Nanomedicine: Visions, risks, potential

Berlin-Brandenburg Academy of Sciences and Humanities
19 and 20 April, 2012
About the conference “Nanomedicine: Visions, Risks, Potential”

Nanotechnology is frequently judged to be a key technology of the 21st century. Although not all research areas that were awarded this honorary title in the past have so far fulfilled all the expectations, thinking of nanotechnology as a highly important research area surely is justified. Especially in the field of medicine nanotechnology may help to develop new and effective applications. However, as with many modern technologies, there are considerable moral concerns about the consequences nanotechnology may have for humans and their environment.

The Spring Conference of the Europäische Akademie Bad Neuenahr-Ahrweiler GmbH aims at discussing recent trends in the development of nanotechnological methods in medical applications with experts from different involved fields of research from an interdisciplinary perspective. There will be sessions on scientific and technical aspects of nanomedicine, on risk and other ethical issues as well as on the social impact of nanomedicine in the context of science, industry and the public.

About the Europäische Akademie

The Europäische Akademie GmbH deals with the scientific study of the consequences of scientific and technological advances for individuals, society and the natural environment. The main focus is on the examination of foreseeable mid- and long-term processes that are especially influenced by the natural and engineering sciences and the medical disciplines. As an independent scientific institution, the Europäische Akademie pursues a dialogue with the world of politics and society at large.

The Europäische Akademie is a non-profit corporation with limited liability. It is mainly financed by allowances granted by the Federal State of Rhineland-Palatinate and the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt e.V., DLR); furthermore, a number of third-party funds are received, e.g., from the German Federal Ministry of Education and Research, BMBF). The Managing Director of the company is Ass.-jur. Stefan Latussek (since 1 March 2012). Founding Director of the academy was Professor Dr. phil. Dr. phil.h.c. Carl Friedrich Gethmann (1996–2012).

The work of the Europäische Akademie is based on the assumption that the sciences, in addition to providing specialised scientific information, also are responsible for furnishing orientational knowledge (normative standards). To achieve this, an interdisciplinary approach is required, bringing together the results from the natural sciences, engineering sciences and medical disciplines with thematically relevant studies in philosophy, jurisprudence, economics and social sciences. Furthermore, the foreseeable results of research and development will be related transdisciplinarily to society’s expected needs and positions. In the course of its work, the Europäische Akademie takes up and develops approaches towards technology assessment, ethics of technology and medical ethics (see more at www.ea-aw.org).

About the NanoDiaRA consortium

The interdisciplinary consortium “Development of Novel Nanotechnology Based Diagnostic Systems for Rheumatoid Arthritis and Osteoarthritis (NanoDiaRA)” is subsidized by the European Union (FP7) and consists of 15 European partners from university and non-university institutions. The Europäische Akademie GmbH, organizer of the spring conference, is its administrative co-ordinator (www.nanodiara.eu).
Programme

Thursday, 19 April 2012

9:00  Registration

9:30  Welcome and Introduction
      PD Dr. Felix Thiele, Europäische Akademie GmbH, Bad Neuenahr-Ahrweiler, Germany
      Mrs. Maj-Inger Nilsson, European Commission, Brussels, Belgium

Session I: Trends in Nanomedicine (Chair: PD Dr. Felix Thiele, Germany)

9:45  Nanotechnology in diagnostics and treatment of rheumatoid arthritis and osteoarthritis – visions and potentials
      Dr. Ing. Heinrich Hofmann, Eidgenössische Technische Hochschule Lausanne (EPFL), Switzerland

10:30 Nanoparticles for drug delivery – from fiction to reality in pharma
       Professor Dr. Rainer Müller, FU Berlin, Germany

11:15 Break

11:30 Thermotherapy with magnetic nanoparticles: from an idea to products up to the market launch
       Dr. Andreas Jordan, MagForce, Berlin, Germany

12:15 Smart nanoparticles in the biomedical research
       Dr. Gianni Ciofani, Istituto Italiano di Tecnologia, Pisa, Italy

13:00 Lunch

Session II: Risk assessment (Chair: Dr. Jan Mehlich, Europäische Akademie GmbH, Germany)

14:30 Nanomedicine – nanotoxicology: controversial aspects of nanotechnological applications
       Professor Dr. Harald Krug, EMPA, St. Gallen, Switzerland

15:15 From risks to regulation: Regulatory aspects of nanomedicine
       Joel D’Silva, Universiteit Twente, Enschede, The Netherlands

16:00 Break

16:30 Poster session – One-minute-presentations and poster presentations
### Session III: Science, industry and the public (Chair: Dr. Stephan Lingner, Europäische Akademie GmbH, Germany)

<table>
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<th>Time</th>
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| 9:30   | Nanomedicine is more than a matter of risk. The generic tendency to focus on public acceptance and risk perception  
        | *Professor Harro van Lente, Universiteit Twente, Enschede, The Netherlands*  |
| 10:15  | Nanotechnology and society  
        | *Dr. Joscha Wullweber, Universität Kassel, Germany*                          |
| 11:00  | Break                                                                       |
| 11:15  | Nanomedicine: An exceptional regulatory and ethical challenge?  
        | *Professor Roger Brownsword, Kings College, London, UK*                     |
| 12:00  | Lunch                                                                       |
| 13:00  | End of the conference                                                      |
Lecture: Nanotechnology in diagnostics and treatment of rheumatoid arthritis and osteoarthritis – visions and potentials

Osteoarthritis (OA) is a degenerative joint disease caused by cartilage loss in a joint due to e.g. mechanical stress often associated with a secondary inflammatory reaction. OA is currently the main cause of disability among the middle age and elderly populations. In contrast, rheumatoid arthritis (RA) is a chronic inflammatory disease of diarthrodial joints, characterized by chronic synovitis, the infiltration of immune cells (T cells, B cells and macrophages) and an aggressive front of tissue called pannus, invading and destroying local articular structures, which leads to progressive bone and cartilage damage. Effective treatments in RA and OA are based on early detection of disease and monitoring of treatment efficacy.

A new approach is the application of nanotechnology - a key technology of the 21st century. The development of novel Nanotechnology based diagnostic systems for Rheumatoid Arthritis and Osteoarthritis (NanoDiaRA) is the major aim of the EU funded project NanoDiaRA. NanoDiaRA combines for the first time a nanoparticle based approach as a generic platform for the development of various novel diagnostic technologies.

Nanotechnology has the potential to enable early detection and prevention and to essentially improve (i) diagnosis, (ii) treatment and (iii) the follow-up of diseases. In detail, diagnosis includes microarray and imaging technologies detecting with sensitivity and specificity disease-related molecular and cellular processes rather than just outcomes resulting in new therapeutic approaches and potentials for the daily clinical use.
Lecture: Nanoparticles for drug delivery – from fiction to reality in pharma
R. H. Müller
Department of Pharmaceutics, Biopharmaceutics and NutriCosmetics, Free University, Berlin, Germany
www.muller-berlin.com

Paul Ehrlich (1854-1915) developed the concept of the „magic bullet“, the way of treating a disease specifically. Pharmaceutical research focussed since Ehrlich´s time on this goal. Nanoparticles are one potential bullet to realize this concept. Now about 100 years later after Ehrlich it is time to review how much of this fiction turned into reality.

Many different nanoparticulate carriers (nanocarriers) have been developed in the research laboratories, but only a few made it to turn into reality, that means into pharmaceutical products for the benefit of patients. Before reviewing the pharmaceutical nanoproducts, it should be defined what a nanoparticle is. The pharmaceutical definition is that nanoparticles possess a size in the nanodimension, that means from 1 nm to 1,000 nm (= 1 µm). The regulatory definition (e.g. EU cosmetic regulations, FDA in US) is that only particles below 100 nm are nanoparticles. Only products with these particles need to be labelled as nano products. When talking about pharmaceutical nanomedicaments on the market, one needs to differentiate between therapeutics and diagnostics. The presentation focusses on therapeutics only.

The first nano products appeared on the market around 1960, even before the name “nanotechnology” was invented by Norio Taniguchi in 1974. At these times it was still called colloidal science. The first products were nanoemulsions (1) for parenteral nutrition and later delivery of drugs, e.g. the propofol, well known since the death of Michael Jackson.

The second important group of nano products are the liposomes (2). They were invented in the 1960ies. First they appeared on the cosmetic market (product Capture by Dior, 1986), around 1990 the first products were put on the pharmaceutical market. One of the first is the famous Alveofact form the German company Dr. Karl Thomae GmbH. Some of the liposomes developed to very well selling products, e.g. Doxil for cancer treatment, annual sales about 700 million $US.

The third important group are the polymeric nanoparticles (3), invented by Professor Speiser ETH Zurich. In 1974 he used for the first time the word “nanocapsule” for his polymeric particles. Despite many research efforts worldwide for more than 30 years, they remained as “academic” particles, no products for therapy are on the market. Reasons for this are e.g. lack of regulatory status of excipients and lack of large scale industrial production methods. Meanwhile products are in clinical phases.

The successor generation of the liposomes are the lipid nanoparticles (4). The first generation solid lipid nanoparticles (SLN) were developed at the beginning of the 1990ies, the second generation nano lipid carriers (NLC) around 2000. There are meanwhile in cosmetic products, clinical phases are ante portas.

The most successful nanocarriers are the drug nanocrystals (5, 6). They were invented in 1991, in less than 10 years the first pharmaceutical product appeared on the market (Emend). Meanwhile we have block busters, e.g. Tricor with more than 1 billion $US annual sales.

About 10 years ago the public perception was only positive about “nano”. The equation was valid “nano = good”. Meanwhile this changed and public is getting more and more concerned about potential toxicity. To account for this, a nanotoxicological classification system (NCS) (6) was developed, based on the traffic light system green, yellow and red. This science based but simplified system can act as a guide for politicians when making new laws and regulations, and it is also understandable by the consumer.

To summarize: nanotechnology opened completely new perspectives in drug therapy. The scientists and pharmaceutical industry managed to turn fiction into reality. Today´s nanocarriers are systems which enable drugs to become active, e.g. enable to have absorption from the gut into the blood, make
drugs injectable, optimize drug release to optimize treatment efficiency and reduce side effects. In strict sense, the magic bullet concept has not yet been realized, only the nanocarriers itself. However, in the future “smarter” nanocarriers will come, delivering drugs as a “nano taxi” specifically to the desired site of action (7).

References:
7. Müller, R. H., Keck, C. M., Pharmaceutical nanoparticles – from their innovative origin to their future, Int. J. Pharm. 390, 1-2, 2010
Dr. Andreas Jordan
Dr. Andreas Jordan founded MagForce AG and serves on its Management Board. He began his career with studies in biology at the Free University of Berlin, followed by further studies in biochemistry at the Technical University of Berlin. His highly praised doctoral dissertation in 1993 addressed the production of nanoparticles and their application for cancer therapy. This pioneering work was based on research, which began in 1987, long before the subject of nanotechnology had achieved any international significance. He subsequently managed scientific projects for the Berlin’s Virchow Clinic (now Charité) as well as for the Institute for Diagnostic Research, a subsidiary of Schering.

Dr. Jordan has already delivered more than 500 scientific lectures about Nano-Cancer® therapy. He has authored more than 45 articles for peer-reviewed scientific journals and has cleared the way for twelve families of international patents, some of which have been licensed. His contacts to NASA, the National Cancer Institute (NCI), the Institute of Nanotechnology (IoN), the U.S. Food and Drug Administration (FDA), and such renowned U.S. hospitals as the University of California, San Francisco (UCSF), the Cleveland Clinic Foundation (CCF) and Duke University, as well as throughout Asia, continue to provide an essential foundation for his professional activities through the world.

Lecture: Thermotherapy with magnetic nanoparticles: from an idea to products up to the market launch
Andreas Jordan
Max-Dohrn-Str. 8, Haus 5.2, 10589 Berlin, www.magforce.de/unternehmen/vorstand.html

MagForce AG is a leader in the area of nanotechnology-based cancer treatment. The company’s medical products have received European approval and offer a new approach for the local treatment of brain tumors.

NanoTherm® therapy is based on the introduction of magnetic, iron-oxide nanoparticles into the tumor, and their ability to convert magnetic energy into therapeutic heat. Following injection into the tumor, the particles are activated by a magnetic field that changes its polarity 100,000 times per second, and heat is produced within the tumor. Depending on the duration of treatment and the intratumoral temperatures achieved, the tumor cells are either directly destroyed (thermal ablation) or sensitized for concomitant chemo or radiotherapy (hyperthermia).

NanoTherm® Therapy is a novel therapy that has shown good tolerability in patients. With this new procedure, it is possible to combat brain tumors from the inside out, thereby sparing surrounding healthy tissue. The specific use of targeted heat generated through magnetic nanoparticles has the potential to establish itself, along with surgery, radiotherapy, chemotherapy, as an additional option for the treatment of solid tumors. In addition, MagForce is working to expand the use of NanoTherm® therapy to other solid tumors, specifically for the treatment of prostate and pancreas cancer.
Dr. Gianni Ciofani

Gianni Ciofani received his Master Degree in Biomedical Engineering (with Honors) from the University of Pisa, Italy, in July 2006, with an experimental thesis on a polymeric microparticle system for drug delivery of neurotrophic factors. In the same year, he obtained the Diploma in Engineering (with Honors) from the Scuola Superiore Sant’Anna of Pisa, Italy, with an experimental thesis on carbon nanotube – mediated cell electroporation. From 2006 to 2009 he collaborated with the CRIM Lab of the Scuola Superiore Sant’Anna as Research Assistant and Ph.D. student, working on micro- and nanosystems for drug delivery and cell surgery. He also spent research periods as visiting Ph.D. student at the Waseda University (Tokyo, Japan) and at the Center of Investigation “Principe Felipe” (Valencia, Spain). In January 2010, he obtained his Ph.D. in Bioengineering (with Honors) from the Scuola Superiore Sant’Anna of Pisa, Italy.

Since January 2010, he is Post-Doc researcher at the Italian Institute of Technology unit of the Scuola Superiore Sant’Anna (Pontedera, Pisa, Italy). His main research interests are in the field of nanomedicine, cell surgery, and innovative materials for cell therapy and bio/non-bio interfaces. For his research activity, he has been awarded with several national and international prizes. In collaboration with the European Space Agency, he also carried out researches on human physiology and cell biology in altered gravity conditions (Student Parabolic Flight Campaign 2005 and Spin Your Thesis! 2010 Campaign).

Gianni Ciofani is author or co-author of more than 40 ISI papers, one edited book, 9 book chapters, 2 applications of international patents and several communications to international conferences. He serves as Reviewer of about 40 international journals and is Editorial Board Member of the *Journal of Nanoscience Letters* and of the *International Journal of Biological Engineering*.

Lecture: Smart nanoparticles in the biomedical research

Gianni Ciofani

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Nanoscale structures and materials have been explored in many biological applications because their novel properties and functions drastically differ from their bulk counterparts. Particularly, their high volume/surface ratio, surface tailorability, improved solubility, and multifunctionality open many new possibilities for biomedicine. Moreover, the intrinsic optical, magnetic, and biological properties of nanomaterials offer remarkable opportunities to study and regulate complex biological processes. Since life itself, fundamentally, is a collective of processes at the nanoscale within cells, it is unavoidable and necessary to understand the impacts of the presence of nanomaterials inside the cells when the advantages and promises of nanomaterials for biomedical applications are explored. In this talk, after a short introduction to the major classes of innovative nanoparticles that have gained attention in the recent years, I will focus the topic on the research carried out in our laboratories.

Our group pioneered nanomedicine applications of boron nitride nanotubes (BNNTs), starting from an extensive investigation of their biocompatibility. BNNTs are of significant interest for the scientific community because of their potentially unique and important properties for structural and electronic applications. A BNNT is a structural analogue of a carbon nanotube: alternating B and N atoms entirely substitute for C atoms in a graphitic like sheet, with almost no change in atomic spacing; despite this, carbon and boron nitride nanotubes present many different properties. In this presentation, I show studies on biocompatibility and interactions between BNNTs and living cells. Thereafter, I will introduce some potential useful applications of BNNTs in the biomedical field, that...
range from drug delivery systems, boron carriers for boron neutron capture therapy, and to cellular nanotransducers.

Another class of smart nanoparticles under investigation in our group is represented by barium titanate nanoparticles. Ceramic materials based on perovskite-like oxides are of intense interest because of their applications in electrical and electronic devices. Due to its high dielectric constant, barium titanate is probably one of the most studied compound of this family and still represents the basis for the preparation of multilayer ceramic capacitors and thermistors with positive temperature coefficient of resistivity. We have proposed nanomedicine applications of different types of barium titanate nanoparticles. They have been proven to be non-toxic even at high concentrations, and can be efficiently exploited as protein carriers and as enhancers of the up-take of low molecular weight drugs like doxorubicin.

In the latest years, the use of zinc oxide (ZnO) nanostructures has been proposed in different biomedical applications, however, to date, only a few contrasting results concerning their biocompatibility can be found in the literature. In particular, the application of the extraordinary piezoelectric properties of ZnO nanostructures has poorly been explored for the culture of electrically excitable cells. Here, I will show experiments about adhesion, proliferation and differentiation of two mammalian cell lines (PC12, as model of neuronal cells, and H9c2, as model of muscle cells) over ZnO nanowire arrays. We demonstrated suitability of these arrays in sustaining cellular functions, and their potential in applications that range from tissue engineering to minimally invasive sensing and/or stimulation.

I will conclude highlighting the challenges of nanomedicine in the next future, confirming the urgent need to exploit the rapid advances in nanomaterials for biomedical applications. The merging of different disciplines such as bioengineering, materials science, chemistry, physics, biology, as well as medicine, will be essential for the successful exploration of the applications of nanomaterials inside cells, and for effective and realistic applications in the clinical practice.
Professor Dr. Harald Krug

Professor Dr. Harald F. Krug, born in 1952, is Member of the Board of Directors and Head of the Department „Materials Meet Life“ at Empa (St. Gallen) in Switzerland. Previously, he headed the Department of Molecular and Environmental Toxicology at the Karlsruhe Institute of Technology, Germany. He studied Chemistry and Biology at the University Kassel and made his PhD-Thesis at the University of Göttingen in 1982 on the Regulation of circadian rhythmicity. He was postdoctoral stipend at the GSF Research Centre (1983-86) in Munich and changed his position to be a group leader at the research Centre in Karlsruhe. At the University of Karlsruhe he got a professorship in 1996 where he had his teaching activities and is appointed as “Titularprofessor” at the University of Berne since August 2008.

Until 2009 he was the speaker of the “NanoCare” consortium (2006-2009), a cooperation project of 13 industry, research and academic partners which carries out investigation on the possible adverse biological effects of nanomaterials funded by the German Ministry of Education and Research. Professor Krug was awarded in 2006 with the cwi-Award of the German Ceramic Society and in 2007 with the Research Award for „Alternatives for Animal Testing“ of the State Parliament of Baden-Württemberg. He has authored over 100 publications, including journal articles, book chapters, and technical reports.

His main interests are focused on the molecular mechanisms of nanoparticles/nanomaterials and the establishing and validation of new cell culture/tissue models for studying the toxicity of nanomaterials.

Lecture: Nanomedicine – nanotoxicology: controversial aspects of nanotechnological applications

Harald. F. Krug
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The implementation of nanotechnological developments especially in the fields of cosmetics and medicine which means that the products come in close contact to the human body is under intense discussion. The specialty of nanomaterials to have very new properties with regard to their chemical, physical but also biological behavior opens a wide range of different applications and this leads to some concern about their possible activities within living organisms and the environment. Is there reason for the assumption that nanomaterials may behave as asbestos? Do they move everywhere within the body? Can they be controlled? Do they possibly transport other critical substances to places which those never would have reached without their nano-vehicles? These and more critical questions came up during the past years and should be taken carefully into consideration when thinking about new developments in the field of nanomedicine.

Hence, nanosafety considerations become a substantial part of many funding programs, international conferences and regulatory activities worldwide and many international working groups are taking care of this topic. Since the term “Nanotoxicology” appeared the first time within a title of a publication in 2004 [1] confusion about its implementation and the objectives starts. One year later, the relationship to the former research on ultrafine particles has been highlighted [2] and the “new discipline” started its success story. Whereas the number of publications regarding nanotoxicological issues from that time increases dramatically each year (from around 150 in 2004 to nearly 1800 in 2011; PubMed-Database) clarity about possible risks dropped.

Besides the fact that more and more products contain nanoparticles (NP) and thus have to be tested to be safe for the customer there is no general opinion how to approach this target. It has been shown
that many of the used methods are not adapted for NP and thus results are often false-positive or false-negative. Not only we could demonstrate the interference of NP with the assay systems which often is neglected [3], solvent problems have not been addressed [4] and the appropriate controls are missing as well as the characterization of the materials tested [5].

Taking all these critical points into account especially nanotoxicology has to establish a new strategy in the future as has been postulated in 2009 [6]. Recently, we made some very important recommendations which should lead to more detailed and reliable information about the biological activity of specific nanomaterials [7]. Moreover, it has been published in 2011 that the definition of nanomaterials is not only very difficult to achieve but “will also fail in to capture what is important for addressing the risks” [8]. Nevertheless, harmonization of testing strategies and methods has to be achieved very quickly as otherwise the confusion about the results published will increase the uncertainty and the proper use of nanomaterials in all fields of interest.

Joel D’Silva

Joel D’Silva is affiliated researcher at the Department of Legal and Economic Governance Studies at the University of Twente, Netherlands. He is also Life Sciences and International Trade Manager at the European Association for Chemical Distributors (Fecc), Brussels. Prior to this he was a research fellow at the Faculty of Law – KU Leuven, Belgium on a funded project on the legal regulation of nanotechnologies (2008-2010). Joel is a lawyer with a masters from the University of Warwick (UK) and masters from KU Leuven (Belgium). He has researched and published on various aspects of science, technology and regulation including health and safety, product liability, intellectual property, trade and environmental implications.

Lecture: From risks to regulation: Regulatory aspects of nanomedicine

Joel D’Silva
Department of Legal & Economic Governance Studies (LEGS), University of Twente, Netherlands; Email: joel.dsilva@telenet.be

Nanomedicine holds enormous promise for the improved prevention, detection and treatment of a range of diseases and medical conditions. While the potential benefits of nanomedicine appear—at this nascent period of development—to be enormous, uncertainty surrounds the potential risks of many nanomedical products. Concerns about the adequacy of regulatory oversight also threaten to impede the development and commercialization of nanomedicine-based products. It is becoming increasingly clear, therefore, that appropriate and effective regulatory structures will be fundamental to the successful implementation and commercialization of nanomedicine if the technology is to fulfill its promise.

There are no specific nanomedical laws in the European Union (EU), nor indeed in any other jurisdiction, at this time; this does not mean that they are “unregulated” (Van Calster 2006). Rather, such products are regulated in the same way as their non-nanotechnology counterparts, with existing legislation on medicinal products and devices, tissue engineering and other advanced therapies being applicable to nanomedicine-based products and processes.

Medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules. The general medical legislation is supported by a series of guidelines (Table 1).

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<td>Committee for Medicinal Products for Human Use (CHMP)</td>
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<td>Innovation Task Force (ITF)</td>
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<td>New and Emerging Technologies (N&amp;ET) Working group</td>
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<td>Medical products for Human Use—Directive 2001/83/EC</td>
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<td>Authorisation and supervision of medicinal products—Regulation (EC) No 726/2004</td>
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<td>Advanced Therapy Medicinal Products (ATMP)—Regulation 1394/2007/EC</td>
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<td>Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH)—Regulation (EC) 1907/2006</td>
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Table 1. Regulatory bodies and legislation in the European Union relevant to nanomedicine.
The identification of potential health risks arising from nanosized residues is largely speculative at this point in time because of the embryonic nature of many nanomedicine applications. Studies have reported data on the toxicity of certain nanomaterials under certain laboratory conditions, but to date many of these studies have been inconclusive and contradictory and must therefore be considered within the context of these limitations. Studies have, for example, examined the toxicological effects of nanoparticles, quantum dots, fullerenes and carbon nanotubes. This research has indicated that the small size of engineered nanomaterials and nanoparticles can imbue them with novel properties that are potentially useful across many fields including nanomedicine. However, the comparatively higher reactivity, mobility and/or other properties of some nanomaterials when compared to their larger-scale counterparts may, in some instances, alter their toxicity. Free, insoluble and/or biopersistent nanoparticles are of particular concern because, under certain circumstances, some commentators believe that there is a higher likelihood of such particles entering the body, reacting with cells and giving rise to tissue damage.

European chemicals regulation has been consolidated and integrated with the creation of REACH. There are no provisions in REACH that refer explicitly to nanomaterials. However, nanomaterials are covered by the “substance” definition in Article 3 of REACH. In June 2008, the European Commission (EC Communication 2008) concluded that with respect to potential health, safety and environmental risks posed by nanomaterials, the current EU legislative framework was, in principle, adequate to effectively regulate nanoscale substances. In coming to this conclusion, however, the Commission did acknowledge the need for fundamental scientific research to be undertaken in order to determine if the existing standards and risk assessment methodology underpinning the regime, as set out in the Annexes of the REACH Regulation, are appropriate for nanoscale substances. Until the state of the art has evolved adequately so as to be able to answer such questions, testing will continue to be carried out in accordance with the existing guidelines.
Professor Harro van Lente

Professor Harro van Lente is Associate Professor of 'Emerging Technologies' at the Department of Innovation and Environmental Studies, University of Utrecht. He is Programme Director of the MSc course Science and Innovation Management. He is also Socrates Professor of Philosophy of Sustainable Development at Maastricht University.

Harro van Lente studied Applied Physics (MSc 1988) and Philosophy of Science & Technology (MSc 1988) at the University of Twente. In his PhD thesis (1993), Promising Technology, he studied the dynamics of expectations in the development of technology. Since then he has been involved in a wide range of studies in the area of technology, innovation and society. As invited professor in philosophy of technology he stayed 6 months at the University of Oviedo, Spain. At the University of Maastricht he did EC funded research on social learning in the development of multimedia. From 1997 until 1999 he was research manager at KPMG Inspire Foundation, a think tank of the KPMG consulting firm, and was involved in various consultancy projects on innovation and organization.

Harro van Lente is a philosopher and social scientist. His research focuses on innovation, emerging technologies and sustainability. He is one of the founding fathers of the Sociology of Expectations. His current research focuses on the role of needs and expectations in the dynamics of technology and on the possibilities for anticipatory tools. He is especially interested in the dynamics of nanotechnology and hydrogen technologies. He is a senior researcher in the NanoNed Technology Assessment programme. NanoNed is the major player in Dutch research on Nanotechnology (http://www.nanoned.nl).

Harro van Lente developed courses on theories of innovation, philosophy of Technology, national systems of innovation and technology policy. He is Chairman of the Educational Committee of the Dutch research school WTMC (Science, Technology and Modern Culture).

Lecture: Nanomedicine is more than a matter of risk. The generic tendency to focus on public acceptance and risk perception

Harro van Lente

Socrates Professor of Philosophy of Sustainable Development (ICIS, Univ Maastricht) and Associate Professor Emerging Technologies (Innovation Studies, Utrecht University), h.vanlente@uu.nl

New technologies come with great expectations. Nanotechnology in particular is often labeled as a 'disruptive technology' that, due to its enabling and pervasive character, has the potential to become the carrier of the next industrial revolution. Industrial and governmental roadmaps of nanotechnology promise to change most domains of economic and social life: energy production, material use, food production and, indeed, medicine. Various in vitro and in vivo applications are projected in the future and, to some extent, developed and tested. So, it is promised that nanotechnology will have broad, pervasive and beneficial consequences. It will deeply change the way society operates, or, in terms of the EU framework programs, it will be relevant and urgent for all ‘grand challenges’ of European societies.

Yet, when such sweeping statements receive more elaborate attention, that is, when the question of societal embedding of nanotechnology comes to the fore, a reduction of scope is looming. The central argument of my talk is that such a reduction typically takes place in two steps:

(i) the question of societal embedding is reduced to a problem of public acceptance;
(ii) the problem of public acceptance is reduced to a matter of risk perception.

Societal embedding, however, is more than public acceptance. It refers to broader questions about the way economic structures are re-organized, about changing responsibilities and liabilities, about new roles and identities, about new ethical dilemmas. Public acceptance could, in principle, relate to such issues. Yet, to appreciate and assess such issues requires additional intellectual efforts, theories of
socio-technical change and further reflection in general. In my talk I will give examples of the Dutch program on Technology Assessment within NanoNextNL, which is designed to address questions of societal embedding.

Public acceptance, in its turn, refers to more than ‘risk’. Lay people will have more considerations than risk alone and include moral and political arguments as well, such as privacy or solidarity. For developers of nanotechnology (‘enactors’) the possible resistance of the public appears as a barrier and they hope better communication will. The vicious circle is completed when the problem of risk is counteracted by referring to the great promises of nanotechnology: “we cannot afford not to continue the development”.

My thesis of the generic ‘embedding to risk’-reduction has several connections with other pertinent diagnoses of novel technologies in society, in particular the work of Ulrich Beck on ‘risk society’, of Anthony Giddens on ‘reflexive modernization’ and the rich tradition of Science, Technology and Society (STS). I will elaborate the scholarly connections and discuss the practical consequences of nanotechnology being more than a matter of risk.
Dr. Joscha Wullweber

Dr. Joscha Wullweber is an “Akademischer Rat” (Assistant Professor) in the subdivision 'Globalisation & Politics' of the Political Science Department at the University of Kassel. He holds a Ph.D. in political science, an M.A. in global political economy and an M.Sc. in biology. He has received scholarships from the German Academic Exchange Service, the Heinrich Böll Foundation, and the University of Kassel. His M.A. thesis on the commodification of genetic resources was awarded first prize in the global challenges competition of the German Körber Foundation. He is co-representative of International Political Economy, a permanent working group of the German Political Science Association (DVPW), and founding member of the German Working Group on Theories of Hegemony and Discourse. His research interests concentrate on political theory, in particular theories of international relations and international political economy, nanotechnology, critical security studies, financial crises, and intellectual property rights.

Lecture: Nanotechnology and society

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Whether new technologies can prevail as products and applications strongly depends on their degree of acceptance in society. The struggle for such acceptance is demonstrated in an examination of the recent discourse surrounding nanotechnology. It is no accident that attitudes towards nanotechnology to date have tended to be positive. In no small measure this development is the result of successful discourse strategies. This process is problematized from a democratic point of view.
Professor Roger Brownsword
Roger Brownsword is a graduate of the London School of Economics. He is Professor of Law at King’s College London, where he was the founding director of TELOS (a research centre that focuses on technology, ethics, law and society); he is an honorary Professor in Law at the University of Sheffield; and he is a visiting professor at Singapore Management University.
He is a member of the editorial board of the Modern Law Review; he is the general editor of the Understanding Law series of books (in which he has co-authored with John Adams both Understanding Law and Understanding Contract Law); he edited the latest edition of Smith and Thomas’ Casebook on Contract; and he is the founding general editor, with Han Somsen, of the journal, Law, Innovation and Technology. He held a Leverhulme Research Fellowship in 2003-2004, a visiting Fellowship at the University of Tilburg in 2008, and he was a member of the Law panel for RAE2008.
Professor Brownsword has acted as a specialist adviser to parliamentary committees dealing with stems cells and hybrid embryos. From 2004-2010, he was a member of the Nuffield Council on Bioethics, during which time he was a member of the working party on public health. Currently, he is a member of the UK NHS Screening Committee, and he is Chair of the Ethics and Governance Council of UK Biobank.

Lecture: Nanomedicine: An exceptional regulatory and ethical challenge?
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The purpose of this paper is to assess whether there is any sense in which the (unknown and unpredictable) characteristics of materials on the nanoscale call for an exceptional regulatory and ethical response. In particular, is an exceptional response called for where such materials are used in medical products and devices?
Three possibilities will be considered. The first is that we need to have a dedicated regulatory regime for nanomedicine; the second is that, with nanomedicine, the regulation of patient health and safety cannot be orientated around notions of ‘precaution’; and the third is that ‘informed consent’ cannot serve as the ethic that governs the nanomedical relationship between doctors and patients.
The position taken in the paper is that, while the regulation of nanomedicine is a challenge, it is not so exceptional as to be off the existing regulatory radar.
**Poster Session – Overview**

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The secret of Cleopatra´s Beauty –
and how Nanotechnology makes you even more beautiful.

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Keywords: nanoparticles, SLN, coenzyme Q10, dermal delivery, occlusion, nanocrystals

Cleopatra (69 BC-30 BC), the last pharaoh from the ancient Egypt, is described being a great beauty, with aesthetic and sexual appeal (Wikipedia). A bust of her is exhibited also in Berlin, Altes Museum. One of the reasons for her legendary beauty is that she took baths in ass’s milk and honey. Scientifically speaking, the effect on the skin of ass’s milk is attributed to its content of lipophilic natural coenzyme Q10 (Q10), located in the milk droplets. The fine fat droplets of the ass’s milk adhered to her skin, delivering Q10 into the skin.

Nowadays nanotechnology is much more efficient than this process of nature. Nanotechnology means that materials obtain novel physico-chemical properties by transfer to the nanodimension, thus very tiny particles (1 to 1,000 nm) have special outstanding properties. The fat droplets of the ass’s milk are now produced by a nanotechnology process. The materials used are skin-friendly lipids such as kukui oil, red amber oil, shea butter and bees wax etc. They are superior in the composition of omega-unsaturated fats acids with skin-caring effect. Q10 is dissolved in these lipids. In the next step, the lipid blends are transferred into so called „solid lipid nanoparticles“ (SLN) (1, 2) by high pressure homogenization. The SLN particles obtained are much smaller than the milk droplets, therefore they adhere much better on the skin.

The adhesion of SLN repairs damaged lipid films on the skin, increases skin hydration and protects against environmental hazards. In addition, the invisible film creates an occlusion effect (similar to a plastic foil on skin), which increases the penetration of cosmetic actives into the skin. The Q10 penetrates much better into the skin than from milk droplets, leading to higher activity. Products on the market are the Nanorepair series by Dr. Rimpler GmbH (www.rimpler.de).

For even better performance, another nanotechnology can be additionally used, the so called „nanodiamonds“ (3, 4). To protect skin against oxidative stress, e.g. UV irradiation, the skin needs to have sufficient anti-oxidant capacity. To improve the capacity of the skin, antioxidants can be incorporated into cosmetic creams. They can be made highly active by transferring the crystalline antioxidant powder into nanosize, so called nanocrystals (or: nanodiamonds). An example on the market are hesperidin nanocrystals, contained in products by la prairie (e.g. product platinum rare) and by ipam Berlin (ageLine® wo/man one) Nanodiamonds were developed in Berlin, and recognized by the Berlin Brandenburg Innovation Award 2008.

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Adsorption and Photocatalytic Degradation of Human Serum Albumin on TiO$_2$ and Ag-TiO$_2$ Films

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Titanium dioxide is a useful material in the biomedical field as it has excellent biocompatibility based on its non-toxicity and non-inflammatory properties. Furthermore, TiO$_2$ can be excited by UV light to create charge carriers giving rise to photocatalytic redox reactions at the surface and photo-induced super-hydrophilicity. These properties might be exploited for surface decontamination of medical devices and implants. With this in mind, titanium dioxide TiO$_2$ films were prepared on stainless steel substrates using magnetron sputtering. Silver loaded (Ag-TiO$_2$) films were prepared by the photocatalytic reduction of Ag$^+$ from solution. The adsorption of human serum albumin (HSA) was studied. Surface analysis methods used included X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), Raman spectroscopy and atomic force microscopy (AFM). The TiO$_2$ films were predominantly anatase crystal phase and the photoreduced Ag was present at greater than 90% of the silver content as Ag$^0$ on the surface. Ag loading of the TiO$_2$ markedly enhanced the Raman signal (ca. 15-fold), but caused significant changes to the spectrum indicating non-specific binding of protein side chain residues to the Ag. The amide I and III modes remained well-resolved and were used to estimate the conformational change induced by the Ag. Raman analysis showed an increase in the intensity of the band at ~1665 cm$^{-1}$ assigned to the disordered conformation, suggesting that the adsorption to the Ag sites induces conformational changes in the protein. UVB irradiation of the protein contaminated surfaces caused further changes in the protein conformation, consistent with denaturation and enhanced binding and oxidation, thought to be induced through a photocatalytic mechanism.

References:

NANOTECHNOLOGY AND MEDICINE: BETWEEN “OLD” AND “NOVEL” ISSUES … A NEED FOR A NANOETHICS?

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Nanotechnologies, as a result of the convergence between the cognitive sciences, humanities and empirical sciences (the so called nano-bio-info-cogno convergence), open to great opportunities, but at the same time, they contribute to increase the “the circumference of the unknown” suggested by the American Bioethicist Bartha Knoppers.

For this and more others reasons, nanotechnologies are debated between hope and incertitude with regard both the scientific dimension (‘Apocalyptic Nightmares from a side, and ‘Utopian Dreams’ from the other) and bioethical concerns. In fact, nanotechnologies’ applications are debated between those who consider the novelty of these technologies in both techniques and ethical issues, and others who, on the opposite, disagree on the need of a specific bioethical reflection, considering nanotechnology novel only in the technical meaning, that is in the technology itself. In the first case we speak of a nanoethics

Description of the Project:
The aim of the presentation is: 1. to analyze the two different positions between “old” and “novel” ethical issues in nanotechnology applications; 2. to evaluate a place for a nanoethics; 3. to show the favor for a nanoethics 3. to propose a method of evaluation of ethical issues in this field

Nanotechnologies represent a challenge: the novelty of these technologies, in fact, make easier the introduction of synergic actions devoted to the possible applications and, at the same time, to a deeper reflection of the bioethical issues.
Dopamine secretion by PC12 neuron-like cells cultured on nanofibrous poly(3-hydroxybutyrate) substrates


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In the latest decades, the transplantation of encapsulated PC12 cells has been explored as a possible, ethically acceptable strategy for the treatment of Parkinson’s disease (PD) through xenografts [1,2]. Derived from a pheochromocytoma of the rat adrenal medulla, the PC12 cell line in fact exhibits a dopaminergic phenotype which promises to be suitable for the amelioration of PD symptoms upon cell encapsulation. To date, long-term survival and proper dopamine secretion of the cellular constructs after transplantation have already been achieved in preclinical primate studies [3]. Along with these evidences, a great number of studies in the field of biomaterials have shown that physical environmental cues can enhance cell activities, favouring, for instance, cell proliferation and differentiation in vitro [4,5]. For these reasons, we hypothesized that PC12 cells could be responsive to topographical stimuli on the nanometer scale provided by cell culture substrates, and we therefore investigated cell behavior on nanofibers electrospun by a natural polymer, that is poly(3-hydroxybutyrate) (PHB). After 72 h of culture on fibrous substrates, PC12 cells were found highly viable and, coherently to other authors’ findings [4,6], proliferating to a significantly higher extent on fibrous substrates in comparison to standard substrates, thus demonstrating that the fibrous topography enhances cell proliferation. Moreover, PC12 cells were found able to secrete high quantities of dopamine, with values four orders of magnitude higher than those suggested in the literature [3] as effective to improve parkinsonian symptoms. These results encourage further studies on the encapsulation of PC12 cells seeded on PHB nanofibers in the perspective of treatment of Parkinson’s disease [7].

Size Dependent, Multispectral Photoacoustic Response of Gold Nanoparticles

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Photoacoustic (PA) Imaging attracts much attention as an innovative modality for longitudinal, non-invasive, functional and molecular imaging in oncology [1, 2]. Gold nanoparticles (AuNPs) are identified as superior, NIR-absorbing PA contrast agents [3] for biomedical applications [4]. Until now, no systematic comparison of the optical extinction and PA efficacy of water-soluble AuNPs of various geometries and small sizes has been performed.

Here spherical AuNPs with core diameters of 1.0, 1.4 and 11.2 nm, nanorods with longitudinal/transversal elongation of 38/9 and 44/12 nm and hollow nanospheres (HGNs) with outer/inner diameters of 33/19, 57/30, 68/45 and 85/56 nm were synthesized, which specifically absorb light within the optical window of tissues [5]. The diode laser setup with excitations at 650, 808, 850 and 905 nm, allowed correlating the molar PA signal intensity to the molar extinction of the respective AuNPs. Deviations were explained by differences in heat transfer from the particle to the medium [6] and for larger particles by scattering of light [7]. The molar PA intensity of 1.0 nm AuNPs was comparable to the commonly used organic dye methylene blue [8], and rapidly increased with the lateral size of AuNPs.

Challenges and questions in nanomedicine legislation

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The current developments in nanotechnology are expected to change healthcare and medical treatment fundamentally. Especially many hopes are directed towards the areas of minimally invasive diagnostics based on DNA biochips, biosensors and nanoparticle contrast agents, but also drug delivery systems, implant materials and tissue engineering are important examples.

New emerging and innovative technologies like nanotechnology create new challenges for the legislator, not least when the associated products and processes raise concerns about health and environmental hazards and risks. The key challenges and problems related to nanomaterials and its applications in nanomedicine can be summarized as follows:

- “Nanomaterial” is an umbrella term, without broadly agreed general scientific and/or legal definitions. The Commission Recommendation for the definition of the term “nanomaterial” adopted in October 2011 is solely based on the size and comprises natural, incidental or manufactured material containing particles. The consequences of this recommendation for nanomedicine legislation will have to be carefully reappraised. Safety specification for medicinal products is mainly built on drug-substance specific aspects, however new guidance would be warranted to also adequately address the risks posed by nanomaterials itself and the reactivity of associated excipients.

- The level of confidence in existing regulations when dealing with nanotechnology strongly depends both on the type of product considered and the legislative framework to which it has to comply. In order to determine whether a product is a medical device defined in 93/42/EEC or a medicine according to the directive 2001/83/EC the specific legal definitions of both need to be considered, along with the claims for the product, the mode of action on the human body and intended purpose of the product. In contrast to medical device regulation, the legislation of medicinal products requires demonstration of efficacy, not just quality and safety. Nanomedicinal products, however, may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological and immunological properties and combining diagnostic and therapeutic functions. These novel applications of nanotechnology will span the regulatory boundaries between medicinal products and medical devices. Important problems result for the non-uniform legal practice concerning borderline products in terms of their conform classification to existing law.

- Another question is whether existing legislation can be adapted to nanomaterials or whether a new regulatory framework should be developed. Most political decision makers prefer a so-called incremental approach. They favour to adapt the existing legal framework to enable nanotechnology regulation and amending it in order to deal with the unintended implications of this technology. This approach has a number of challenges, limitations and potential gaps since existing legislation is not designed to accommodate some specific aspects of nanomaterials like novel risks and risk assessment methodologies. Some scholars as well as some stakeholders argue that the limitations of the incremental approach are so serious that an entirely new regulatory framework for nanomaterials is needed.
Quantum dot migration in the lymphatic system of mouse after subcutaneous injection

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Key words: quantum dots, fluorescence imaging, lymph nodes, biodistribution

Quantum dots (QD) are semiconductor nanoparticles in the size range of 2-10 nm and they are extensively studied for the applications in fluorescence imaging as they are bright, photostable fluorophores and can be easily chemically modified for biological functionalization. Lymph node imaging has important therapeutic and prognostic significance in patients with newly diagnosed cancers. More to add, intraoperative imaging of lymph nodes have limited modalities and new clinical approaches are required. We used Balb/c mouse model to study migration and biodistribution of CdSe/ZnS QD coated with polyethylene glycol after subcutaneous injection by the means of fluorescence imaging, fluorescence spectroscopy and confocal microscopy. 2 h after injection QD distribution in the body was compared with the organic dye Rhodamine B. The results show, that QD are impermeable to specific dermal structures like epidermal basement membrane and dense connective tissue fibers which restrict QD passage to epidermis, hair follicles, muscle fibers, nerves etc. QD are mainly drained from the injection site via lymphatic system and QD fluorescence can be observed in the regional lymph nodes and lymph vessels with high contrast to surrounding tissues during 2 hours. On the contrary, Rhodamine B represents a small molecular mass fluorophore and, therefore, it is highly permeable to biological barriers which leads to rapid systemic distribution in the body with no selective accumulation in lymphatic system. To conclude, the subcutaneously injected QD posses limited diffusion in dermal tissues which results in the specific migration through the lymphatic system. QD represent a perfect contrast agent for intraoperative fluorescence lymph node imaging and it is a great model for nanoparticle biodistribution studies.
Cytotoxicity and hERG ion channel activity of ultrasmall gold nanoparticles

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Gold nanoparticles (AuNPs) are of great interest in biomedical applications, for example as drug carriers or as contrast agents in radiology or in photoacoustic imaging. However, the very properties of AuNPs may also hold risks of adverse side effects. In this work we report the size dependent cytotoxicity for a series of gold nanoparticles (AuNPs) in the size range of 0.8 nm – 15 nm, which are stabilized by covalently bound triphenylphosphine-monosulfonate (TPPMS) ligands. We will show that a cytotoxicity maximum appears for 1.4 nm sized AuNPs (Au1.4MS), whereas the toxicity in vitro can widely be reduced when ligands are thiol molecules, which bind more strongly to the AuNP surface. Furthermore we will show that the cytotoxic Au1.4MS exhibits electrophysiological effects on potassium ion channel (hERG) expressing HEK 293 cells. This is demonstrated by patch clamp experiments with a variety of phosphine- and thiol-stabilized AuNPs which show that the ligand functionalization of AuNPs greatly influenced the electrophysiological response of HEK 293 cells, thus mirroring cytotoxicity. Phosphine-stabilized AuNPs irreversibly block hERG channels, whereas thiol-stabilized AuNPs of similar size have no effect. We hypothesise that Au1.4MS partially sheds weakly bound TPPMS ligands exposing the bare gold surface that may irreversibly block the ion channel.
Psychosocial and ethical implications of portable diagnostic lab-on-a-chip systems (LOC’s) for point-of-care (POC) and direct-to-consumer (DTC) applications

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Given the approach of personalized medicine, technological devices for biomarker expression are more frequently used for individualized diagnosis, monitoring, and screening. Within a conventional approach, biomaterials are shipped to a stationary lab for analysing the material or the respective material is stored within a biobank for short-, mid- or long-term observation purposes. The use of portable lab-on-a-chip systems (hereafter: LOC’s) for personalized point-of-care diagnostics avoids the need to “give away” the biomaterial. This issue is of high relevance, given ethical debates on transferring and storing personalized human biomarkers. Moreover, diagnostic devices for medical home care have become increasingly flexible within the last decades. Naturally, this development refers to technological innovations such as ambulatory assessment, home monitoring, and telediagnostics. Currently, one could draw a line from this history mobilization of diagnostic devices to the emerging field of developing LOC’s for diagnostic purposes.

Our project aims at investigating the ethical and psychosocial impact of the implementation of highly integrated portable lab-on-a-chip systems (LOC’s) used for point of care diagnostics on patients and healthy persons as well as health professionals in home care and health-related direct-to-consumer contexts. Previous psychosocial research on related telediagnostic technologies has primarily focused on psychological barriers and subjective outcome parameters. In this project we highlight the issues of de-professionalization of diagnostic applications and de-contextualization of health-related information processing. Preliminary results provide recommendations to address the issues of medicalization as well as the linkage between health literacy, self-care and autonomy of patients/lay persons.
Nano Taxis to the Brain

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Keywords: nanoparticles, drug targeting, brain delivery, apolipoprotein E

Ideally the drug should be delivered to the part of the body (target) where it should act. This increases the therapeutic efficiency. At the same time reduction of drug concentration in other parts of the body where the drug should not act reduces potential side effects. This concept postulated by Ehrlich is being tried to be realized by various approaches in pharmaceutical research and product development. One approach is to use nanoparticles (1). The nanoparticles are loaded with drugs, then they need to be administered to the body and via a „homing device“ (target seeker) they should find their target area.

Some parts of the body are especially protected against „intrusion“ of foreign materials including drugs. The brain as important organ is one of these areas, protected against the blood by the blood brain barrier (BBB). Therefore targeting to the brain is a special challenge. We need to develop a „drug taxi“ which efficiently finds its way to the brain in the labyrinth of the blood vessels in the body. The concept consists of two parts, first finding a suitable taxi, secondly equipping the taxi with a kind of GPS system directing it to the brain. The first part of the concept is injecting drug-loaded nanoparticles as taxis intravenously. These nanoparticles need to be well tolerated by the body (= nanosafe) and biodegradable. These are nanoparticles made from natural lipids of the body, solid lipid nanoparticles (SLN) (2), or alternatively drug nanocrystals (3, 4). The nanocrystals consist of pure drug only (100%), therefore they can carry a high drug load to the brain.

In the second part, the particles need to be directed to the brain. For this a natural effect is exploited. After injection of particles, blood proteins adsorb on the particle surface. The adsorbed proteins determine to which cells of the body the particles adhere (5). The surface properties of the nanoparticles are adjusted this way, that they preferentially adsorb the blood proteins binding to the blood brain barrier (in this case it is apolipoprotein E). This adsorption occurs automatically in the body, therefore represents a smart approach for targeting.

Similar to a taxi transporting different passengers, the nanoparticles can be loaded with different drugs. The GPS location system using blood proteins can be extended to „transport“ to different organs of the body, e.g. bone marrow, liver, spleen.

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Multifunctional Magneto-Micelles (MMMs) for targeted dual MRI/fluorescent imaging of cancer

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Early stage diagnosis of cancer is the key for successful treatment and positive patient prognosis. Therefore, sensitive tracking and molecular imaging technologies are required for the advancement of healthcare.\textsuperscript{1,2} Multifunctional nanoparticles as cancer recognition markers have been proved as sensitive tools for a reliable diagnosis. In particular, superparamagnetic iron oxide nanoparticles (SPIONs) with several integrated properties provide enormous capacity for cancer diagnostics. Therefore, controlling and combining multiple components in one nanoparticle becomes a critical step in creating a robust ‘all-in-one’ system for precise diagnosis.\textsuperscript{3}

In this project, multifunctional magneto-micelles (MMMs) were developed to efficiently incorporate four essential components (1) clustered SPIONs inside the core of the micelle for ultrasensitive MRI detection; (2) “stealth” polymeric shell for long circulation blood time and bioavailability; (3) encapsulated fluorophore for fluorescent imaging capabilities; (4) monoclonal antibody (mAb) for targeting capabilities and induced receptor-mediated endocytosis. Full structural and morphological characterisation of MMMs included TGA analysis, FTIR, TEM, DLS and zeta potential to demonstrate the integrity and stability of the hybrid system. The undergoing research on targeted MMMs has shown superior affinity and selectivity towards the tumor antigens overexpressed on pancreatic cancer cells compared to their non-targeted counterparts.

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METAL NANOPARTICLES: SYNTHESIS, RISK ASSESSMENT, PHARMACEUTICAL PERSPECTIVES

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The protocols for synthesis of metal nanoparticles (gold, silver, iron, copper, bismuth) in water medium by the methods of chemical reduction have been developed. Physicochemical properties of synthesized metal nanoparticles (form, size, particle charge, pH etc.) have been determined. All synthesized metal nanoparticles are characterized by biosafety and biocompatibility using well-known as well as developed toxicological, physiological, biochemical, molecular-genetic test-parameters of the determined biological systems such as microorganisms, eukaryotic cells’ cultures and mammals.

Most safety types of synthesized metal nanoparticles according to the used biosafety test-parameters are studied for their application as potential pharmaceutical substances. Gold nanoparticles’ high affinity to the tumor cells in the in vitro and in vivo experiments has been shown.

Perspectives of gold nanoparticles application as vector for target drug delivery as well as pharmaceutical substance in treatment of cardio-vascular diseases are investigated. Silver nanoparticles antimicrobial activity against pathogen test-strains S. aureus MRSA, P. aeruginosa, E. coli, B. subtilis, E. faecalis has been revealed. Bismuth nanoparticles’ high bactericidal action against high pathogen strains S. typhimurium, E. coli, B. anthracis has been determined.

Copper nanoparticles high antimicrobial activity against clinical isolates - causative agents of urological infections (Candida, C. freundii, K. ozaenae, E. faecalis, S. aureus, P. aeruginosa) has been revealed. The probiotic bacteria cells’ growth rate and energy potential increase on 20-40%, antagonistic activity stimulation against pathogenic test-cultures S. typhimurium, S. aureus, S. sonnei, Candida albicans etc. as result of the probiont-strains interaction with metal nanoparticles (gold and iron) in certain size and concentration have been determined. Obtained results indicate high pharmaceutical perspectives of synthesized metal nanoparticles. Biosafety and biocompatibility level of all synthesized metal nanoparticles is necessary criterion for their application as potential pharmaceutical substances.
Functional relevant effects of polyvinylalcohol coated superparamagnetic iron oxide particles on mesenchymal stromal cells

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Polyvinyl alcohol coated superparamagnetic iron oxide particles (PVA-SPIONS) were designed for biomedical applications in the context of rheumatoid diseases. Experiments with rats have shown that intravenous injected SPIONs (for macrophage tracking) accumulate in bones that contain a number of different cell types like mesenchymal stromal cells (MSCs) and hematopoietic stem cells (HSCs). MSCs play a crucial role in tissue regeneration and homeostasis, in bones they also form the HSC niche. We therefore aim to perform a comprehensive analysis of the influence of PVA-SPIONS particles on MSCs. The experiments planned will be performed with human MSCs in vitro as well as rMSC that were incubated with nanoparticles in an in vivo situation.

Since nanoparticles pose a novel class of materials their interaction with common methods and assay needs to be carefully first. Our data shows that PVA-SPION strongly influence the MTS assay and also alter the signal for resazurin based assays. The acquired results were the basis for the design of the experimental set up used to determine the influence of PVA-SPIONS on MSCs. Our first in vitro results indicate no acute toxic effect of PVA-SPIONs on MSCs. Concerning the MSCs from rats that were incubated with PVA-SPIONs in an in vivo situation, we see changes concerning proliferation, apoptosis, metabolic activity and migration.

In the near future we seek to confirm our data from the in vivo incubated rMSCs by continuing our experiments with more animals. We also want to perform functional assays (migration, differentiation) on hMSCs in vitro. Another part of this project will be the development of a labeling protocol for MSCs using the PVA-SPIONS and subsequent in vivo cell tracking experiments.
Influence of PVA coated nanoparticles on survival and functionality of human immune cells

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Background: Nanotechnology has developed into a key technology of the 21st century. Over the recent years, the number of nanotechnical products has received an enormous boost. More and more efforts are being done to use this technology in human medicine for diagnostic and therapeutic purposes. Therefore, crucial questions concern the safety aspects. The focus of our work here was to identify possible effects of nanoparticles on human immune cell function.

Objective: We analysed clinical relevant interactions between PVA coated nanoparticles (spions) and human immune cells.

Methods: 100µl of whole blood obtained from patients with rheumatoid arthritis (RA) or healthy donors were incubated with 100µl serum free RPMI 1640. Functionalised spions were added at varying concentrations, and cells were incubated for 24h. After lysis of erythrocytes, cells were stained for apoptosis and necrosis using Annexin V and 7AAD, respectively. Samples were analysed by flow cytometry. As a second approach, PBMCs were isolated from blood samples of healthy donors and RA patients, and CD4 positive T cells were separated via MACS-Sort. T cells were incubated with/without PHA and/or with/without PVA spions at different concentrations. Activation (CD25 expression) of cells was analysed by flow cytometry. Functionality was determined via proliferation measurements of CFSE (carboxyfluorescein diacetatesuccinimidyl ester) labeled T cells after 72h under normoxic (5% CO2 and 18% O2) or hypoxic (5% CO2 and <1% O2) conditions by flow cytometry.

Results: Altogether, blood samples from 18 healthy donors and 19 patients suffering from RA were analysed for induction of apoptosis and necrosis in different cell types. The results on cell survival did not demonstrate any short-term general toxicity of PVA spions at concentrations less than 1000µg/ml on the several different blood cell subsets examined. Furthermore, T cells were isolated from 14 healthy donors and 9 RA patients for functional analysis. There is no influence of PVA spions on T cell activation and proliferation at concentrations less than 1000µg/ml.

Conclusion: PVA coated nanoparticles at concentrations up to 1000µg/ml (i) do not increase the frequencies of apoptotic or necrotic human immune and (ii) do not impair crucial functional activities of human T cells such as activation and proliferation.
Antibacterial Effects of Au ions and Gold Nanoparticles on Nosocomial Acinetobacter spp.

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Nosocomial infections are the infections acquired from hospitals emerging after 48-72 h from hospitalization or within 10 days after discharge due to various microorganisms. Hospital infections are a crucial health problem for patients and hospitals [1, 2]. In recent years due to usage of wide spectrum antibiotics, Acinetobacter spp. are often isolated from nosocomial infections in intensive care units. Acinetobacter spp. are known substantial factors of hospital infection through living even under poor conditions and acquiring multi-resistance to various antibiotics. 35 Acinetobacter sp. strains recovered from clinical isolates identified as hospital infection factors were studied. In this study, the antibacterial activity was examined using Au+ ions and AuNPs. We synthesized AuNPs at about 20 nm size with using citrate reduction method was reported earlier [3, 4]. UV and TEM measurements was used to confirm shape and size of AuNPs. In this work, the antibacterial efficiency of Au⁺ ions and AuNPs at various concentrations was investigated by interacting them with different nosocomial Acinetobacter spp. under in vitro conditions. The agar-well-diffusion method was applied to determine the antibiotic activity of particles. For further studies it is aimed to combine chemotherapeutic agents which have antibacterial effects with AuNPs to enhance antibacterial effects against pathogens.

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Glyco-DNA Gold Nanoparticles: Lectin-Mediated Assembly and Dual Stimuli Response

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DNA functionalized gold nanoparticles (Au NP-DNA) have been investigated in numerous studies since more than a decade as they combine the outstanding optical characteristics of gold nanoparticles with the molecular recognition capabilities of DNA. Due to their multivalent DNA ligand shell Au NP-DNA exhibit cooperative binding properties associated with higher binding constants and a sharper melting transition as compared to free DNA. Au NP may act as optical sensors since the resonance frequency of the particle plasmon depends on the surrounding medium. This enables e.g. the monitoring of the specific self-assembly of the Au NP forming networks.

Here we demonstrate the formation and properties of glyco-DNA-gold nanoparticles with a multivalent presentation of DNA-glyco ligands, which assemble by binding of the matching lectin to the specific carbohydrate termini of the glyco-DNA ligands. These particles are equipped with two reversible binding modes which enable the reversible dissociation by two independent external stimuli: temperature induced DNA duplex melting and displacement of the DNA-glyco ligands from the carbohydrate recognition domains of the lectin by competition with free sugar. Hence, the multifunctional system introduced could be of interest in the design of stimuli-responsive materials in general, as well as of potential interest, e.g., for novel in vitro assay approaches or for targeted diagnostics or therapy.