ROADMAPS AT 2015 ON NANOTECHNOLOGY APPLICATION
IN THE SECTORS OF:
MATERIALS, HEALTH & MEDICAL SYSTEMS, ENERGY

All roadmaps reports are under revision of the European Commission, final approval from the EC is pending.
NanoRoadMap is a project co-funded by the 6th Framework Programme of the EC

Impact of Nanotechnology in Health and Medical Systems

Roadmap Report
Impact of nanotechnology in Health and Medical Systems

Roadmap Report on Nanotechnology in Health and Medical Systems

Partners:

AIRI/Nanotec IT

Willems & van den Wildenberg (ES/NL)

VDI/VDE-IT (DE)

Institute of Nanotechnology (UK)

MATIMOP (IL)

Technology Centre (CZ)

VTT (FI)

Yole Développement (FR)

Author: VDI/VDE - Innovation und Technik GmbH (VDI/VDE-IT)

Date: December 20th, 2005
The present document is a roadmap report prepared by VDI/VDE-Innovation und Technik GmbH (VDI/VDE) in the framework of the Nano-RoadMap (NRM) project, co-funded by the 6th Framework Programme (FP6) of the European Commission.

This roadmap report is mainly based on the input received by experts participating in the Delphi-like panel. It is one of the key deliverables of the NRM project and is issued for discussion and information purposes. The views expressed do not necessarily reflect those of the European Commission.
Table of contents

1 Introduction ......................................................................................... 7
  1.1 Definition ........................................................................................ 9
  1.2 Background .................................................................................... 9
  1.3 Goals .............................................................................................. 10
  1.4 Results ........................................................................................... 10
  1.5 Methodology .................................................................................. 11
2 Drug encapsulation/ drug delivery/ drug targeting..................................... 14
  2.1 Introducing the subject ................................................................... 14
  2.2 Scientific and technological aspects ................................................. 18
    Trends & needs during the next decade .............................................. 18
    Impact of nanotechnology in the field considered ................................ 19
    Advantages of nanotechnology over existing/alternative technologies ... 21
    Technology evolution ........................................................................ 22
    Trends, challenges and discontinuities .............................................. 23
    Time – to – market ............................................................................. 24
    Gaps and barriers ............................................................................. 27
    Most present and future relevant applications of nano-related products ... 31
  2.3 Non technological aspects .............................................................. 33
    Market trends for application ............................................................ 33
    Infrastructure requirements ............................................................... 37
    Educational requirements ................................................................. 37
    HSE issues ......................................................................................... 38
    European competitive position ......................................................... 40
  2.4 Recommendations .......................................................................... 42
  2.5 Annexes .......................................................................................... 44
    Statistics ............................................................................................ 44
    List of participants ............................................................................. 46
3 Molecular Imaging/ Biophotonics/ Medical Imaging .................................. 48
  3.1 Introducing the subject ................................................................... 48
  3.2 Scientific and Technological Aspects ................................................. 51
    Trends & needs during the next decade .............................................. 51
    Impact of nanotechnology in the field considered ................................ 53
    Advantages of nanotechnology over existing/ alternative technologies .... 55
    Technology evolution ........................................................................ 57
    Trends, challenges and discontinuities .............................................. 57
    Time – to – market ............................................................................. 58
    Gaps and barriers ............................................................................. 60
    Most present and future relevant applications of nano-related products ... 64
  3.3 Non-technological aspects ............................................................... 65
    Market trends .................................................................................... 65
    Infrastructure requirements ............................................................... 67
    Educational requirements ................................................................. 68
    HSE issues ......................................................................................... 68
    European competitive position ......................................................... 69
  3.4 Recommendations by the Delphi panel ............................................ 70
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 Annexes</td>
<td>72</td>
</tr>
<tr>
<td>Statistics</td>
<td>72</td>
</tr>
<tr>
<td>List of participants</td>
<td>75</td>
</tr>
<tr>
<td>4 Biochips/ High Throughput Screening/ Lab-on-a-chip devices</td>
<td>76</td>
</tr>
<tr>
<td>4.1 Introducing the subject</td>
<td>76</td>
</tr>
<tr>
<td>4.2 Scientific and Technological Aspects</td>
<td>79</td>
</tr>
<tr>
<td>Trends &amp; needs during the next decade</td>
<td>79</td>
</tr>
<tr>
<td>Impact of nanotechnology in the field considered</td>
<td>82</td>
</tr>
<tr>
<td>Advantages of nanotechnology over existing/alternative technologies</td>
<td>85</td>
</tr>
<tr>
<td>Technology evolution</td>
<td>86</td>
</tr>
<tr>
<td>Trends, challenges and discontinuities</td>
<td>86</td>
</tr>
<tr>
<td>Time – to – market</td>
<td>88</td>
</tr>
<tr>
<td>Gaps and barriers</td>
<td>91</td>
</tr>
<tr>
<td>Most present and future relevant applications of nano-related products</td>
<td>94</td>
</tr>
<tr>
<td>4.3 Non-technological aspects</td>
<td>96</td>
</tr>
<tr>
<td>Market trends</td>
<td>96</td>
</tr>
<tr>
<td>Infrastructure requirements</td>
<td>98</td>
</tr>
<tr>
<td>Educational requirements</td>
<td>99</td>
</tr>
<tr>
<td>HSE issues</td>
<td>99</td>
</tr>
<tr>
<td>European competitive position</td>
<td>99</td>
</tr>
<tr>
<td>4.4 Recommendations by the Delphi panel</td>
<td>100</td>
</tr>
<tr>
<td>4.5 Annexes</td>
<td>102</td>
</tr>
<tr>
<td>Statistics</td>
<td>102</td>
</tr>
<tr>
<td>List of participants</td>
<td>104</td>
</tr>
<tr>
<td>5 Biomolecular Sensors</td>
<td>105</td>
</tr>
<tr>
<td>5.1 Introducing the subject</td>
<td>105</td>
</tr>
<tr>
<td>5.2 Scientific and Technological Aspects</td>
<td>109</td>
</tr>
<tr>
<td>Trends &amp; needs during the next decade</td>
<td>109</td>
</tr>
<tr>
<td>Impact of nanotechnology in the field considered</td>
<td>111</td>
</tr>
<tr>
<td>Advantages of nanotechnology over existing/alternative technologies</td>
<td>112</td>
</tr>
<tr>
<td>Technology evolution</td>
<td>113</td>
</tr>
<tr>
<td>Trends, challenges and discontinuities</td>
<td>114</td>
</tr>
<tr>
<td>Time – to – market</td>
<td>116</td>
</tr>
<tr>
<td>Gaps and barriers</td>
<td>118</td>
</tr>
<tr>
<td>Most present and future relevant applications of nano-related products</td>
<td>123</td>
</tr>
<tr>
<td>5.3 Non-technological aspects</td>
<td>124</td>
</tr>
<tr>
<td>Market trends</td>
<td>124</td>
</tr>
<tr>
<td>Educational requirements</td>
<td>125</td>
</tr>
<tr>
<td>Infrastructure requirements</td>
<td>126</td>
</tr>
<tr>
<td>HSE issues</td>
<td>127</td>
</tr>
<tr>
<td>European competitive position</td>
<td>127</td>
</tr>
<tr>
<td>5.4 Recommendations by the Delphi panel</td>
<td>128</td>
</tr>
<tr>
<td>5.5 Annexes</td>
<td>130</td>
</tr>
<tr>
<td>Statistics</td>
<td>130</td>
</tr>
<tr>
<td>List of Participants</td>
<td>132</td>
</tr>
<tr>
<td>General conclusion and recommendations</td>
<td>133</td>
</tr>
<tr>
<td>6 Glossar</td>
<td>135</td>
</tr>
<tr>
<td>References</td>
<td>136</td>
</tr>
</tbody>
</table>
1 Introduction

Metabolism happens on the molecular cellular level. Although the knowledge about these complex processes seems to double every few years, they are still not fully understood to diagnose diseases at a very early stage, to treat and prevent them efficiently. Present medical practice is based on treatment of diseases once well defined and secured symptoms are occurring. In many cases curing can't be achieved because the disease has spread all over the body, involving too many organs and affecting the in body repair system too much.

A huge number of patients suffer and still many people are dying from side-effects caused by drugs and a lot of promising agents can’t be applied to patients due to their insolubility and thus the lack of suitable formulations.

Huge expectations have been raised to the impact nanotechnology will have on the medical sector. With improved biochip devices, new and more specific acting drugs will be found and synthesised. Complex biocompatible biochips, for example, covered with membrane fragments or living cells, will accelerate the search for and the testing of new agents and will advance the discovery of new markers for the detection of certain diseases as well as molecular

![Figure 1: Future development of diagnostics and therapy by the means of advanced medical tools](image-url)
and metabolic disorders. Specifically functionalised nanomaterials will form the interface between living matter and the technical devices.

In interaction with nano enabled molecular imaging techniques, a quantum leap is expected to occur in medical diagnostics, being shifted from the currently pursued symptom based approach to an early state diagnostics (Figure 1).

This offers totally new possibilities for specific therapies and healing must be newly defined. Moreover, the origins and development of diseases will be understood in order to repress emerging misdirected processes. The more is known about them and the earlier they can be detected, the better and more efficiently they can be defended.

Besides targeted drug delivery, nanotechnology is going to find new applications in the area of toxin removal. Recently, injectable nanodispersions have been shown to remove toxins from the bloodstream, including high concentrations of lipophilic therapeutics, illegal drugs, and chemical and biological agents.

Due to quantum phenomena, occurring at the scale of single atoms and small molecules, nanotechnology will bring up new materials with improved and novel physical, chemical and biological properties. New architectures from individual biomolecules and biomacromolecules will possess novel functions and biomaterials properties in the dimensional range between 0.1 - 1000 nm. Although dimensions over 100 nm can hardly be defined as “nano”, structures

![Figure 2: Nanotechnological impact on the topics covered](image)
of this size still have a biological relevance.

Nanoparticles, used for example for drug delivery are up to 400 nm in diameter and more\(^2\).

This is still small enough to be biologically significant. Thus, nanotechnology is going to revolutionise the medical sector. Some of the expected most important improvements are pointed out in figure 2.

By means of nanotechnology in interaction with other basic sciences and technologies it will be possible to increasingly discover and map the complex cellular machinery and to diagnose and treat diseases by the aid of appropriate drugs.

1.1 Definition

“Technology roadmapping is a technology management tool that attempts to plan and forecast the necessary steps toward achieving one or more technology goals. Technology roadmaps are different from project plans in that roadmaps attempt to emphasize the uncertainty in the forecast rather than create a linked set of tasks.

The value of a technology roadmap includes: communicating vision, encouraging collaborative thinking, garnering necessary resources to solve technology challenges, creating contingency approaches and consensus view for decision making.\(^3\)"

1.2 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 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)

1.3 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 become operational to a higher extend.

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.

1.4 Results

The document on hand is an analysis and synthesis of the opinions of a limited number of international experts gathered in a Delphi-like methodology which has been applied to four specific subjects. These subjects were derived from a focusing process and constitute narrow areas of application in the field of health and medical systems. The chosen narrow areas are considered to be distinct, however do interface to varying degrees with each other and the field of nanoscale materials. The focusing process for the health and medical roadmap was application oriented (“technology pull”) whereas the process for identifying subjects for the materials and energy roadmaps was driven by material properties and functionalities (“technology push”).

The structure of dedicated questionnaires was simultaneously aimed at being highly selective, covering the four topics in a sufficiently distinct manner, comparable to a high extend, concise as well as manageable by the experts. Based on the appraisal of the present state of the art room was given for perspective views and opinions on technical and non-technical barriers and possible means to overcome them.

Due to the intended limited number of experts questioned the results cannot be considered as statistically solid.
The present document constitutes the final version compiling the documents prepared for each of the four topics. Expert feedback was encouraged at the several national and the international conferences.

1.5 Methodology

General approach

For the roadmap exercise the Delphi-approach was applied by:

- Selecting top international experts on the field
- Preparing an on-line questionnaire dedicated to 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
- 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 website.

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, health and safety aspects), but also economic aspects and infrastructure requirements were performed.
The 11 topics identified, even not being completely homogenous in terms of scope or classification, were intended to adequately cover the field of bio-nanotechnology.

The following list was agreed upon by the different partners of the NRM project (similar classifications can be found in 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, regarding aspects like for example the degree of innovation, expected technological improvement, positive impact on human life, market size of application or speed, accuracy and functionality of therapy, four topics were selected (and validated in dialogue with the European Commission). The criteria were agreed upon with the European Commission and thoroughly discussed, involving international experts in the field of nanotechnology. 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

These topics must be regarded in a holistic way. This is visualised by the following figure, which illustrates how the topics affect for example the pharmaceutical value chain:

![Figure 3: Pharmaceutical value chain and involvement of the four technologies](image)

The topics represent enabling tools to arrive at an improved, highly individualised medicine and medical care. Interaction results in the fact, that progress in one of them affects the other. On the way towards an individualised medicine, promoted by nanotechnology, many challenges (technical, economic, social, ethical,..) have to be met.

Roadmaps elaboration

One roadmap report has been prepared for each of the four aforementioned topics. The preliminary results of these roadmap-exercises were integrated in one document and were presented in one international and eight national conferences in October and November 2005.
2 Drug encapsulation/ drug delivery/ drug targeting

2.1 Introducing the subject

Despite outstanding achievements in the diagnostic and therapeutic medical sector, the pre-symptomatic detection and defence of diseases like cancer, cardiovascular affections, 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, annually over two million adverse drug reactions occur and the annual number of fatal casualties as consequence of pharmaceutical side-effects only in the USA is bigger than 100 000 people, referring to the FDA/ Centre for Drug Evaluation and Research. Thus, the need for more specifically and efficiently acting drugs is very urgent. Research in pharmacogenetics is currently done. Due to the combination of personal compatibility with pharmaceutical effectiveness, it will be increasingly possible to harmonise the particular therapy with the patient's genetic makeup for drug metabolism, absorption, transport, and elimination, leading to a predictive medicine. This individualised approach will be maintained by nanotechnology and will be increasingly used to create systems that can deliver drugs to distinct areas within the body.

All participants of our Delphi panel were of the opinion that nanotechnology will provide pharmaceuticals with suitable properties which cannot be achieved in utilizing other concepts.

Nanoparticles will play one of the most important roles in future drug based therapy, due to their unique biological, chemical and physical properties. Nanoparticles are usually defined as particles with a size up to 100 nm. As mentioned before, the medical sector builds an exception because even particles, being bigger than 100 nm can have a biological relevance. In drug delivery, particles up to 400 nm and more show characteristics that will revolutionise the drug sector. Given their very small size, nanoparticles are able to enter human tissues and cells quickly. Particles smaller than 50 nanometers can enter most cells very well, while
those smaller than 20 nanometers can move through the walls of blood vessels. As a result, nanoscale devices can easily interact with molecules on both the cell surface and within the cell, often in ways that do not alter the behavior of those molecules.

Nanoparticles provide a unique opportunity for rapid delivery of active compounds and can be used to cross the blood retina barrier or the blood brain barrier (BBB) which represents a major barricade for a lot of chemical entities. The BBB is formed by endothelial cells surrounding the brain blood capillaries which are connected by tight junctions. Consequently, hydrophilic agents can’t pass the BBB. In addition, the endothelial cells possess extremely efficient efflux transporters that pump back most of the lipophilic drugs that normally would pass the cell membranes and then gain access and enter into the cells. Predominantly due to their size, nanoparticles can pass through the endothelial cell membrane. In case they contain therapeutic drugs, they can be used as “nanoscaled ferries”. Thus, the “insoluble” drug molecules will become in a way “soluble”, being deliverable directly to the eye or to the central nervous system in order to treat optical or neurological disorders. “Smart Drug Delivery Systems” which are presently searched for, should protect the drug against decomposition during it’s transport to it’s destination, accumulate actively or passively within target tissue and release the transported drugs in a controlled time-dose profile.

The enhanced individualisation of therapies, using targeted, specifically interacting drug containing shuttles, which release the transported agent in a controlled, well-dosed manner, will drop the particular drug amount and diminish side-effects due to lower intracorporeal drug concentrations and to defined local action. Moreover, nanoparticle based drug delivery is expected to considerably shorten the duration of therapies.

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 presently key targets.

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.
Impact of nanotechnology in Health and Medical Systems

Drug delivery/ drug encapsulation/ drug targeting

Figure 4: Most appropriate types of used nanoparticles in drug encapsulation/ drug delivery/ drug targeting

Inorganic Nanoparticles is the generic term for several nanoparticles including for example metal oxide- and non-oxide ceramics, metals, calcium phosphate, gold, silicate and magnetic nanoparticles. So called “nanoshells” combine various inorganic elements or materials. They typically have a silicon core which is sealed in an outer metallic cover. By varying the ratio of wall to core, the shells can be precisely tuned to disperse or absorb very specific wavelengths of light. Polymer nanoparticles involve various natural or biocompatible synthetic polymers like polysaccharides, poly lactic acid, poly lactides, poly acrylates, poly alkyl cyano acrylates, poly alkyl vinyl pyrrolidones or acyl polymers. They include rationally designed macromolecular drugs, polymer-drug and polymer-protein conjugates, polymeric micelles containing covalently bounded drugs, and polyplexes for DNA delivery. 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 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 lipo-
some nanoparticles 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. Some of the others experts are of the opinion that there are enough particles but a standardisation of their characterisation is urgently needed.

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.

Besides the above mentioned areas which will be influenced by it nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferably used with injectable drugs. The injection often results in a rapid rise of drug concentration which afterwards drops exponentially over time. This may cause difficulties with toxicity during the first (rising) phase and with drug efficacy during the second (dropping) phase, when the drug concentration falls below the medicative range.
Implantable time release systems may help to minimize peak plasma levels and reduce the risk of adverse reactions. Thus, the effective period can be extended without frequent re-dosing and drug action will be more predictable.

### 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. They 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 need further development for offering a wider product portfolio. More predictive medicine has a lower ranking and seems 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.

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 to this. 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 occurrence 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 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 connected 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 and can be interpreted that there is no expected direct impact on prevention but a rather indirect.

The developing grade of nanotechnological impact within the three application areas diagnosis, therapy and prevention is hardly to define accurately. 19 % 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 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. An significant impact by a factor of 10 is not seen to be likely.

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 regarded as a general enabling 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. As mentioned before, 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 it in amounts significantly large enough. 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.

Figure 9: Various advantages of nanotechnology over existing technologies
The magnetic/ thermal behaviour of certain types of nanoparticles combined with other specific properties opens a wider spectrum of therapeutical methods such as nanoparticles based thermotherapy.

All 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 by the experts consulted.

Assuming that the benefits which nanotechnology offers to the medical sector will exceed the risks and possible negative effects of nanoparticles, thousands of nanoparticles which will be well defined and characterised in a standardised manner will be available. They can be easily provided with the needed functionalisation for their specific therapeutical purpose and their specificity and effectiveness will be rapidly measurable in highly parallelised experimental setups like membrane- or cellchips. The deepened and more distinctive knowledge about the very specific acting agent, its predictable interaction with the target, its kinetic and predictable metabolism within the body in the forefront of any drug internalisation will lead to shortened experimentally validated approvals. 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 that match particular drugs, are discovered.

On the way to this scenario there are several technical and non technical challenges to be met which are listed further on.
Trends, challenges and discontinuities

Despite the huge expectation to nanoparticles, the technology is still at its early stage and there are a lot of challenges to meet.

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 for example several clinical trials. 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. Thus, one main challenge is to establish a sort of building block by which means required nanoparticles with particular functionalities can be combined pragmatically. For this purpose there is a need for rapid screening methods, for example high-throughput cell- or membrane biochips to efficiently find the right particle for the particular medical task. This does not only imply the possibly nanostructured biochip device which contains the biological, pharmaceutical and nanotechnological probe but also new, brilliant fluorescent dyes and a highly sensitive detection equipment, i.e. sophisticated excitation sources.

One of the biggest further 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 in 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. According to most of 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. With a deepened knowledge of the nanoparticles' properties, e.g. their specific interaction with biomolecules, cellular structures or their degeneration and controlled drug release and advanced know-how of disease genesis including the cellular metabolisms, there will be much more specifically acting drugs and an increasing number of specific applications which the experts within our panel demand. 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 appli-
cations. Furthermore they may interact with totally different targets due to
the patients genetic constitution. 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 pro-
teins 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 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 table 1.

**Table 1: Estimated global production rates for various nanomaterials and devices based on
international chemical journals and reviews (2003–2004), and market research (BCC
2001). Source: “Nanoscience and nanotechnologies” The Royal Society & The Royal Acad-
emy of Engineering, July 2004**

<table>
<thead>
<tr>
<th>Application</th>
<th>Material/device</th>
<th>Estimated production rates (tonnes/annum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skincare products</td>
<td>Metal oxides (titanium dioxide, zinc oxide, iron oxide)</td>
<td>10³, 10⁴, 10⁵ or less</td>
</tr>
<tr>
<td>ICT</td>
<td>Single-wall nanotubes, nano-electronics, opto-electro materials (titanium dioxide, zinc oxide, iron oxide), organic light-emitting diodes (OLEDs)</td>
<td>10³, 10⁴ or more</td>
</tr>
<tr>
<td>Biotechnology</td>
<td>Nanocapsule, targeted drug delivery, bio-compatible, quantum dots, composites, biosensors</td>
<td>less than 1, 1, 10</td>
</tr>
<tr>
<td>Instruments, sensors, characterisation</td>
<td>MEMS, NEMS, SPM, dippen lithography, direct write tools</td>
<td>10³, 10⁴, 10⁵–10⁶</td>
</tr>
<tr>
<td>Environmental</td>
<td>Nanofiltration, membranes</td>
<td>10³, 10⁴, 10⁵–10⁶</td>
</tr>
</tbody>
</table>
Nevertheless, drug delivery is expected to be one of the most profitable application of nanotechnology in medicine over the next two decades. During their transit through the body to the target, drugs need to be protected to maintain their biological and chemicals properties or to stop them affecting those parts of the body they travel through. Once a drug arrives at its destination, it needs to be released at an appropriate rate for it to be effective.

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 our experts to evaluate the stage of maturity of specific technical challenges of nanoparticles in the pharmaceutical sector.

The results which are shown in figure 10 reflect the relative importance of the particular nanoparticle properties and their implementation in applications within the next decade predicted in five (2010) and in ten (2015) years from now and give an integrated view on different development stages of the regarded 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 nanomaterial.

**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.

![Figure 10: Average technology stage of specific technical challenges of nanoparticles in the pharmaceutical sector](image)

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 being a relatively young technology having to experience 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 meddicative 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. Anyhow, a quarter of participants suppose not the nanoparticles to be the constraint or limiting factor 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 methods that can provide chemical

Figure 11: Expected evident bottlenecks in R&D in drug encapsulation/ drug delivery/ drug targeting
(molecular) characterisation at the nanoscale which have to be urgently de-
veloped as well as the sensitivity and specificity of functionalised nanoparti-
cles 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 2:

Table 2: Expected barriers in the development of particular types of nanoparticles

|                     | Technical | Economic | Medical | Infrastruc-
|---------------------|-----------|----------|---------|----------
| General             | X         | X        |         |          |
| Liposomes           | X         | X        |         |          | X        |
| Polymer Nanopart-
|icles              | X         | X        | X       | X        | X        |
| Nanocrystals        | X         | X        |         | X        | X        |
| Polymer Therapeu-
tics                  | X         | X        |         |          | X        |
| Inorganic Nanopar-
ticles            | X         | X        |         |          | X        |
| Chip-based techn-
|ology             | X         | X        |         |          |

The specifications of these barriers, given by the participants, are listed
below in table 3.

Table 3: Specified expected barriers in the development of particular types of nanoparticles

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Medical</th>
<th>Infrastructural</th>
<th>Environmental impacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomes</td>
<td>Too large in size and biokinetics as well as production is still too expensive</td>
<td>Production is still too expensive</td>
<td>Not yet analyzed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Polymer Therapeutics</strong></td>
<td>cell- + protein interactions are not resolved</td>
<td>Cost effective systems in relation to applications are needed to identify</td>
<td>Regulation of IP, contracts, time-line of cooperation</td>
<td>Not yet analyzed</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Polymer Nanoparticles</strong></td>
<td>A broader scale of materials with specific properties (e.g. biocompatible materials) have to be developed</td>
<td>Biokinetics as well as cell- and protein interactions are still not resolved</td>
<td>Low financing opportunities for late stage (growth phase) start-up companies and limited financial support for clinical evaluation</td>
<td>Production is still too expensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total biocompatibility, non-toxicity and biodegradability of the products are needed</td>
<td>Close co-operation of many teams within an international project / network is necessary,</td>
<td>Close co-operation of nanoscience, medicine and physics is needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Impact of Nanotechnology in Health and Medical Systems

**Drug delivery/ drug encapsulation/ drug targeting**

<table>
<thead>
<tr>
<th>Material Type</th>
<th>Challenges</th>
<th>Financial Support</th>
<th>Regulatory Approval and Safety Testing</th>
<th>Manufacturing Capabilities</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanocrystals</td>
<td>Stability problems in particles or liposomes have to be solved</td>
<td>Limited financial support for clinical evaluation</td>
<td>Moderate</td>
<td>Companies are not equipped for nanotechnology manufacturing</td>
<td>Not yet analyzed</td>
</tr>
<tr>
<td>Inorganic Nanoparticles</td>
<td>Biokinetics and cell- + protein interactions are not resolved</td>
<td>High costs of production</td>
<td>High costs of production</td>
<td></td>
<td>Potential toxicity</td>
</tr>
<tr>
<td>Chip based technology</td>
<td>Design of miniaturised systems for in vivo and ex vivo sensing</td>
<td>High costs of production</td>
<td>Must be cost effective</td>
<td></td>
<td>Potential toxicity</td>
</tr>
</tbody>
</table>
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 pharmaceutical 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. 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.

As can be seen in figure 12, most of the relevant applications of nanoparticles in health are supposed to be in drug targeting. Drug delivery will be enhanced 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
The importance of nanotechnology in this technology is supposed to level off by the experts. 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[^7], 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.

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 targets, a bioinorganic interface in form of a biological or molecular coating or layer should be attached to the nanoparticle.

![Diagram of nanoparticles with various properties and functions](image)

Figure 13: Typical configurations utilised in nanoparticles applied to medical or biological problems
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.

As stated above, one of the main goals of nanotechnologically improved drug formulations is to target the agents in a specific, well dosed and well localised manner, preferably tuned to the respective local and time-dependent intracorporeal needs.

One example are loaded nanoparticles, i.e. Nanoshells, which attach to the specific site of action and release temperature-dependent their payload when illuminated with the proper wavelength, since they convert high-level radiation into low-level radiation and heat.

A similar example is the usage of hyperthermia and thermoablation to destroy malignant cells. This therapy is based on the injection of specifically coated magnetic nanoparticles in an aqueous dispersion into a tumour and subsequent heating in an alternating magnetic field. Temperatures are ranging from 43-46°C (hyperthermia) to 47-70°C (thermoablation).

2.3 Non technological aspects

Market trends for application

The world pharmaceutical market in 2004 was about $ 506 billion. 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. Due to a study by BCC the potential of nanoscaled drug delivery systems is estimated at $ 50 million in 2007.

Dependent on the source, several statistics about the governmental funding and investment in nanotechnology research and the respective past and future development exist. They all display an increasing worldwide investment in this sector, reaching from five-fold to more than ten-fold in the past six years. 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.
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 (figure 14) one third of the experts 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 probe14.

Figure 14: Percentage of the market that will be captured by nanotechnology in gene sequencing

Most of the experts agree upon the market share of nanotechnology in target identification to range between 5 and 25% (figure 15) and in formulation to range between 25 and 50% (figure 16), indicating that these are the main categories which can be influenced by nanotechnology.
In lead development (figure 17) about 40% of the experts estimate the percentage of the market which will be captured by nanotechnology to run from 5 to 25%. The impact of nanotechnology in this area will be seen in the nanotechnological optimisation of production processes (i.e. catalysis, nanoparticle based gene transformation) as well as in improvement of peripheral equipment (i.e. surface coating of high-throughput devices for de-
etection and analysis, improved laser crystals for optimised excitation of fluorescence marked molecules, etc.).

**Figure 17:** Percentage of the market that will be captured by nanotechnology in *Lead development*

**Figure 18:** Percentage of the market that will be captured by nanotechnology in *Target validation*
Impact of nanotechnology in Health and Medical Systems

Drug delivery/ drug encapsulation/ drug targeting

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 seemed not to be a crucial factor for their activities in this field.

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.

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. This seems to be a very important issue and should be strongly emphasised. Furthermore there is a need for the support and funding of technology transfer from a research status into products. According to some experts, in general there is a good to very good state of basic research and on the other side several application driven projects can be governmentally supported by respective funding programs. The crossover between these two poles is rarely filled and there is a gap prior to the production transfer. This means a huge financial risk for small and medium sized enterprises and often cannot be afforded by them.

A furthermore important aspect, especially in the pharmaceutical sector is that product approval processes typically are very long which means that health benefits to users and economic benefits to companies usually take longer to realise than in other domains. In consequence, matured drugs must be kind of “blockbusters” to regain the invested money for long and complex drug development. The more individualised a future medicine is going to be, the smaller is the relevant target group and market. Thus, the approval processes for tailored, widely individualised pharmaceuticals have to be shortened without loss of quality in analogy to already existing orphan drug states.

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 of the size of proteins and can interfere with normal cellular signalling pathways. In several scientific experiments, it has been shown that nanoparticles can for example be assimilated by the brain, that they can cause acute inflammation with secondary effects such as cancer or that combustion nanoparticles cause worsening of heart disease, atherosclerosis and asthma.

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 discus-
sion 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.

“The economic growth in the field of nanotechnologies will lead to an increased variety and increased volumes of engineered nanoparticles that are produced. Even if exposure assessments and data are still lacking it is foreseeable that some degree of exposure to engineered nanoparticles - for various segments of the population and for the environment – will occur to an increasingly extend over the coming years. Keeping in mind that these "free nanoparticles" can enter the human body over various pathways (inhalation, ingestion or via the skin) or disperse into the environment, it is important to understand the implications for human health and the ecosystems. To assess the risks of nanoparticles, established methods of chemical safety assessments have to be modified to address the special characteristics of nanoparticles. The main difference to the assessment of bulk materials is the fact that additional parameters like size, shape or surface properties will come into play. The same reason that makes nanoparticles technologically interesting leads to the fact that they represent a new category of (potentially) toxic substances.

The interaction with the human body and their health effects are expected to be different from molecules as well as from bulk materials of the same composition. It is necessary to understand both, the hazards associated with nanomaterials and the levels of exposure, that are likely to occur. In both areas, the existing knowledge is quite limited and it will be necessary to generate and establish new data in the future.

When bulk materials are made into nanoparticles, they tend to become chemically more reactive – this is why they are very interesting as catalysts. Even chemically inert materials like gold or platinum are able to catalyse chemical reactions in nano-powder form. Many studies indicate that nanoparticles generally are more toxic when incorporated into the human body than larger particles of the same materials. Experts are overwhelmingly of the opinion that the adverse effects of nanoparticles cannot be reliably predicted or derived from the known toxicity of the bulk material\(^{16}\). The biggest concern is that free nanoparticles or nanotubes could be inhaled, absorbed through the skin or ingested.

For the majority of nanoparticles the toxicological, ecotoxicological data needed to perform a hazard analysis are still lacking. Even if the details are not yet clear, it is evident that the interaction with the human body will de-
Impact of nanotechnology in Health and Medical Systems

Drug delivery/ drug encapsulation/ drug targeting

pend on various parameters such as chemical composition, particle size, surface area, biopersistence and surface coatings among others. Therefore, until a theory of the impact of nanoparticles on human health has been established, each nanomaterial should be treated individually when health hazards are evaluated. A systematic risk screening will be helpful to establish the basic know-how to understand the interaction with the human body and the environment and to establish the theoretical framework needed. Besides toxic effects, the interaction of nanoparticles that have entered cells opens a wide field of potential effects resulting from the interaction with cell structures such as ribosomes and DNA.\textsuperscript{17}

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 figure 19). 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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure19.png}
\caption{Worldwide position of European industry and science compared to other regions}
\end{figure}
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 Science Foundation should be mentioned which gives a scientific look on nanomedicine and which raises the issue of international competitiveness.18

“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.”

Forming synergistic collaborations with drug and medical device companies represents one of the most obvious routes of achieving such multidisciplinary 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

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 in figure 20.

Figure 20: “Europe should reinforce its future activities in...” Estimations by the expert panel within drug delivery/ drug encapsulation/ drug targeting

According to the experts future activities should predominantly be reinforced in targeted drug delivery. About 50% of the experts ask for a stronger emphasis in drug encapsulation, tissue engineering, molecular imaging and diagnostic systems on the technical side. On the non-technical side the clarification of a potential interaction of nanoparticles with living organisms
Impact of nanotechnology in Health and Medical Systems
Drug delivery/ drug encapsulation/ drug targeting

is seen to be very important, followed by a need for better public understanding and a thorough risk assessment. Especially the need for a better public understanding should be handled in a very sensitive way. This cannot be understood as the simple causality that once there is a better public understanding of scientific backgrounds, an increasing acceptance will occur. Thus, the dialogue between proponents and antagonists of nanotechnology must be conducted very carefully.

Besides the challenges that have to be met in order to overcome the mentioned gaps and barriers, further recommendations can be summarised from this report:

- The experts within the nanoparticle roadmap named inorganic nanoparticles, especially ceramics, metals, silicates and non-oxide ceramics to be the most common nanoparticles, whereas in drug delivery a lot of other types (polymer nanoparticles, liposomes etc.) are of pharmaceutical relevance. Since the world pharmaceutical market is respectable, more future effort is to be put in researching and developing the particular needed particles for these applications.
- Several experts state that there is a need for the investigation of further nanoparticles
- A standardisation of nanoparticle characterisation is urgently needed. One mentioned possibility to guarantee for this need is the establishment of specialised institutions in analogy to the German federal institute of material research and testing (BAM).
- Need for multidisciplinary centres with advanced knowledge on materials development and own pilot production facilities
- “Orphan drug status” for tailored, widely individualised pharmaceuticals is crucial
- Development of inter-disciplinary expertise across a range of suitable technologies
2.5 Annexes

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 invited to participate without being related to a special topic in advance. Seven of them answered, three of them within the pharmaceutical topic. About 65% 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 (54%) came from academia. 34% came from industry, 15% from public research organisations and 8% from private research organisations. Most of the participants (58%) are engaged in drug delivery, 39% deal with drug targeting and about 23% are busy in drug encapsulation (multiple answers were possible). 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.
**List of participants**

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert Anderson</td>
<td>Polymer Laboratories</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Udo Bakowsky</td>
<td>Philipps-University Marburg</td>
<td>Germany</td>
</tr>
<tr>
<td>John Daicic</td>
<td>Ytkemiska Institutet AB (YKI)</td>
<td>Sweden</td>
</tr>
<tr>
<td>Ruth Duncan</td>
<td>Welsh School of Pharmacy, Centre for Polymer Therapeutics</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Mike Eaton</td>
<td>Celltech Group</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Ben-Jacob Eshel</td>
<td>Tel-Aviv University</td>
<td>Israel</td>
</tr>
<tr>
<td>Paolo Facci</td>
<td>University of Modena and the Region of Emilia, Department of Physics</td>
<td>Italy</td>
</tr>
<tr>
<td>Monia Gentile</td>
<td>Center for Applied Research in Micro and Nano Eng., (CRIM)</td>
<td>Italy</td>
</tr>
<tr>
<td>Ian Gilmore</td>
<td>Surface and Nano-Analysis, National Physical Laboratory, Teddington (NPL)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Heinrich Hofmann</td>
<td>Section de Science et Génie des Matériaux - SMX, EPFL</td>
<td>Switzerland</td>
</tr>
<tr>
<td>P.J. Jansens</td>
<td>Netherlands Institute for Scientific Information Services</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Andreas Jordan</td>
<td>MagForce Applications, GmbH</td>
<td>Germany</td>
</tr>
<tr>
<td>Elmar Keßenich</td>
<td>BASF AG</td>
<td>Germany</td>
</tr>
<tr>
<td>Rafi Korenstein</td>
<td>Department of Physiology and Pharmacology, Sackler Faculty of Medicine,</td>
<td>Israel</td>
</tr>
<tr>
<td>Wolfgang G. Kreyling</td>
<td>Focus Network Aerosols and Health</td>
<td>Germany</td>
</tr>
<tr>
<td>Claus Michael Lehr</td>
<td>Department of Biopharmaceutics and Pharmaceutical Technology, Saarland University</td>
<td>Germany</td>
</tr>
<tr>
<td>Armin Leng</td>
<td>Merck KgaA</td>
<td>Germany</td>
</tr>
<tr>
<td>Mauro Magnani</td>
<td>University Urbino, Institute of Biochemistry</td>
<td>Italy</td>
</tr>
</tbody>
</table>
**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  
Finland

**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

Special thanks to **Professor Dr. Wolfgang Meier**, Institute of Physics, University of Basel, Switzerland, who mentioned valuable aspects within the topic which were integrated into the document.
3 Molecular Imaging/ Biophotonics/ Medical Imaging

3.1 Introducing the subject

Medical Imaging comprises all imaging technologies utilized in the medical field. There are four main medical imaging modalities — X-ray (including computer tomography, CT), magnetic resonance imaging (MRI), radiopharmaceutical imaging, and ultrasound. In X-ray imaging contrast agents are introduced into the body to give clear images, e.g. of organs and soft tissues, from X-ray scans. In magnetic resonance imaging (MRI), contrast agents are introduced into the body to make images from MRI scans. In radiopharmaceutical imaging, products are incorporated which concentrate in particular organs or tissues and can be traced to give a clear image. In ultrasound imaging, contrast agents are given into the body to make ultrasound scans and in radiotherapy, products are designed for the treatment of cancer and other conditions such as thyroid disease. Radiopharmaceutical imaging always requires a diagnostic product, while the other three modalities may or may not use a diagnostic product, depending on the procedure. Each modality is rapidly evolving to meet the growing demands of modern healthcare requirements. Overall, the emphasis in technology advancement is to improve the speed, efficiency and functionality of instrumentation, lower its cost and hence, increase accessibility.

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 produced images reflect cellular and molecular pathways and in vivo mechanisms of present diseases 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\textsuperscript{19}. 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 being 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 fibre optics. Biophotonics uses light beams and other forms of energy to diagnose and monitor medical conditions. It can be described as the science of generating and using light (photons) to image, detect and manipulate biological materials. One technology among this field is the Photodynamic Therapy (PDT) in which drugs, called photosensitizers or photosensitizing agents and particular types of light are used to delete pathogenic tissue in a specific manner. In the first step of currently performed PDT for cancer treatment, a photosensitizing agent is injected into the bloodstream. The agent is absorbed by cells all over the body but stays in cancer cells longer than it does in normal cells. Approximately one to three days after injection most of the agent has left normal cells but remains in cancer cells. When the photosensitizers within the tumour cells, are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. To date, the U.S. Food and Drug Administration (FDA) has approved the photosensitizing agent Photofrin\textsuperscript{®} for use in PDT to treat the symptoms of gullet cancer and a special form of cell lung cancer. Since the light needed to activate most photosensitizers cannot pass far into the tissue and thus, PDT cannot be used to delete large or metastasized tumours, researchers continue to study ways to improve the effectiveness of PDT in focussing on the development of photosensitizers that are more powerful, which do more specifically target cancer cells, and are activated by light that can penetrate tissue and treat deep or large tumours. Researchers are also investigating ways to improve
equipment and the delivery of the activating light. Nanotechnology is going to promote biophotonics and consequently PDT by facilitating the targeting of photosensitizers which are incorporated in the above mentioned targeted drug delivery vehicles. Thus, Biophotonics could be used more efficiently in disease defence, e.g. anti-cancer therapy. After vesicles have docked to their target, sick tissue (e.g. tumour cells) are going to be destroyed.

In terms of the most appropriate types of nanoparticles in Molecular Imaging there are no clear preferences. The experts participating in our Delphi exercise named dendrimers, linear polymers, filled phospholipids, microbubbles and “other”. These, were nano-caged compounds, multimeric (or unimeric) micellar assemblies as well as inorganic nanoparticles with tuneable physical properties (figure 21).

**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. They form a subgroup of polymer therapeutics (see figure 5). Dendrimers can be made out of nearly anything that can branch (metal atoms, organometallic groups, or purely organic materials) and they can have a variety of functionalities depending on the application. 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 in ultra-sound applications. 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 diagnosis 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 superparamagnetic 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.

The recently often mentioned quantum dots are like "artificial atoms". The structures of 1 nm in diameter are made of materials such as silicon. They can be made to emit light at different wavelengths. The colour of the emitted light depends on the size of the dots. The larger the dot, the longer becomes the wavelength of the emitted light, moving towards a red colour. The smaller the dot, the bluer is the emitted light. Just by changing the dot size of a single material, a sample board of colours can be emitted.

3.2 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 clinical treatments. 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 diseases, and evaluation of treatment. This is reflected in the experts’ estimations (figure 22) according to which more future emphasis has to be put in individualisation of therapies (78%), followed by specific acting pharmaceuticals and theranostics (56% each) in which the latter is defined as the clinically targeted integration of diagnostics and therapeutics. 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 another expert, a 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 (figure 23). 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.

Figure 23: Impact of nanotechnology in certain medical emphasises during the next decade
Estimations of the experts within the Molecular Imaging sector
Regarding the potential of nanotechnological based molecular imaging and biophotonics to detect and medicate special diseases there is a clear

![Figure 24: The impact of nanotechnology in the healing of the shown diseases in 2015 will be...](image)

Estimations of the experts within the Molecular Imaging sector negation with a few exceptions, i.e. cancer, vascular and cardiovascular diseases as well as viral infections (figures 24-26). The supposed impact of

![Figure 25: The impact of nanotechnology in the healing of the shown diseases in 2015 will be...](image)

Estimations of the experts within the Molecular Imaging sector
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 benefit 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 nanoparticle targeting 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 net-
works 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 (figure 27).

![Figure 27: “The most revolutionary properties of nanoparticles are...” Estimations of the experts within the Molecular Imaging sector](image)

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 and monitor the location and possibly the action of a potential drug in an animal model, before phenotypic changes become obvious, and afterwards start to move into human studies. Moreover, by improving the possibilities of medical imaging and moving deeper and deeper into the molecular level, it is likely that preclinical trials prior to human studies can be accelerated, once drugs with unfavourable bio distribution and/or pharmacokinetics can be ruled out and pharmacokinetics can be detected and analysed in a highly parallel and highly efficient manner.
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

Research in biology 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 non-invasive 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. Neverthe-
less the technology is still at its early stage and there are huge challenges to meet.

Nanotechnology in molecular imaging within living subjects offers more theoretical and practical challenges than in vitro or cell culture detection, primarily because the probes need to be biocompatible, additional delivery barriers have to be overcome and special in vivo amplification strategies are needed to be developed. 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 to overcome biological barriers efficiently. 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 (figure 28) 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 hy-
Impact of nanotechnology in Health and Medical Systems
Molecular Imaging

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.

Figure 28: Average technology stage of specific technical challenges of nanoparticles in the medical imaging sector
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 within our Delphi panel the targeting of nanoparticles will be sufficiently investigated in 2015 that the Photo Dynamic Therapy, which is regarded to be presently in an applied status, will enter mainstream applications. The directed transport through biological barriers is expected to be at the stage of first applications. Since this transport happens more or less passively, obviously much more effort has to be put in improved active and well targeted transport processes.

Gaps and barriers

Nanotechnology is a relatively young technology which means that several gaps and barriers exist.

![Figure 29: Expected evident bottlenecks in R&D in molecular imaging](image)

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 (figure 29). 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. The most basic barrier 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.

Table 4: Expected barriers in the development of particular types of nanoparticles

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Medical</th>
<th>Infrastructural</th>
<th>Environmental impact</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Filled phospholipids</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Microbubbles</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dendrimers</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inorganic nanoparticles with tuneable physical properties</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Impact of nanotechnology in Health and Medical Systems

Molecular Imaging

<table>
<thead>
<tr>
<th>Linear polymers</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimeric or “unimeric” micellar assemblies</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

The specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in table 5:

**Table 5**: Specified expected barriers in the development of particular types of nanoparticles

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Infrastructure</th>
<th>Environmental impact</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Patient safety; stability</td>
<td>Product development is too expensive</td>
<td></td>
<td>Toxicity concerns and disposal routes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Analytical technique development for nanoscaled chemical surface analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filled phospholipids</td>
<td>Investments for instruments are mandatory for successful work</td>
<td>Bottom up interdisciplinary work is important</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microbubbles</strong></td>
<td><strong>Dendrimers</strong></td>
<td><strong>Inorganic nanoparticles with tuneable physical properties</strong></td>
<td><strong>Linear polymers</strong></td>
<td><strong>Mutimeric (or unimeric) micellar assemblies</strong></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breakthroughs on research (e.g. coating)</td>
<td>Suitable manufacturing process and quality control with industrial level</td>
<td>See text below</td>
<td>See text below</td>
<td></td>
</tr>
<tr>
<td>Close collaboration between industry, academia and regulatory bodies</td>
<td>The relatively high cost of “pure” dendrimers could be overcome by the use of hyperbranched linear polymer systems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Integration of European medicines evaluation agency (EMEA) to change approval process</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Linear polymers**: Technical barriers are the non degradability of many of the responsive polymer systems and even the non responsive "simple" hydrophilic carriers. This may result in significant bioaccumulation. Therefore,
the development of fully or partially degradable systems is important without loss of scalability & economic viability of the products.

**Multimeric or unimeric micellar assemblies:** Stable micellar assemblies & polymersomes, plasma half life & targeting efficiency of certain therapeutics are often limited by intercellular compartmentalisation into non productive vesicles which lowers efficiency. Current efforts towards responsive micellar systems for triggered release are addressing such issues and 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.

**Figure 30:** Most important applications of nanotechnology in the medical sector
According to the experts, the main impact of nanotechnology will occur in molecular therapy (figure 30). 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 above mentioned semiconductor nanocrystals, called quantum dots promise to provide greatly enhanced capabilities for medical imaging and diagnostics. They show increased intensity of fluorescent light emission when illuminated with excitation radiation which leads to an increased brightness, they have longer lifetimes for fluorescing, and emit over a narrow spectrum, resulting in much more colours than obtainable with conventional materials. Thus, quantum dots allow for efficient multicolour imaging of biological samples and should be especially useful for fluorescence imaging in living tissues, where signals can be obscured by scattering and competing intrinsic emissions. Coated with biocompatible layers or proteins they may not be recognised by living cells as toxic. Quantum dots could possibly be used to repair damaged neural pathways or to deliver drugs by activating the dots with light.

The experts expect the probability that nanotechnology will play an important role in medical imaging 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.

### 3.3 Non-technological aspects

#### Market trends

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 considerable 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 expected 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 field21.
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 (figure 31). 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%.

**Figure 31:** Most important applications of nanotechnology in the medical sector

*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 seems 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. Regarding the increased linkage between industry and academia combined with a greater internationality, some of the experts underlined the value and effectiveness of existing supporting programs, i.e. the Marie-Curie fellowships and emphasised the further need for such support actions.

Furthermore the establishment of an European health institute (comparable to NIH) was demanded to bundle and streamline biomedical research, reduce bureaucratic burden in 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 imaging field. Especially in terms of production processes shortened and more simplified approval procedures are required. Existing regulations demand for a totally new production permission if known and well characterised basic components, i.e. nanoparticles, used as contrast media, are functionalised. This means that the whole process, including every single step, has to run a long and time-consuming approval process, even if manufacturing doesn’t change up to the functionalisation step. Moreover, the integration of the European medicines evaluation agency (EMEA) has been asked for, to change and improve approval processes.

As already argued before, also the experts within the molecular imaging topic state that bottom-up interdisciplinary work is important to handle and master the complex challenges and tasks to combine and network the various sciences and technologies in order to develop smart and highly target-oriented products for modern applications.

**Educational requirements**

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

There is a need for focussing and multidisciplinary education, with chemistry, biology, physics and medicine being basics which still should constitute the fundament and the “nano” requirements to net these sciences. All experts within the molecular imaging field 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 or 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. Since the categories drug encapsulation/ drug delivery/ drug targeting and molecular imaging are very close in terms to the nanotechnological impact and do partly overlap, the above presented opinions and statements are valid also for this topic.

European competitive position

The Delphi panel on molecular imaging has a relatively high proportion of industrial participants. Figure 32 illustrates the quite consistent experts view on the competitive position of Europe in comparison to the global situation. It is stated to range between good and satisfactory in all size categories of industry.

![Figure 32: Worldwide position of European industry and science compared to other regions](image)

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 excel-
lent 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.

### 3.4 Recommendations by the Delphi panel

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

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.

![Graph showing recommendations](image-url)

**Figure 33: “EU should reinforce its future activities in...”** Recommendations by the experts within the molecular imaging topic.
In addition the Delphi panel has expressed their opinion on the need to reinforce European endeavours in non-technological aspects (figure 34).

![Figure 34: “EU should reinforce its future activities in...” Recommendations by the experts within the molecular imaging topic]

In interpreting the result and comparing it to the other topics examined it certainly has to be considered, that each topic-specific expert group is expressing opinions from their particular point of view. Main activities have to be put in technological aspects. Nanoparticle targeting, molecular imaging and development of diagnostic systems are emphasised by the experts.
3.5 Annexes

Statistics

Within the topic molecular imaging/biophotonics we asked 20 international experts from 9 countries. In addition 32 experts were invited 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.

Nine experts answered in total, the international distribution is shown in the left figure: 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.

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

**Figure 35:** Background of participating experts (main foci)

**Figure 36:** main activities of the participating experts within the molecular imaging sector
microdissection and downstream applications, drug delivery, activated nanoparticles by external field, optical coherence tomography; bioendoscopy, 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.
List of participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabio Beltram</td>
<td>National Enterprise for NanoScience and Nanotechnology</td>
<td>Italy</td>
</tr>
<tr>
<td>Mark Eccleston</td>
<td>University of Cambridge, New Museums Site, Department of Chemical Engineering</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Ian Gilmore</td>
<td>National Physical Laboratory Teddington (NPL)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Alex Knight</td>
<td>National Physical Laboratory (NPL)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Ruth Knüchel-Clarke</td>
<td>Medizinische Fakultät der RWTH-Aachen</td>
<td>Germany</td>
</tr>
<tr>
<td>Laurent Levy</td>
<td>Nanobiotix Prologue Biotech</td>
<td>France</td>
</tr>
<tr>
<td>Ralf Raue</td>
<td>Philips Medical Systems</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Tobias Schäffter</td>
<td>Philips Medical Systems</td>
<td>Germany</td>
</tr>
<tr>
<td>Karin Schütze</td>
<td>PALM Microlaser Technologies AG</td>
<td>Germany</td>
</tr>
</tbody>
</table>

We like to thank Dr. Andreas Briel, Schering AG, Germany who gave us an exclusive interview and mentioned valuable aspects within the topic which were integrated into the document.
4 Biochips/ High Throughput Screening/ Lab-on-a-chip devices

4.1 Introducing the subject

Biochips, broadly defined, are measurement devices, combining electronics and biology for research and diagnosis. They can hold and analyze in a highly parallelised way 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 infectious diseases. Through permanent technological advancements, the former rather passive elements become increasingly active devices. This appreciably leads to a reduced differentiation between biochips (i.e. lab-on-a-chip devices) and biomolecular sensors.

The tremendous diversity of biochips derives from the wide range of possible detection methods. Among these are electronic devices such as field effect transistors, microelectromechanical system (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, DNA fragments 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 highly parallel analyses of genes and gene products and thus make a whole new experimental approach possible in molecular biology.

![Figure 37: Most appropriate types of nanotechnologies in biochips/ HTS/ lab-on-a-chip devices](image_url)

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 on to 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 (e.g. light trapping, transmission, opaqueness, fluorescence, waveguides, “light valves”, anti reflection, etc.),
- Mechanical (e.g. wear/ abrasion resistance, hardness, scratch resistance, dry lubrication, reduced strain-to-failure, etc.),
- Electrical (e.g. energy potentials, binding energies, conductivity, insulation, etc.),
- Chemical (e.g. water repellence, anti-fogging, chemical barriers and chemical inertness, oxygen or moisture barriers over polymers, antimicrobial surfaces, etc.),
- Magnetic (e.g. data storage) and
- Thermal characters (e.g. application of multi-layered thin films allows, for instance, blocking the travel of atomic vibrations that produces heat flow while still allowing an electron flow as a current application in thermoelectric devices).

**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.

**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\(^2^4\).

**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.

### 4.2 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 technique to generate hypothesis. Studies using microarrays have served to advance understanding of disease processes and are going to accelerate knowledge gain about fundamental biochemical processes. With the evolving technology, it will become a tool for clinical medicine, providing a rich source of information on disease susceptibility, diagnosis and prognosis.

Regarding the trends and needs in biochip technologies during the next ten years, two-thirds of the experts within this topic demand for more emphasis in implantable biosensors, and the individualisation of therapies (figure 38). Both implies a maturation and improvement of existing biochip devices to become for example biocompatible, more precise, reliable etc. 58% of the experts are of the opinion, that future medicine will need more pre-

![Figure 38: “Future medical practice will need more...” Estimations of the experts within the biochip topic](image)
dictive medicine. Besides the deepened knowledge about the complex cellular processes this could imply genetic testing of individuals to forecast a genetic susceptibility to future diseases. This individual, predictive and probably preventive approach sounds in a way auspicious. However, its realisation has to be handled with care, since a lot of questions about ethical concerns and privacy laws have to be discussed and answered. In a more general view it is certainly a surplus to establish causalities between distinct metabolic processes and certain diseases. 50 % 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. 33 % of the experts are of the opinion that theranostics, as an integrated diagnose and therapy, will be of added future benefit. These results differ slightly from those for the drug delivery and molecular imaging sectors which participants (48 % resp. 56%) expect a further emphasis in theranostics. Predictive medicine is rated only by 28 % of the experts within the drug sector expect to need a future emphasis.

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 nano-structuring, which will offer novel ways to design and create biochip architectures, to coat surfaces, and produce building blocks for small devices as

![Figure 39: “Most important current and future applications of nanotechnology in the medical sector, part 1” Estimations of the experts within the biochip topic](image-url)
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 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 (figures 39, 40). 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.

Figure 40: “Most important current and future applications of nanotechnology in the medical sector, part 2” Estimations of the experts within the biochip topic
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 firstly in gene identification and gene sequencing with both DNA microarrays and better imaging tools and secondly 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 through a quantum leap in sensitivity and will decrease cost and errors. In identification of suitable drugs, the expected nanotechnological impact is also rather high and is expected to enable the development of

![Image](https://i.imgur.com/123456789.png)

**Figure 41: The impact of nanotechnologically improved biochips in the shown topics in 2015 will be…” Estimations of the experts within the biochip sector.**

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.

Figure 42: The impact of nanotechnologically improved biochips in the shown topics in 2015 will be...” Estimations of the experts within the biochip sector.
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 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 microreactor technology**.

Figure 43: The impact of nanotechnologically improved biochips in the shown topics in 2015 will be…” Estimations of the experts within the biochip sector
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 (figure 44). 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.

![Figure 44: Most revolutionary properties of nanotechnology in biochip sector](image)

These qualities will lead to improved biochip devices, such as lab-on-a-chip 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.
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 is 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 sector are evolving, one of them being the point-of-care market, in which companies are developing simple, low-cost blood screening tests for easy and rapid detection of e.g. 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.

Trends, challenges and discontinuities

A key challenge to the biochip industry is a 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 table 6:

Table 6: Estimations of the experts about major challenges within the biochip sector, and how nanotechnology is going to help to realise them.

<table>
<thead>
<tr>
<th>The major challenges of biochip technologies within the next 10 years</th>
<th>How is nanotechnology to help realising those trends?</th>
</tr>
</thead>
<tbody>
<tr>
<td>While the hardware technological background is sound, the biological components need further studies to improve stability, reproducibility and performance related to the specific needs.</td>
<td>Funding on fundamental aspects of nanotechnology without a clear commercial target, is vital.</td>
</tr>
<tr>
<td>Sample handling and delivery as well as the interfacing of the nanosensor with the macroworld</td>
<td>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 micro-analysis that happened in the sixties</td>
</tr>
<tr>
<td>Finding a cheap way of biochip production while improving their quality, in terms of density and chip-to-chip reproducibility</td>
<td>Novel production methods, better density, better characterisation tools, chip-to-chip reproducibility, better characterisation and imaging tools</td>
</tr>
<tr>
<td>Solving standardisation and reproducibility problems which are impeding medical diagnostic applications</td>
<td>Providing inexpensive high throughput solutions</td>
</tr>
<tr>
<td>To ensure a quality control technology as required by the regulatory bodies for diagnostics</td>
<td>Production technologies for spotted arrays that give yields close to 100%</td>
</tr>
<tr>
<td>To bring down costs and increase throughput to reach the status quo of</td>
<td>Miniaturization and parallel processing</td>
</tr>
</tbody>
</table>
### Impact of Nanotechnology in Health and Medical Systems

**Biochips/ High Throughput Screening/ Lab-on-a-chip Devices**

<table>
<thead>
<tr>
<th>today's analyzers</th>
<th>Long term stability of the biologic components</th>
<th>Chemically well defined surfaces, interdisciplinary work of material scientists and biologists to create biomimetic structures and architectures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reliable and cost-effective large scale production of robust devices utilization of self-assembly techniques in fabrication reimbursement through health care systems</td>
<td>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 diagnostic applications are concerned. Nanotechnology can bring about potential advantages with respect to sensitivity and selectivity of detection.</td>
</tr>
<tr>
<td></td>
<td>Will be driven by applications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Highly sensitive, selective biosensors, system integration: how to integrate the different enabling components</td>
<td>Mainly from the sensor point of view with regards to improvement in sensitivity and selectivity via new functionalised nano-bio interfaces.</td>
</tr>
<tr>
<td></td>
<td>Lowering the manufacture costs. Solutions that then become affordable to the wider community → technology platform</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Development of cell-based biochips</td>
<td>Realisation of cell compatible surfaces and realisation of tools for cell manipulation and characterization</td>
</tr>
</tbody>
</table>

**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.
Impact of nanotechnology in Health and Medical Systems
Biochips/ High Throughput Screening/ Lab-on-a-chip devices

(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. This result indicates the huge estimations which are coupled to nanotechnology in the particular applications. The fact that whole genome arrays are stated to be mainstream arrays assumes that there is a market for these devices. Presently they are, due to reproducibility and standardisation problems as well as high costs predominantly used in research applications. One of the main challenges which have to be met in implantable biochips is biocompatibility. According to the experts, research in this area should be emphasised during the next years. Otherwise they cannot enter, as expected, the first application stage. Besides the biocompatibility there are various other barriers to overcome, among them the stability of biomolecules which are linked to the sensors and thus the lifetime of such an implant, the occurring proliferation of surrounding cells and a subsequent occlusion of sensor components and the
demand for being maintenance-free. Non invasive devices seem to be much more interesting than invasive because they can be maintained and they do not encounter body fluids. To realise such non invasive measurement devices, highly sensitive sensors are needed. Nanotechnology is about to allow for this kind of simplified modules because of the generation of, for example, new and more intensive dyes which will be detectable in a more sensitive way through sophisticated diagnostic components.

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.

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 table 7.
### Table 7: Expected barriers in the implementation of particular nanotechnologies

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Infrastructural</th>
<th>Environmental impact</th>
<th>Ethical concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin films, layers and surfaces</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biopolymers</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dendrimers</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

The specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in table 8:

### Table 8: Specified expected barriers in the implementation of particular nanotechnologies

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Infrastructural</th>
<th>Environmental impact</th>
<th>Ethical concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin films, layers and surfaces</td>
<td>By nanofabrication within five years</td>
<td>Lower cost and improve quality of thin films</td>
<td></td>
<td>Long-term: education of interdisciplinary researchers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Durability and reproducibility. These barriers will be overcome when more reliable characterisation tools will be in place.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impact of nanotechnology in Health and Medical Systems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biochips/ High Throughput Screening/ Lab-on-a-chip devices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lack of adequate physical description</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral resolution of analytics on nanoscale have to be developed</td>
<td></td>
</tr>
<tr>
<td>Compatibility to application must be improved</td>
<td></td>
</tr>
<tr>
<td>Expensive equipment</td>
<td>Embryonic market, urgent need for appropriate applications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Biopolymers</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and synthesis of functionalised nanoparticles</td>
<td>Cost effective production</td>
</tr>
<tr>
<td>Compatibility to application must be improved</td>
<td>Facilities and procedures required for volume manufacturing</td>
</tr>
<tr>
<td>Identify biopolymers for coating compatible with the desired assay</td>
<td>Toxicity and biodegradability issues must be investigated</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td></td>
</tr>
<tr>
<td>Relatively expensive, pure material is often not available in EU</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Carbon nanotubes</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of proper reproducibility for industrial production</td>
<td></td>
</tr>
</tbody>
</table>
### Impact of nanotechnology in Health and Medical Systems

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

<table>
<thead>
<tr>
<th><strong>Nanoparticles</strong></th>
<th>Quantity production will take more than 10 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compatibility to application must be improved</td>
<td></td>
<td>Data for the effects on environment is required</td>
</tr>
<tr>
<td>Limited knowledge on reaction kinetics at production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Dendrimers** | Not further specified by the experts in this topic, however barriers have been formulated in the topic of drug delivery |  |

---

**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 in form of a specifically designed chip architecture 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 (figure 46-48).

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 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 **nano-biosensors** / **nanoelectrodes**, which will couple nanostructures with biomaterials such as enzymes, DNA, receptors and antibodies. They can be incorporated into "lab-on-chip devices", capable of performing reactions, separation and detection, doing sensitive measurements of very small amounts of important molecules such as neurotransmitters, carbohydrates, pollutants, or proteins.

![Ranking of nanotechnologies in distinct diagnostic topics](image)

**Figure 48**: Ranking of nanotechnologies in distinct diagnostic topics

### 4.3 Non-technological aspects

**Market trends**

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 volatile, 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\textsuperscript{25}.

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\textsuperscript{26}. 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\textsuperscript{27}, 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.

![Figure 49: Percentage of market captured by nanotechnology](image-url)
Impact of nanotechnology in Health and Medical Systems
Biochips/ High Throughput Screening/ Lab-on-a-chip devices

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 (figure 49). 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 protein-chips and bead based chips is 5 to 25% and in cell chips less than 5 up to 25%. These results underline the huge estimations in nanotechnology, postulating its potentials in this area.

In another question the experts were asked for the estimated development of the worldwide market for various applications during the next decade, namely assay development and HTS, basic research, choice of suitable therapies/doses, food production /food safety, forensic medicine, gene identification, gene-sequencing, identification of suitable drug candidates, medical diagnostics, Point-of-Care diagnostics, predictive medicine, theranostics, therapy monitoring and toxicology screening. 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.

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. More scientific technical experts must be included in the discussion and strategic decision making process in their topics. In this regard the European technology platform on nanomedicine which recently built-up was mentioned to be the right tool for connecting academia with industry needs, to start the dialogue between governments and users as
well as suppliers of the technology. This platform is expected to engage and connect world leading European scientists and committee members.

Another need is a proper taxation to promote venture capital and private equity investments, according to the experts.

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.

In principle, the same aspects which have been mentioned before are valid also for the biochip sector. The experts stated that the main thing to focus on is a higher interaction between industry and academia facilitating an effective technology transfer and multidisciplinary education.

**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
Impact of nanotechnology in Health and Medical Systems

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

deposited, and their reactions read by detectors, onto chips. The field already attains actual sales of products, and it represents a 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.

**Figure 50:** Worldwide position of European industry and science compared to other regions

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.

### 4.4 Recommendations by the Delphi panel

Trends, challenges and major gaps and barriers in the technological evolution which will lead to technological conclusions, have been asked to be named by the Delphi panel and are 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.

![Graph](image)

**Figure 51**: Europe should reinforce its future activities in….

In interpreting the result and comparing it to the other topics examined it certainly has to be considered, that each topic-specific expert group is expressing opinions from their particular point of view.
4.5 Annexes

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 catalysts for chemical reactions.

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.
List of participants

**Andrew Campitelli**  
MiniFAB, Pty Ltd, Bio Micro Nano Technology  
Austria

**Darvas Ferenc**  
THALES Nanotechnology Ltd.  
Hungary

**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 ofTuebingen  
Germany

**Dalibor Štys**  
Academic&University Centre, University of South Bohemia  
Czech Republic

**Hagen Thielecke**  
IBMT - Fraunhofer Institute for Biomedical Engineering  
Germany
5 Biomolecular Sensors

5.1 Introducing the subject

Biosensors are highly integrated analytical devices, incorporating a biological or biomimetic sensing element (receptor or recognition system), a signal converter or transducer and an amplifier. The main aspect, that specifies biosensors in comparison to other bioanalytical configurations, is the integration of biochemical recognition element and transducer. The aim of a biosensor is to generate discrete or continuous digital electrical signals which are proportional to a single analyte or a related group of analytes. 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 biologic, i.e. enzymes, antibodies or nucleic acids, receptors, organelles or intact cells or biomimetic elements, such as aptamers, peptide nucleic acids, synthetic ribozymes, synzymes or ionophores.

Figure 52: Schematic diagram showing the main components of a biosensor. The biocatalyst (a) converts the substrate to product. This reaction is determined by the transducer (b) which converts it to an electrical signal. The output from the transducer is amplified (c), processed (d) and displayed (e)\(^2\).
There are several criteria to classify biosensors, according to i.e. transducers, bioactive components, or immobilization techniques used. If the classification is based on the recognition process of the analyte, two basic sensor types can be distinguished, termed after the respective recognition reaction. These are affinity sensors and catalytic sensors. **Affinity sensors** are based on the specific bonding capacity of biological molecules. Subsequently, modifications of electron densities, light absorption, layer thickness, surface stress or refraction index can be detected by optoelectronic sensors, potentiometric electrodes, piezoelectric sensors or field effect transistors. **Catalytic biosensors** are based on the molecular recognition of substrates by biocatalysts and their subsequent conversion into products which are detected via an enzyme electrode. The enzyme electrode is a combination of any electrochemical probe (amperometric, potentiometric or conductimetric) with a thin layer of immobilised enzyme.

Sophisticated biosensors must show several specifications such as high specificity, stability over a large number of assays and minimal probe pretreatment. Furthermore the response should be accurate, precise, reproducible and linear over the useful analytical range, without dilution or concentration. It should also be free from electrical noise. For invasive use in clinical situations, the probe must be tiny and biocompatible, having no toxic or antigenic effects and the biosensor should be sterilisable. Market driven requirements are the price and the usability. The complete biosensor should be cheap, small, portable and capable of being used by semi-skilled operators.

**Figure 53:** Most appropriate types of nanotechnologies in Biomolecular sensors

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 combination of nanotechnology, biology, microtechnology and advanced materials will offer new devices which will be able to detect
and manipulate atoms and molecules. The small size of these sensors will lead to reduced weight, low power requirements, greater sensitivity and thus, to a totally new medical diagnosis at the cellular/molecular level.

In terms of the most appropriate types of nanotechnologies for their particular aims, the experts participating in our Delphi exercise, alike those for the field of Biochips/HTS/Lab-on-a-Chip, named thin films, layers and surfaces and nanoparticles, followed by biopolymers, carbon nanotubes, nanoporous materials and molecular imaging being mostly used in their devices (figure 53). 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 the same characters as mentioned in the biochip part (see chapter 4.1). They are shortly listed in figure 54. **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. **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. This diverse and versatile class of materials has potential applications in many sectors of the economy. In biosensors they may be used as self-assembling monolayers, as electronic and photonic conductive elements. The self assembling monolayers can serve as matrices for electronic and photonic conductive elements having 1-10 nanometer thicknesses and mm lengths. Biopolymers can function as transducers of light to electric pulses (photon/electron transducers) with applications in information storage and retrieval. **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. **Molecular engineering** can be described as the manufacturing and control of the structure and function 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. **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. **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.

5.2 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. 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 (figure 55). 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. The advantage of non-

![Figure 55: “Future medical practice will need more...” Estimations of the experts within the biomolecular sensor field](image-url)

Predictive medicine; 92%
Theranostics; 46%
Closed loop control systems; 54%
Individualisation of therapies; 62%
Implantable biosensors; 85%
Devices for selfdiagnoses; 38%
non-invasive diagnostics; 8%

Impact of nanotechnology in Health and Medical Systems
Biomolecular Sensors
invasive diagnostic is quite considerable, since several existing challenges become more marginal, among them the need for biocompatibility. Others of course will increase, such as the sensitivity to detect the slightest concentrations of analytes outside the body, for example in sweat or breath.

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 above mentioned demands. All of the involved experts predict nanotechnology to be unique in providing biomolecular sensors 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 to provide them with several new functions. 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 (figure 56). 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, which is the targeted and specific therapy on a cellular/molecular level, 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 remains on the same level as today, which indicates that there is 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 2015 which 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 be interpreted that nanotechnological impact will automatically decrease on this issue once a biocompatibility is achieved. Probably that is expected to happen before 2015. Eventual breakthroughs in tissue engineering for ultimate biocompatibility and thus an alternative to biosensors
may alter the time frame for and the importance of artificial implantable bio-sensors, although not being in the focus of this report, are expected to take place only at a later stage.

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.

**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 (figure 57). 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 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** inexpensive disposable nanobased biosensors will improve quality control in food chain management. The development of highly specific, affordable sensors in the food sector will significantly enhance consumer protection and add to providing confidence in the products quality. 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**

As stated before, 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 and biorecognition elements, 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. Nanotechnology is expected to meet the above mentioned demands of biosensors to different degrees as shown in figure 58.

**Figure 58**: Most revolutionary properties of nanotechnology in biomolecular sensor field

One of the most important advantages of future biosensor devices which are improved by nanotechnology is the opportunity to provide highly integrated, complex biosystem devices with new functions and sensor and actuator elements for combined diagnosis and therapy (theranostics). The possible abolition of a necessary internal calibration, due to an enhanced sensitivity and an improved accuracy and precision will involve the development of faster, cheaper and smaller biomolecular sensors.

Nanotechnology will lead to a new generation of biomolecular sensors with new functionalities. They will be able to detect several new analytes in a more precise, cheaper and more sensitive way than today.

**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 ex-
erts 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, for the design of sensor architectures 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_

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 table 9:
Table 9: Estimations of the experts about major challenges within the sector biomolecular sensors and how nanotechnology is going to help realising them

<table>
<thead>
<tr>
<th>Major challenges</th>
<th>Realise trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability of bio components is still an issue for other applications than glucose monitoring.</td>
<td>Proteins engineered for stability</td>
</tr>
<tr>
<td>Integration of the various enabling components which are needed for system integration towards highly sensitive, selective biosensors.</td>
<td>Mainly from the sensor point of view with regards to improvement in sensitivity and selectivity via new functionalised nano-bio interfaces.</td>
</tr>
<tr>
<td>Provision of low cost solutions in order to making biosensors affordable to the wider community.</td>
<td></td>
</tr>
<tr>
<td>Sensors capable of fast and automatic multianalyte detection in clinical laboratories and home self-diagnostics.</td>
<td>The technology should enable the controlled immobilisation of biological and synthetic molecular assemblies for preparation of biorecognition layers on physical transducers.</td>
</tr>
<tr>
<td>Implementation, public acceptance</td>
<td></td>
</tr>
<tr>
<td>Integration, intelligence to integrate data, minimally invasive methods and reduction of collateral interactions with biomaterials.</td>
<td>Enabling miniaturisation, although energy consumption remains an issue, possibility to embed data processing systems and telecommunication capabilities.</td>
</tr>
<tr>
<td>Stability of the sensing element</td>
<td></td>
</tr>
<tr>
<td>A balance between technical innovations and the possibility to apply these innovations in the biomedical field for a long time.</td>
<td></td>
</tr>
<tr>
<td>Linking sensor technologies to medical information technologies to improve diagnostics and theranostics; then applying this to preventative measurements</td>
<td>By improving the quality of biological information being obtained</td>
</tr>
<tr>
<td>Developing and expanding clinical-science joint ventures</td>
<td></td>
</tr>
<tr>
<td>Going to online detection in biofluids, increasing the number and specificity of markers for diseases, reducing the detec-</td>
<td>Creation molecularly non-fouling layers based e.g. on peg, new real-time signal transduction routes, mul-</td>
</tr>
</tbody>
</table>


tion limit and increasing reliability. tiplexed 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. Multidisciplinarity and an effective and expedited technology transfer are 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 (figure 59).

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.

Figure 59: Average technology stage of specific technical challenges of nanoparticles in the biochip sector

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, and 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 expectations 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.

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. The barriers, expected by the experts within the biosensor field to occur in various kinds of nanotechnologies are listed below in table 10.
Table 10: Expected barriers in the implementation of particular nanotechnologies

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Infrastructural</th>
<th>Environmental impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin films, layers and surfaces</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biopolymers</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular engineering</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymeric nanogels</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 specifications of these barriers, given by the participants, and the proposals how to overcome them, are listed in table 11:

Table 11: Specified expected barriers in the implementation of particular nanotechnologies

<table>
<thead>
<tr>
<th>Barriers to success</th>
<th>Technical</th>
<th>Economic</th>
<th>Infrastructural</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin films, layers and surfaces</td>
<td>Homogeneity</td>
<td>Low return of investment in diagnostics at present</td>
<td>More clinical studies related to diagnostics are needed</td>
<td></td>
</tr>
</tbody>
</table>
Non-specific response to biological media makes the application of sensor difficult for medical diagnostics. The development of bio-recognition 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.

<table>
<thead>
<tr>
<th>Controlled production; should be solved by 2010 by increasing collaborative interdisciplinary ap-</th>
<th>To regain confidence in the biosensors field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approaches</td>
<td>Characterisation tools are required - not all are available</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Adsorption of proteins on the surfaces</td>
<td></td>
</tr>
<tr>
<td>Need monodispersed particles of different shapes and materials by a chemical synthesis route</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Carbon nanotubes</strong></td>
<td></td>
</tr>
<tr>
<td>Manufacturing constrains, volume of product, testing</td>
<td></td>
</tr>
<tr>
<td>Particular skills, especially synthetic chemistry and physical skills are needed.</td>
<td>Inability to secure funding</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Nanoparticles</strong></td>
<td>Toxicology</td>
</tr>
<tr>
<td><strong>Biopolymers</strong></td>
<td>Long term stability</td>
</tr>
<tr>
<td><strong>Molecular engineering</strong></td>
<td>Engineering molecules to replace existing systems (e.g. aptamers replacing antibodies, molecular imprints, polymers); will improve by 2010 given effort currently being expended</td>
</tr>
<tr>
<td>Molecular nanopositioning is hard self assembly plus nanolithography by 2012</td>
<td>Nanoscale patterning by EBL is too expensive. NIL may be a solution by 2009</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td>Lack of potential PhD students with necessary multidisciplinary skills</td>
</tr>
</tbody>
</table>
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 diagnostic sector with a major part being monitoring systems 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. To realise this future trend, lots of efforts have to be put in raising the level of information about the particular marker molecules. Thus, the investigation of new markers has to be strongly emphasised.

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 and a wide range of aids for geriatric care. Also devices for general practitioners without highly sophisticated technical support to underpin the diagnosis will be possible. 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 collection and use of the vast amount of data that could be compiled may also be a restraining factor in the widespread adoption of sensors in health care. Data protection schemes are in place already to overcome these reservations.

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 con-
struction materials - thereby providing more comprehensive readings than a few scattered "macrosensors". Nanotechnology also promises to create integrated devices that combine both the sensor itself and the mechanism that converts what is sensed into useful information.

5.3 Non-technological aspects

Market trends

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 biochemistry, bioreactor science, physical chemistry, electrochemistry, electronics and software engineering. According to a report from Business Communications Company, Inc. the global market for biosensors is projected to grow from $6.1 billion in 2004 to $8.0 billion in 2009, at an AAGR (average annual growth rate) of 5.8%.

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 analyses 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. In the perception of the participants former forecasts 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, nanotechnology, biomicroreactor 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 were not of an 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 steadily increasing.

![Figure 61: “Most important for the growth and prosperity of European nanotechnology is...”](image)

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 carrying 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 (figure 61). “Other” stands for a needed support for late development (prototyping) and cross laboratory trials.

**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 nanomaterials 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**

Figure 62 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.

5.4 Recommendations by the Delphi panel

For the biomolecular sensor field, 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 (figures 62, 63). In interpreting the result and comparing it to the other topics examined it certainly has to be considered, that each topic-
specific expert group is expressing opinions from their particular point of view.

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.

Figure 63: Europe should reinforce its future activities in....
5.5 Annexes

Statistics

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.

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

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

We like to thank Professor **Frieder Scheller, University of Potsdam, Germany**, who gave us an exclusive interview and various valuable hints which were integrated in the document.
6 General conclusion and recommendations

Great expectations are put into future diagnostic systems. Advanced medical devices will help foremost to learn more about the complex biomolecular processes that control life. Secondly it will be possible to therapy diseases in a much more specific, precise and well defined way than today. Nanotechnology will facilitate technological quantum leaps in several medical fields. There are quite a few technological developments that promise enhanced diagnostic possibilities, new ways to monitor patients, new ways to treat diseases like cancer and to reduce or attempt to avoid side effects. For example, nanoparticles can be used as carriers for targeted drug delivery. Their ability to penetrate certain protective membranes in the body, such as the bloodbrain barrier, can be beneficial for many drugs. This could open the way for new drugs from active substances that have not been able to pass clinical trials due to less precise delivery mechanisms. Nanosensors and lab-on-a-chip-technologies will foster early recognition and identification of diseases and can be utilized for continuous monitoring of patients with chronic diseases. New therapeutic methods for the treatment of cancer with the help of nanoparticles are presently investigated.

The experts within our Delphi panel pointed out several challenges and the respective technical and non-technical needs. The technical needs are listed in the particular roadmap report. Most of the non-technical needs, however, are more common and therefore should be mentioned again in these concluding remarks.

One of the most immediate issues is the need to develop interdisciplinary expertise across a range of suitable technologies.

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. The need for focussing and multidisciplinary has to start with the particular multidisciplinary education. The required need for 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 were also formulated by the experts of almost every topic. A first approach to fill the gap between the various scientific approaches (technology push) and on the other hand the application
driven requirements, needed by the industry, and the need for a better networking is the formation of a technology platform in nanomedicine, as recently announced. Furthermore there is a need for the support and funding of technology transfer from research status into products. A furthermore important aspect is the need for facilitated product approval processes. In this regard, the integration of the European medicines evaluation agency (EMEA) has been asked for, to change and improve them.

The establishment of an European health institute (comparable to NIH) was demanded to bundle and streamline biomedical research, reduce bureaucratic burden in funding and to learn from best practice.

Although most 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, discussion of the safety of nanoparticles should address specific points. Safety should relate to environmental exposure, manufacturing exposure, as well as any proposed clinical use. Therefore each nanomaterial should be treated individually when health hazards are evaluated. A systematic risk screening will be helpful to establish the basic know-how to understand the interaction with the human body and the environment and to establish the theoretical framework needed.

What happens over the next few years will determine how the public comes to view it. A transparent discussion of benefits and risks will help people reach a considered, balanced view. This will enable a greater public acceptance, which, in turn, will enable society as a whole to profit from these fundamental technological developments while, at the same time, the risks are kept under control.
7 Glossar

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptamers</td>
<td>DNA or RNA molecules that have been selected from random pools based on their ability to bind other molecules. Aptamers have been selected which bind nucleic acid, proteins, small organic compounds, and even entire organisms. These novel molecules have many potential uses in medicine and technology.</td>
</tr>
<tr>
<td>Ionophores</td>
<td>Hydrophobic molecules, which bind selectively to a given metal ion and increase its cell permeability. The inner part of ionophores is made of polar groups forming a tetra- or octahedral geometry that fits and encloses a specific ion. Ionophores shield the charge of the ion to be transported, enabling it to penetrate the hydrophobic interior of the lipid bilayer.</td>
</tr>
<tr>
<td>Ribozymes</td>
<td><em>ribonuclease</em> enzyme, also called RNA enzyme or catalytic RNA. RNA molecule, that catalyzes a chemical reaction.</td>
</tr>
<tr>
<td>Synzymes</td>
<td>Synzymes are artificial enzymes. Generally, synthetic polymers or oligomers with enzyme-like activities. They must possess two structural entities, a substrate-binding site and a catalytically effective site.</td>
</tr>
<tr>
<td>Theranostics</td>
<td>The term theranostics describes the use of diagnostic testing to diagnose the disease, choose the correct treatment regime and monitor the patient response to therapy.</td>
</tr>
</tbody>
</table>
References

2. Roadmap Report on Nanoparticles, author W&W
7. IMS Health
8. Magforce nanotechnologies AG, Germany and MFH Hyperthermiesysteme GmbH, Germany
9. sources: Global Pharma Forecasts and IMS
Small sizes that matter: Opportunities and risks of Nanotechnologies, report by Allianz and OECD, June 2005

ESF Scientific Forward Look on Nanomedicine, February 2005


Roadmap Report on Dendrimers, author W&W, 2005

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

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

Roadmap Report on Nanoparticles, author W&W, 2005

Roadmap Report on Dendrimers, author W&W, 2005

BCC, 2003: Protein Chips: Where To?

DZ-Bank, Technology Trends: Biochips, 2001

BioPerspectives, 2002

http://www.lsbu.ac.uk/biology/enztech/biosensors.html

Roadmap Report on Nanoparticles, author W&W, 2005

Roadmap Report on Nanoporous materials, author W&W, 2005


Roadmap Report on Dendrimers, author W&W, 2005


AZoNanotechnology News Item, 31 May 2005

'Enzyme Technology', M. Chaplin, C. Bucke (Cambridge University Press, 1990), online at http://www.lsbu.ac.uk/biology/enztech/biosensors.html