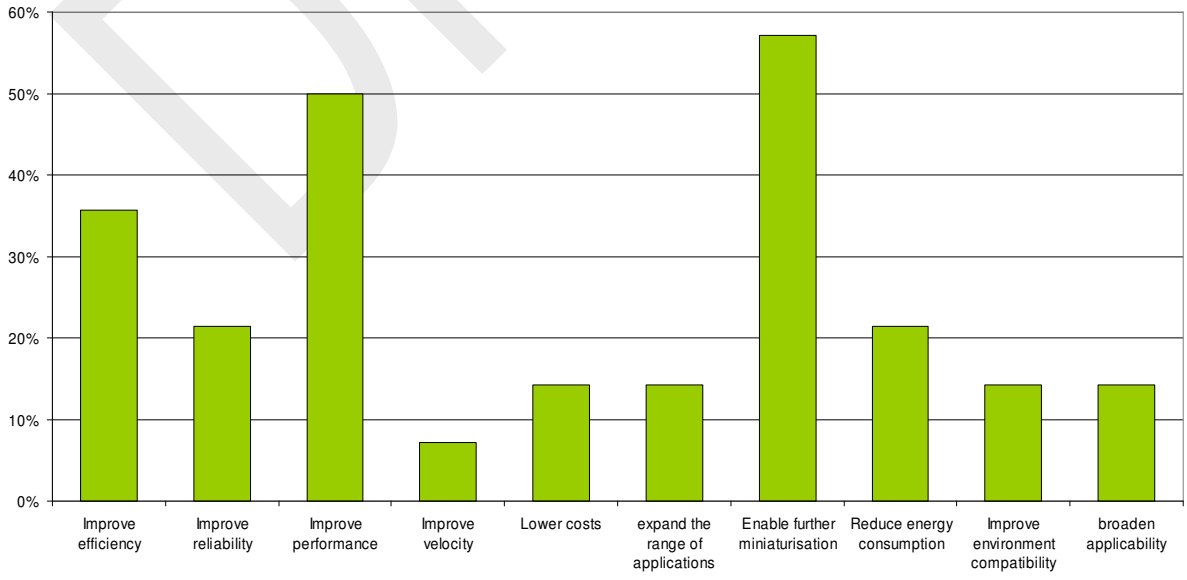
parallelised as multiple components in single, manageable devices. These sensors are expected to act as fast and automatic multianalyte detection units in clinical laboratories and home self-diagnostics

(point of care diagnostics). In **in vivo diagnostics** nanotechnology will enable new contrast for imaging, directed particles (e.g. targeted magnetic, radio-labelled or long wavelength luminescent nanoparticles), new implantable devices for specific medical applications (e.g. localised diagnostics giving potential for real-time monitoring biochemistry and localised therapy). Furthermore the impact of nanotechnology will occur in immediate integration of high density of reliable data over time and space/volume which will provide information on condition profiles. In **food production** nanotechnology will offer the potential to detect foodborne pathogens very rapidly. Thus, the production process can be monitored and nanobased biosensors will improve quality control and hence food chain management. **In food safety** cheap disposable nanobased biosensors will be producible which as well will improve quality control in food chain management. The development of highly specific, affordable sensors in the food sector will enhance consumer protection making headlines of sold decomposed food in supermarkets to become history. The impact of nanotechnology in **environmental analysis** will occur in affordable sensor array networks, according to few experts.

Advantages of nanotechnology over existing/alternative technologies

The most exciting prospect of nanotechnology in biosensors compared to existing or alternative technologies is its ability to enable further miniaturisation and to improve performance and efficiency of biomolecular nanosensors. Highly sophisticated biosensors imply the use of extreme specific biocatalysts, being stable under normal storage conditions and showing good stability over a large number of assays. Immobilisation and compartmentalisation of different biomolecules and cofactors / coenzymes is desirable to allow for manageable devices with multiplex detection. The response of advanced biosensors should be accurate, precise, reproducible and linear over the useful analytical range, without dilution or concentration. It should also be free from electrical noise. Biosensors which will be used for invasive monitoring in clinical situations, have to be tiny and biocompatible, without having any toxic or antigenic effects. For applications in fermentation vessels they should be sanitised. The complete biosensor should be cheap, small, portable and capable of being used by semi-skilled operators.

Nanotechnology is expected to meet these demands to different degrees according to the experts as shown below.



Most revolutionary properties of nanotechnology in biomolecular devices compared to existing/alternative technologies

Technology evolution

Nanotechnology provides a wide range of new technologies that will optimize biosensor devices. This is reflected in the experts estimations upon the role, nanotechnology will play in biomolecular sensors. 86 % of the experts predict the probability, that nanotechnology will play a major role in biosensor technology to be very high.

With the invention of the oxygen electrode in 1956 by Leland C. Clark and its subsequent modification with enzymes the history of biosensors started. In some areas, i.e. glucose monitoring, biosensors have meanwhile become a mature technology. Today, biosensors are making an ever increasing impact on the manufacturing industry areas where there are requirements to detect minute concentrations of specific substances. They are also being used in an environmental capacity, to detect contamination, and also in safety monitoring and the food industry.

Current nanotechnology permits the operation on the scale of atoms and molecules. This promises to have a dramatic impact on sensor design and capabilities and advance their format as well as lower their price. The main problem consist in the interaction of biorecognition layer with biological environment on a molecular level. Thus, technologies for a controlled preparation of biorecognition layers at a nanometer scale are necessary. Nanotechnology has become a key technology in sensor development. Sensors can now exploit novel properties of materials at the nano-scale. Chemical and biological materials operate at the nano-scale, hence nanotechnology is well suited to design of chemical and biological sensors. Effective biosensing needs reduction and integration, precisely what nanotechnology can contribute with. Miniaturisation and automation of sensor/lab on a chip systems will vastly increase their breadth of use.

Comparable to biochips, there are partly the same application areas for biomolecular sensors. One of them being the point-of-care market, in which companies are developing simple, low-cost blood screening tests e.g. for certain toxins or even for specific proteins that indicate acute diseases. They can be used in hospitals and perhaps later in local medical centres. The second is the clinical diagnostics market. Sensors for this market also speed up diagnosis of diseases and make them more specific with a lot of added values for the patient, beginning with a greater individualisation and ending with more specificity, efficiency and the shortened stay in hospital.

Trends, challenges and discontinuities

One of the major reasons for the low market penetration and few success stories of biomolecular sensor devices are the difficulties making them sensitive enough to enable practical use. Today's sensor technologies are, due to cost issues, relying on semiconductor processes that are one or two generations old. Thus, nanotechnology is about to permit a quantum leap in biosensing. The major challenges in biosensor technologies within the next ten years and the estimation how nanotechnology will help to realise that trend, are listed in the following table:

Major challenges	**Realise trends**
Stability of bio components is still an issue for other applications than glucose monitoring.	Proteins engineered for stability
Highly sensitive, selective biosensors, systems integration: How to integrate the different enabling components. Cost: How the manufacture of low cost solutions can become affordable to the wider community.	Mainly from the sensor point of view with regards to improvement in sensitivity and selectivity via new functionalised nano-bio interfaces.
Sensors capable of fast and automatic multi analyte detection in clinical laboratories and home self-diagnostics.	The technology should make possible the controlled immobilisation of biological and synthetic molecular assemblies for preparation of bio-recognition layers on physical transducers.
Implementation, public acceptance	
Integration, intelligence to integrate data, minimally invasive methods and reduction of collateral interactions with biomaterials.	Enabling miniaturisation, although energy consumption remains an issue, possibility to embed data processing systems and telecommunication capabilities.
Stability of the sensing element	
A balance between technical innovations and the possibility to apply these innovations in the biomedical field for a long time.	
Linking sensor technologies to medical information technologies to improve diagnostics and theranostics; then applying this to preventative measurements	By improving the quality of biological information being obtained
Developing and expanding clinical-science joint ventures	
Going to online detection in biofluids, increasing the number and specificity of markers for diseases, reducing the detection limit and increasing reliability.	Creation molecularly non-fouling layers based e.g. on peg, new real-time signal transduction routes, multiplexed protein detection systems, new ultra sensitive detection routes and lab-on-a-chip.
To attract scientists into the analytical community from other fields to generate “fresh ideas”	Functional devices will require fundamental research which is supported by follow-on funding. Closer links between interested stakeholders and academics are necessary. Multidisciplinary and an effective and expedited technology transfer is crucial.

Time-to-market

To learn more about the marketability of special nanotechnology driven applications and the expected time to market for such applications within the medical sector the experts were asked to evaluate the stage of maturity of specific technical challenges of biosensors in the diagnostic area.

The results which are shown in the following diagram reflect the relative importance of the particular nanoparticle properties and their implementation in applications within the next decade predicted in five years from now (2010) and in ten years from now (2015) and give an integrated view of the various stage of development of the applications.

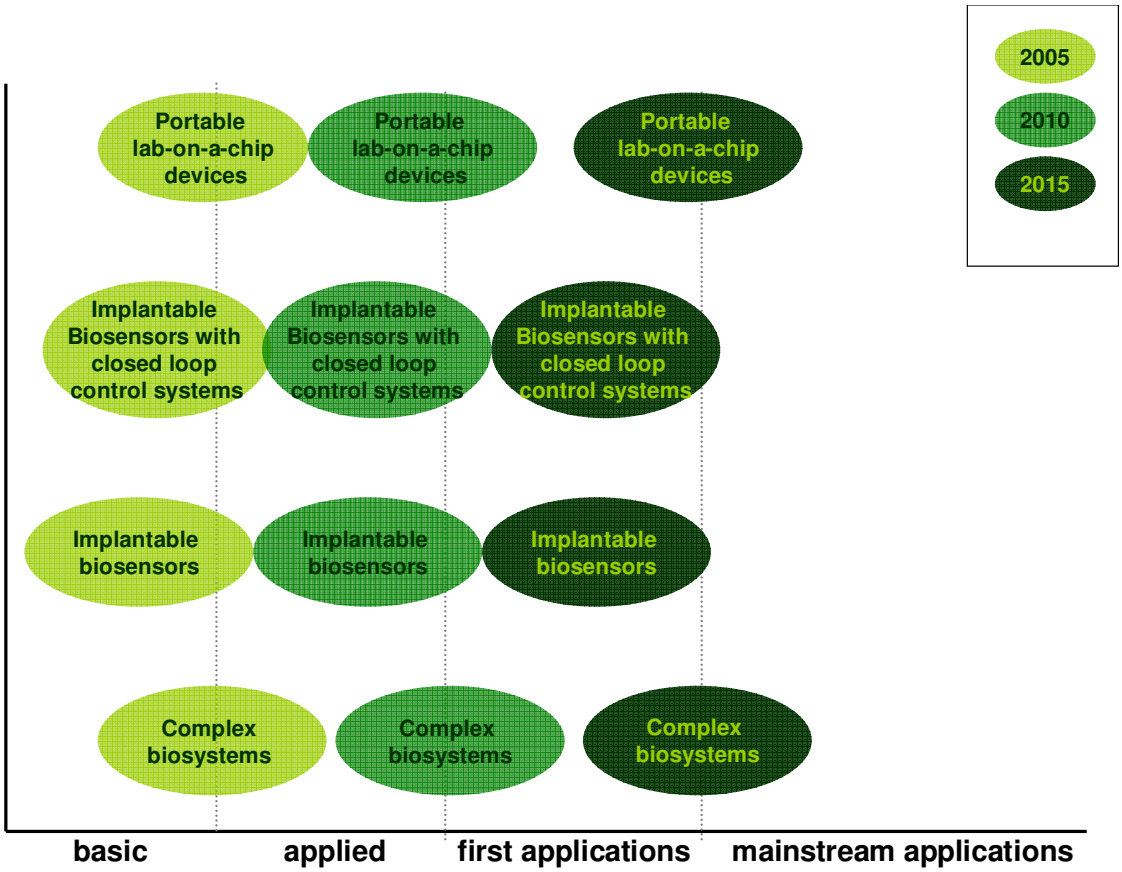
The generic distinctions in the graph chosen for the sequential phases in the innovation cycle have been taken as follows:

Basic Research & Development Phase (**basic**): Applications in this phase have received the interest of one or more researchers in the world. Some applications might still be in early development, while other are tough to develop and need a lot of basic research to be fully understood. The object of basic R&D is to validate the original hypothesis. Many applications are currently in this phase as researchers are still struggling to understand basic properties of nano-material.

Applied Research & Development Phase (**applied**): After the hypothesis is validated, research typically (but not necessarily) moves from pure research labs to more commercial labs and companies. Applied R&D will eventually result in a proof of concept, a successful demonstration model. While the production issues might not have been solved yet, a successful prototype/model has been validated.

Product Research & Development Phase (**first applications**): After first demonstrator models and prototypes, initial, usually prohibitively expensive, small numbers of products may be produced. If these prove successful, companies will seek to enhance production to gain market share. Generally at some point, demand increases sufficiently to offset the investment needed to start production. This phase ends at a point when feasibility has been proven and production is to start.

Production level and incremental research (**mainstream applications**): The final development phase, when production has reached significant numbers and research focuses on incrementally improving the products.



According to the experts there are few mainstream applications in 2015, among them portable lab-on-a-chip devices. All technical developments are expected to proceed in a linear manner, assuming that all challenges (technical, economic, infrastructural, environmental) can be met. This result partly differs from the analogue in biochips, in which sophisticated portable lab-on-a-chip devices and implantable biosensors were predicted to be broad mainstream applications. Whereas the development of portable lab-on-a-chip devices is expected to proceed in a linear manner, the progression in implantable sensors arrays is supposed to take discontinuous courses with a "jump" between 2010 and 2015. This result indicates the huge estimations which are coupled to nanotechnology in the particular applications. Implantable biosensors being used as closed-loop control systems are stated to remain in a medium state of development after 2010 by the biochip experts. The estimation of maturity of various applications, especially the difference between the two groups of experts indicates that the time to market, based on the technical evolution is hardly to predict. The results show that progress in developing biosensors is expected to happen. As the new technology becomes more commonplace and more affordable, global demand for products will increase.

Gaps and barriers

Biosensors are, like biochips, applied in several research areas like cytology, evolutionary biology, pharmacology, toxicology or molecular diagnostics. Accuracy and reliability are crucial for the analysis of biological parameters. These depend to a critical degree on the chip platform design. Thus, technical barriers have to be overcome.

	technical	economic	infrastructural	environmental impact	other
Thin films, layers and surfaces	X	X	X		
Carbon nanotubes	X	X			
Nanoparticles	X			X	
Biopolymers	X				
Molecular engineering	X				
Polymeric nanogels	X				

The barriers which are expected in connection with special kinds of nanotechnologies are predominantly of technological and partly of economic character. The experts who answered within the drug encapsulation sector stated general barriers, which apply to the biochip and biosensor field, especially in thin films, layers, and surfaces. These are analytical methods that can provide chemical (molecular) characterisation at the nanoscale which have to be urgently developed.

The barriers specified by the experts within the biosensor field to occur in various kinds of nanotechnologies are listed in the table shown to the left.

The specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in the table below:

Barriers to success	**Technical**	**Economic**	**Infrastructural**	**Environ-ment**
Thin films, layers and surfaces	Homogeneity	Low return of investment in diagnostics at present	More clinical studies related to diagnostics are needed	
	Non-specific response to biological media make the application of sensor difficult for medical diagnostics. The development of biorecognition layers consisting of molecular receptors immobilized on surfaces with minimum non-specific adsorption of biological molecules is a prerequisite for the detection in biological media. prevention of surface induced blood reactions, such as fibrin clot formation, is a prerequisite for operation of implanted sensors.			
		To regain confidence in the biosensors field		
	Controlled production; should be solved by 2010 by increasing collaborative interdisciplinary approaches			
	Adsorption of proteins on the surfaces			
	Need monodispersed particles of different shapes and materials by a chemical synthesis route		Characterisation tools required-not all are available	

Barriers to success	**Technical**	**Economic**	**Infrastructural**	**Environment**
	Currently investigating and hopeful of success in the next 3 years. Barriers depend on success in synthetic chemistry AND that our theoretical prediction that drive the chemistry are correct. Otherwise there will be no benefit in a putative device			
Carbon nanotubes	Manufacturing constrains, volume of product, testing			
	Particular skills, especially synthetic chemistry and physical skills are needed.	Inability to secure funding		
Nanoparticles	Toxicology			Impact of nanoparticles on organism and ecosystems has to be investigated
Biopolymers	Long term stability			
Molecular engineering	Engineering molecules to replace existing systems (e.g. aptamers replacing antibodies); will improve by 2010 given effort currently being expended			
	Molecular nanopositioning is hard self assembly plus nanolithography by 2012	Nanoscale patterning by EBL is too expensive. NIL may be a solution by 2009		
Polymeric nanogels	Lack of potential PhD students with necessary multidisciplinary skills			

Most present and future relevant applications of nano-related products

It is undeniable that a combination of a molecular device attached to something, e.g. a surface, nanotube, molecular wire or something else, will find application in the biosensor field.

Biosensors are still novel products with high production costs, combined with relatively low volumes and limited market penetration. Although the market is not well developed, there are several successful products already available. These products almost exclusively focus on the pharmaceutical business, where a major part is the monitoring system for home blood glucose used by people suffering from diabetes. There is an urgent need to develop rapid, simple, cost-effective medical devices for screening multiple medical diseases simultaneously and to monitor infectious pathogens for early medical diagnosis.

Nanobiosensors provide new and powerful tools for monitoring in vivo processes within living cells, leading to new information on the inner workings of the entire cell. Such a systems biology approach could greatly improve the understanding of cellular function, thereby revolutionizing cell biology.

Future possible markets for biosensors are numerous. Once the sensors become more refined and production costs are reduced, the produced volume will increase and biosensors will be used in various applications. Examples of specific applications that will emerge are personal health monitors, devices for on-site trauma treatment, devices for a 'barefoot doctor' and a wide range of aids for geriatric care. The primary restraint on increased use of sensors in health will be clinical approval, both for safety and cost effectiveness of the systems that emerge. Concerns over the use of the vast amount of data that could be collected will also be a restraint on the adoption of sensors in health care.

Although the sensor market is fragmented, nanotechnology has some unique capabilities that suggest that it will have a large impact in many of the market's most important segments. Nanosensors are inherently more sensitive than any other kind of sensor, making them a future choice where lives are at stake. In addition, their small size and potentially low cost means that they can be widely deployed - perhaps being embedded in construction materials -- thereby providing more comprehensive readings than a few scattered "macrosensors" Nanotechnology also promises to created integrated devices that combine both the sensor itself and the mechanism that converts what is sensed into useful information.

Regarding the expected impact of nanotechnology the experts were asked to give a ranking upon the impact of nanotechnology in distinct diagnostic topics in which biochip devices also will play a more or less important role with "1" mapping a huge and "5" a rather negligible impact.

2.3 Non-technological aspects

Market trends for each application

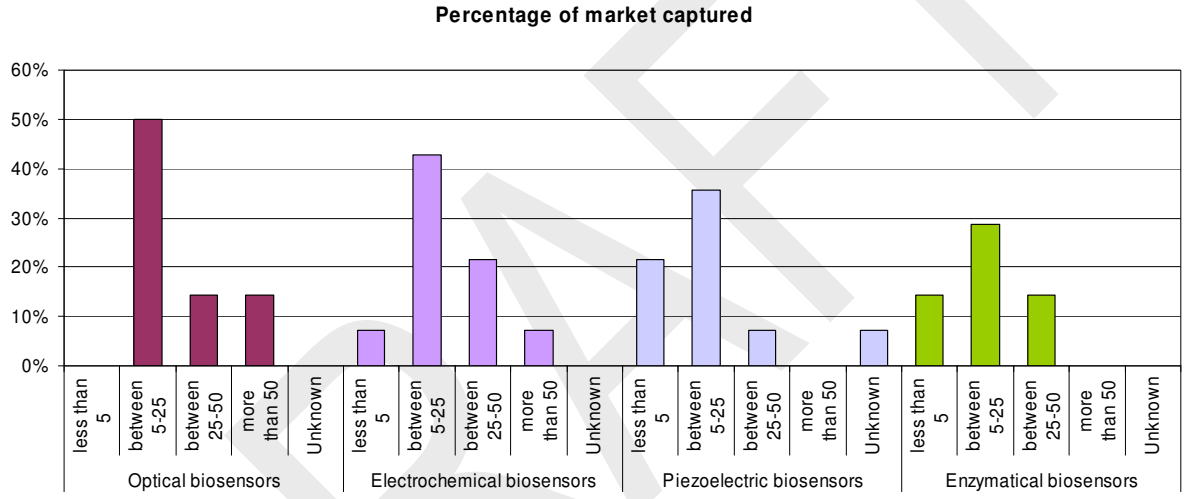
Biosensors represent a rapidly expanding field, at the present time, with an estimated 60% annual growth rate; the major impetus coming from the health-care industry (e.g. 6% of the western world are diabetic and would benefit from the availability of a rapid, accurate and simple biosensor for glucose) but with some pressure from other areas, such as food quality appraisal and environmental monitoring. The estimated world analytical market is about bn£12 per year of which 30% is in the health care area. There is clearly a vast market expansion potential as less than 0.1% of this market is currently using biosensors. Research and development in this field is wide and multidisciplinary, spanning bio-

chemistry, bioreactor science, physical chemistry, electrochemistry, electronics and software engineering[8].

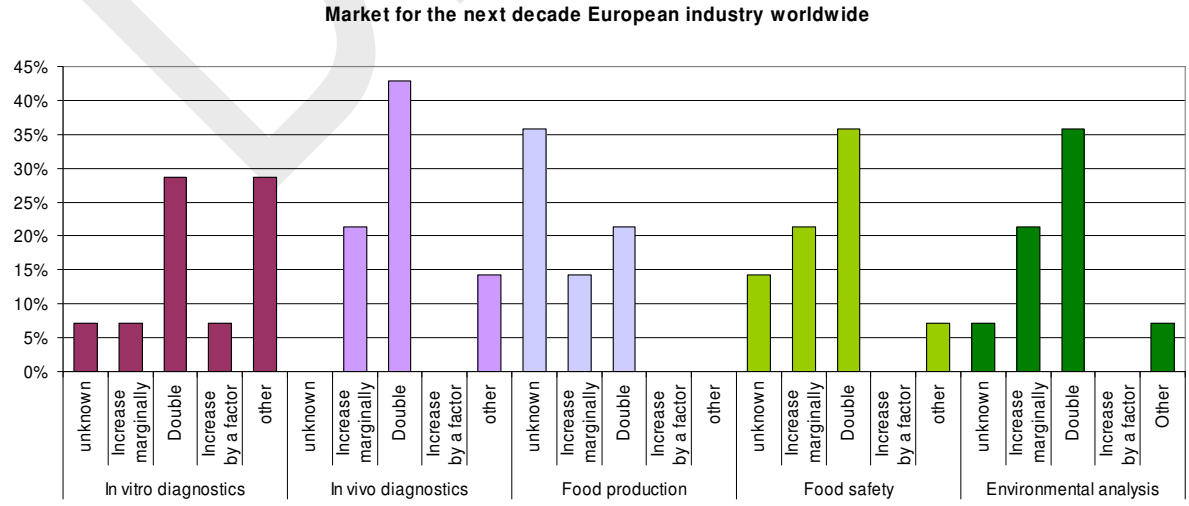
In 2004, total global nanosensor sales were estimated at $190 million and are expected to rise at an average annual growth rate (AAGR) of 25.5% to $592 million by 2009. In 2003, the nanosensors market mainly consisted of nanochemical sensors (chiefly ultrasensitive gas sensors), nanobiosensors (nano-LC systems) and nanoforce sensors (scanning probe microscopes). Nanochemical and nanobiosensors will grow significantly through 2009, at AAGRs of 53.1% and 32.9%, respectively[9].

To get a more specific view of the market, the experts were asked to appoint their estimation about which percentage of the market will be captured by nanotechnology in several categories in 2015. In optical biosensors there were main accordances between the experts who suppose it to be 5 to 25 %.

Electrochemical biosensors, piezoelectric biosensors and enzymatical biosensors are predicted to be affected to the same degree, with a slight decreasing participation of the experts due to their focus lying mainly on optical biosensors.



40 % and 28 % of the experts estimated the percentage of market which will be captured by nanotechnology to double in *in vitro* and in *in vivo* diagnostics, respectively. Since the markets for food safety and environmental analysis were also stated to double within the next decade, these probably are



"political" or rather "diplomatic" votes. In fact it is very difficult to get present market data. Former fore-

casts are often useless because firstly they differ depending on the considered market and secondly due to various reasons they rarely become true.

Several participants estimated the nanotechnological market in the particular fields to develop to an "other" degree. Unfortunately they did not quantify their votes rendering them without usable conclusion.

Educational requirements

Research and development in this field is wide and multidisciplinary, spanning biochemistry, bioreactor science, physical chemistry, electrochemistry, electronics and software engineering.

Regarding the educational offer in nanotechnology the participants differ on whether the European is sufficient to manage the raising knowledge demand in the field or not. Half of them assume that the educational offer is adequate, almost the other half negates.

Those who aren't of the affirmative opinion explained there choice. According to this "technology is still a poor relation to educational offer, including education by research". "Nanotechnology is the application of fundamental sciences - often multidisciplinary- but the fundamental science is essential. There is a continual erosion of this knowledge base through a lack of interest in young people coming through to study sciences, regardless of trendy sounding nanoscience degrees that are appearing".

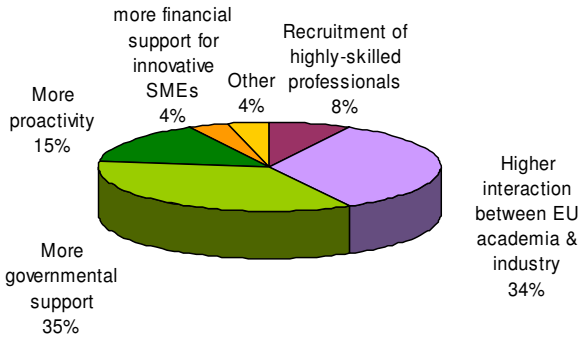
Infrastructure requirements

There is a predominately recommending opinion of the development of instrumentation costs for the manufacturing, characterisation and manipulation of nanotechnology in the particular areas. Most of the experts state that the costs are increasing steadily.

One of the experts who disagreed upon this statement pointed out that "the fundamental scientific research is as costly as it always has been - there is nothing special about the miniaturisation of the sensor - as the fundamental chemistry remains chemistry. It has always been small.."

Most of the experts agree upon the need for multidisciplinary centres with advanced knowledge on materials development and own pilot production facilities to be essential for supporting the European industry in taking its products to the final market.

According to the experts estimations most important for the growth and prosperity of European nanotechnology is a higher interaction between industry and academia facilitating an effective technology transfer as well as higher governmental support. "Other" stands for a needed support for late development (prototyping) and cross laboratory trials.



Most important for growth

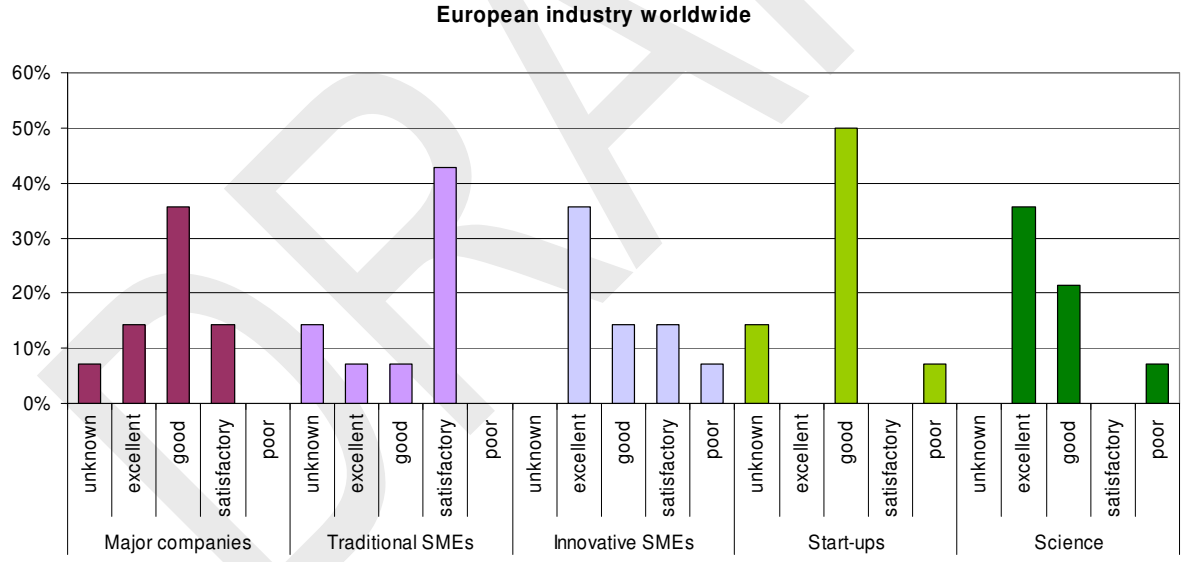
HSE issues

Regarding a potentially HSE hazard raised by nanotechnological processes being involved in the products the experts are developing/ working with, most of them (90%) negated. The explanation of one expert who affirmed was, that new tools to monitor the toxicology of e.g. nanoparticles will soon be available.

All of the experts are of the opinion that HSE impact studies on certain types of functionalised nano-materials are needed. One participant proposed to make “in vitro tests by new toxicological analyses”. Hazard is possible to occur and must be thought of, whilst designing the devices.

European competitive position

The graph illustrates the experts view on the competitive position of Europe in comparison to the global situation. It is stated as being mainly satisfactory to good in all size categories of industry. Major companies are not seen as holding mainly an excellent position. Within the traditional SMEs the position is stated as being satisfactory with some statements claiming good and excellent positions. Innovative SMEs are rated excellent to a higher degree and poor to a lesser degree due to their core-business expected to be closer to scientific excellence. Start-up companies do gain a firmer rating in good compared to traditional SMEs according to the experts.

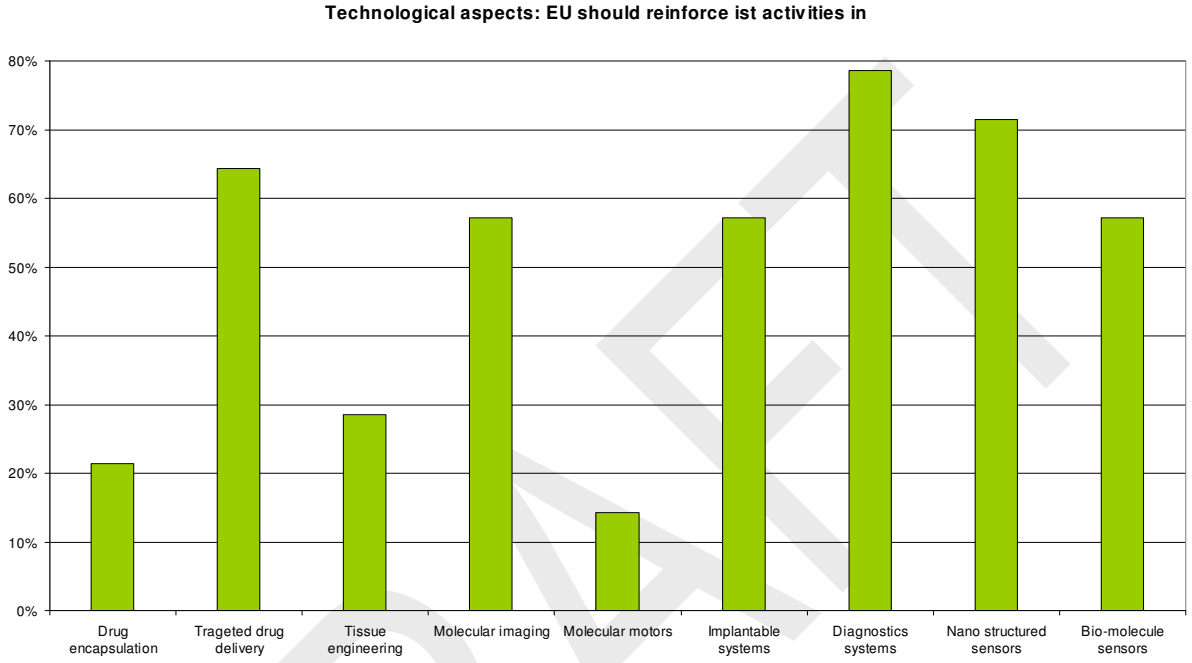


Apart from the specific ratings in the various size categories of industry a stronghold in an *excellent* and *good* worldwide position is claimed in science.

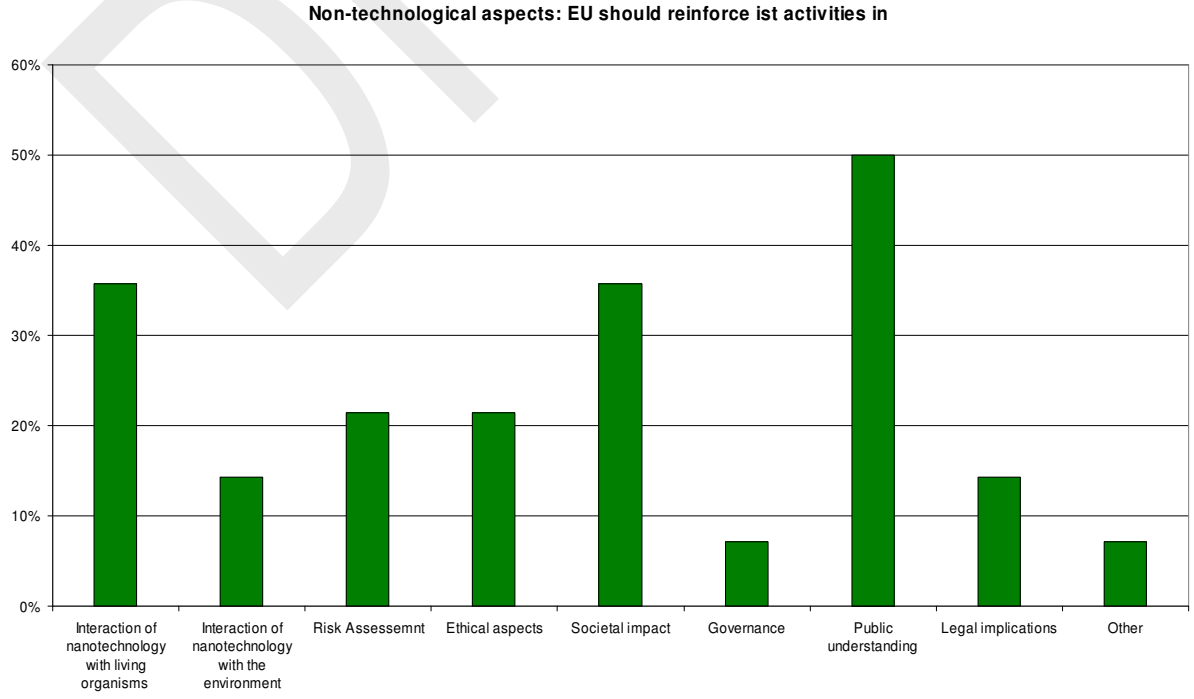
2.4 Recommendations by the Delphi panel

Trends, challenges and major gaps and barriers in the technological evolution which will lead to technological conclusions have been identified by the Delphi panel and described in this document.

The Delphi panel has expressed their opinion on reinforcing European endeavours in the field with regard to technological aspects are illustrated below.



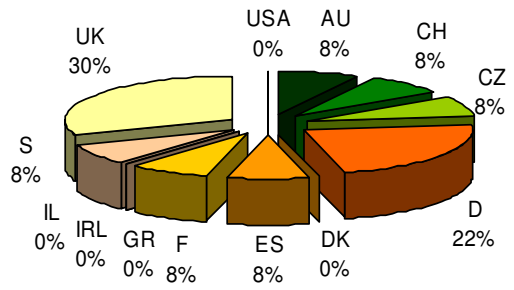
In addition the Delphi panel has expressed their opinion on the need to reinforce European endeavours in non-technological aspects. The given fields of possible actions were complemented by 'other' namely telecommunication and integration with intelligent context aware systems.



3 Annexes

3.1 Statistics

International spreading of the participants



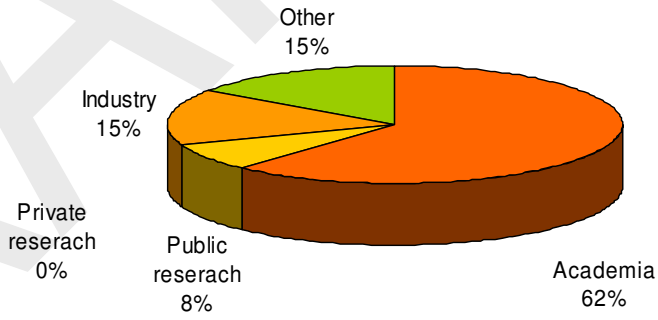
Within the topic biomolecular sensors we asked 28 international experts from 14 countries. Moreover there were 32 experts pleased to participate without being related to a special topic in advance. Six of them answered to our questionnaires, one of them within the topic biomolecular sensors.

13 experts answered in total, the international distribution is shown in the diagram shown beside.

The experts who have been invited to participate were spread over universities, university research

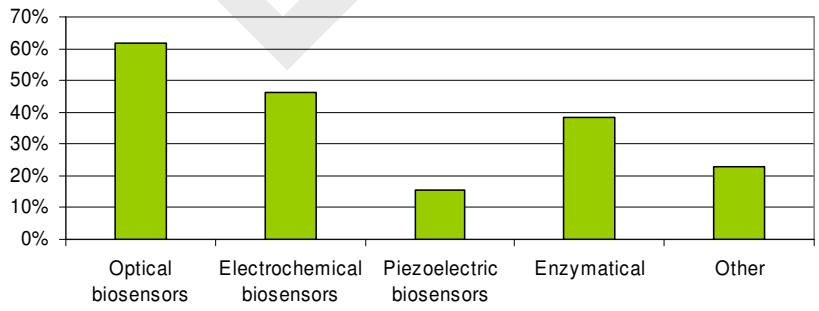
centres, public research organisations, private research organisations and industry. Nevertheless most of the participants (62%) came from academia.

Organisation type



The main foci of the experts who answered is in nanotechnology to improve biosensor properties (62%), followed by biosensor platforms (54 %). There was also expertise in peripheral biosensor devices (38%), biosensor content (38 %), nanoparticles (31 %), and bioinformatics (15%).

Kind of biosensors



The participants are working mostly with optical biosensors (62%). “Others” were indicated to be simulation of biosensors, sensors with living cells and MEMS biosensors.

3.2 List of Participants

Frank Bier FhG für Biomedizinische Technik, Molekulare Bioanalytik & Bioelektronik Germany	**Loic Blum** University of Lyon, 1-PCML France	**Eduard Brynda** Institute of Macromolecular Chemistry ASCR Czech Republic
Andrew Campitelli MiniFAB, Pty Ltd, Bio Micro Nano Technology Australia	**Tony Cass** Imperial College London, Department of Biological Sciences United Kingdom	**Shervanthi Homer-Vanniasinkam** University of Leeds Medical School, United Kingdom
Petros Koumoutsakos Institute for Computational Science The Switzerland	**Mirco Lehmann** Micronas GmbH Germany	**Holger Löwe** IMM Mainz GmbH Germany
Carlos Martinez-Riera Conselleria de Sanitat, Centro de Proceso de Datos Espania	**Calum McNeil** University of Newcastle upon Tyne United Kingdom	**Duncan Sutherland** Chalmers University of Technology, Göteborg Sweden
Michael Watkinson Queen Mary University of London United Kingdom		

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Institute of Nuclear Chemistry and Technology, Dorodna 16, 03-195 Warsaw, Poland
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