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Review Article

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History and Possible Uses of Nanomedicine Based on Nanoparticles and Nanotechnological Progress

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Abstract

Nanomedicine is a key science of the 21st century. Although the production and use of nanosized particles had taken place in several ways in ancient times and hundreds of years ago, nanomedicine as a modern interdisciplinary science was first established in the nineties of the last century only. The basis of this new science derives from the development of an array of ultramicroscopic devices and the studies of cellular, molecular and finally atomsized structures in biology, chemistry and physics in the 20th century. The nanotechnological approach, first framed in the 1950's by Richard P. Feynman, was the constitutive force to establish nanomedicine as a paramount section in science and medical treatments. From the beginning nanomedicine developed rapidly, driven by tremendous progress in techniques. Its historical evolvement and diversification into a wide range of medical applications (e.g. tissue engineering) and its increasing relevance for a large bunch of disease categories are outlined. Essential application and/or research areas comprise the use of biosensors for diagnostic reasons (including nanoimaging and lab-on-the-chip) and biocompatible nanomaterials (such as liposomes) as drug, vaccine and gene vehicles for therapy, most prominently as nanocapsules for cancer treatment (in connection to hyperthermia, thermoablation and radiotherapy methods where appropriate). Future directions remain multi-fold, the most important ones defined as drug delivery, theranostics, tissue engineering, and magnetofection. Some novel developments (regarding cancer treatment and stent angioplasty) are presented. Regenerative medicine and gene therapy are of rising importance

Keywords: Nanomedicine; History; Feynman; Nanotechnology; Nanoparticles; Drug delivery; Theranostics; Tissue engineering; Magnetofection

Introduction

What if doctors could search out and destroy the very first cancer cells that would otherwise have caused a tumor to develop in the body? What if a broken part of a cell could be removed and replaced with a miniature biological machine? What if pumps the size of molecules could be implanted to deliver life-saving medicines precisely when and where they are needed [1].

Nanotechnology is one of the key technologies of the 21st century. Needless to say, the production and use of the tiniest particles invisible to the naked eye are not a latter-day invention. Examples of the earlier use of nanomaterials are the Lycurgus Cup from the 4th century AD on display in the British Museum in London, some late medieval church windows and also the famous Damascene Swords: When light shines from the outside on the antique Roman cup the cup looks olive green, when illuminated from the inside it shines ruby red and the mythological king depicted on it turns lilac. Colloidal nanoparticles of silver and gold contained in the glass are responsible for this phenomenon. A similar effect is seen in some late medieval church windows, which shine a luminous red and yellow because nanoparticles of gold and silver have been fused into the glass. In 2006 nanometer-size particles of carbon were discovered in a Damascene Sword from the 17th century, these being responsible for the elasticity and resistance of the legendary swords [2]. These special properties of the colors and materials were already being produced intentionally many hundreds of years ago. Medieval artists and forgers, however, did not know the cause of these surprising effects.

Modern nanotechnology is an interdisciplinary science concerning the tiniest of particles and their special chemical, physical and mechanical properties at the meeting points of physics, chemistry, biology, medicine, electronics and information technology. In practice the special areas of nanotechnology overlap and blur the boundaries between the natural sciences. Nanobiotechnology is concerned with molecular intra- and intercellular processes and is of critical importance for nanotechnology applications in medicine. This manifests itself in the diverse interplay between medically relevant nanotechnologies and possible nanobiotechnology applications in human medicine, as illustrated in the diagram (Figure 1).

The expectations of the diagnostic, therapeutic and regenerative possibilities of nanomedicine are immense. They are directed at inexpensive rapid tests for genetic predisposition, viral infection and the first signs of diseases long before symptoms manifest themselves, at medicines and vaccines without side effects, at treatment of cancer, cardiovascular diseases and neurological diseases, such as Alzheimer's and Parkinson's diseases, at establishing long-lasting, well-tolerated organ implants, at targeted control of cell and tissue growth and at stimulation of neuronal activities. The nanomedicine vision of the future is early detection of pathological changes at the molecular level by means of unambiguous imaging methods and minimally invasive treatment of the patient with individually tailor-made medicines as soon as the disease is in the development stage.

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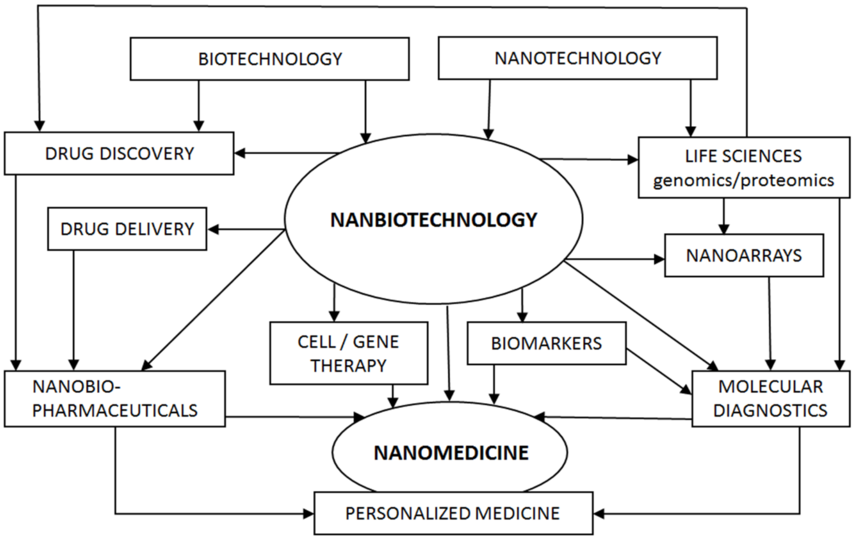

Figure 1: Importance of nanobiotechnology in medicine [17].

Although these possibilities are still a long way off, nanotechnologies have the potential to fundamentally change medicine in the coming decades. And because not only the methods of diagnosis and therapy but also how we deal with health, illness and old age will change, it is important also to consider the sociological consequences and ethical aspects of nanomedicine alongside the prospects.

History of Nanomedicine

Nanomedicine is a young science. How nanotechnology can be of use to medicine, medical technology and pharmacology has only been researched since the 1990s. Nanotechnology itself has only existed for a few decades. After the invention of high resolution microscopy it evolved simultaneously in biology, physics and chemistry in the course of the 20th century and spawned new disciplines such as microelectronics, biochemistry and molecular biology. For nanomedicine, nanobiotechnology knowledge which investigates the structure and function of cells as well as intra- and intercellular processes and cell communication is of prime importance. This research only became possible at the beginning of the 20th century when the door to the nanocosmos was burst open with the invention of innovative microscopes.

Nanoporous ceramic filters were indeed already being used in the 19th century to separate viruses, and around 1900 Max Planck and Albert Einstein produced theoretical evidence that there must be a range of tiny particles which obeyed their own laws. These particles could not be made visible however-the necessary instruments for this had yet to be invented.

In 1902 structures smaller than 4 nanometers were successfully detected in ruby glasses using the ultramicroscope developed by Richard Zsigmondy and Henry Siedentopf [3]. In 1912 Zsigmondy applied for a patent for the immersion ultramicroscope, with which it became possible to investigate the behavior of colloidal solutions. From 1931 onwards significantly better resolutions were achieved with the transmission electron microscope (TEM) developed by Max Knoll and Ernst Ruska than with the light microscopes conventionally used up until then [3]. Insight into the atomic range, however, first became possible with the field electron microscope developed by Erwin Müller in 1936 and its further development to the field ion microscope (FIM), with which in 1951 physicists were able to see individual atoms and their arrangement on a surface [4]. The use of the innovative microscopes in chemistry and biology led to the discovery of cell structures and cell constituents. With the aid of further inventions, such as the voltage clamp (a precursor of the patch clamp technique), understanding of the structure and function of the cell membrane, diffusion processes and systematic cell communication by means of receptors and antibodies according to fixed rules became ever better in the following decades. The mechanisms of maintaining and regulating metabolism, the role of enzymes and proteins and the functioning of the immune system were also researched and effective vaccines developed. The description and understanding of DNA and RNA in the 1950s and 1960s [5,6] led to the concept of genetic diseases and to the vision of cures at the molecular level tailor-made for patients. Finally, direct viewing in the nano range became possible at the start of the 1980s with scanning probe microscopy: Gerd Binnig and Heinrich Rohrer developed the scanning tunneling microscope (STM), with which an individual atom was successfully shown graphically in 1981 [4]. The first atomic force microscope (AFM) was commissioned in 1986 [4]. Using the various methods of scanning probe microscopy, it became possible not only to demonstrate nanoscale structures precisely, but also to position and manipulate them in a controlled way. This opened up diverse possible uses, and new scientific disciplines tailor-made to the nano range, including nanomedicine, arose. The term "nanotechnology" was coined in 1974 by Norio Taniguchi, and its definition is still valid even today: "[...], nanotechnology mainly consists of the processing of separation, consolidation and deformation of materials by one atom or one molecule" [7].

That there would one day be nanotechnologies and the associated possibilities was predicted by the physicist and Nobel prizewinner Richard P Feynman as early as 1959 in his paper *There's Plenty of Room at the Bottom. An invitation to enter a new field of physics* [8]. And although the term "nano" does not occur a single time in it, this paper is regarded as the founding text of nanotechnology. Feynman invited us to consider the production and control of tiny machines on the basis of quantum mechanics, and predicted that the development of more precise microscopes would open up access to the field of individual atoms and that it would be possible to arrange atoms as desired. He even mentioned the use of tiny machines in medicine: "[...] it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and "looks" around. [...] It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organ" [8].

After Feynman staked out the new field of research and awakened the interest of many scientists, two directions of thought arose describing the various possibilities for producing nanostructures. The top-down approach largely corresponds to Feynman's comments on stepwise reduction in the size of already existing machines and instruments. The bottom-up approach revolves around the construction of nanostructures atom for atom by physical and chemical methods and by using and controlled manipulation of the self-organizing forces of atoms and molecules. This theory of "molecular engineering" became popular in 1986 when *Engines of Creation. The Coming Era of Nanotechnology* [9] was published, the first and controversially discussed book on nanotechnology in which the author K. Eric Drexler described the construction of complex machines from individual atoms, which can independently manipulate molecules and atoms and thereby produce things and self-replicate. The possible uses of such "nanobots" or "assemblers" in medicine are described by K. Eric Drexler, Chris Peterson and Gayle Pergamit in their book *Unbounding the Future. The Nanotechnology Revolution* [10] published in 1991, in which the term "nanomedicine" was supposedly used for the first time. The term became established with the book *Nanomedicine* [11] by Robert A Freitas published in 1999 and has been used since then in technical literature. Because the conversion of the visions of Feynman and Drexler of nanoscale robots which patrol the body, render disease foci harmless and detect and repair organs and cells of impaired function is still in the distant future, nanomedicine is concentrated on research into the possibilities of controlling and manipulating cell processes, for example by targeted transport of active substances.

At the beginning of the 20th century Paul Ehrlich attempted to develop "magic bullets" to which drugs were added and which could be used to target diseases and would kill all pathogens after only a single treatment [12]. The Salvarsan he developed is regarded as the first specifically acting therapeutic of this type and marks the start of chemotherapy. The knowledge gained in the course of the 20th century on cells and their constituents and on intra- and intercellular processes and cell communication as well as advances in biochemistry and biotechnology made production of ever more sophisticated "magic bullets" possible. At the end of the 1960s Peter Paul Speiser developed the first nanoparticles which can be used for targeted drug therapy [12], and in the 1970s Georges Jean Franz Köhler and César Milstein succeeded in producing monoclonal antibodies [13]. Since then there has been intensive research into the possible syntheses and uses of various carrier systems and physicochemical functionalization of their surface structure. At the start of the 1990s nanoparticles were modified for the first time for transport of DNA fragments and genes and were sluiced into cells with the aid of antibodies [12,14].

At present biocompatible polymers, liposomes and micelles above all are being researched as carriers for drugs, vaccines and genes. Because of their small size (usually less than 200 nm [15]), nanomaterials are not filtered out of the blood and can circulate in the organism until they reach their target. Active substances can be encapsulated in their hollow interiors and their surface can be modified so that they overcome natural barriers such as cell membranes like "Trojan horses", and with the aid of biosensors (for example antibodies) recognize particular cells and tissue, attach themselves to these and release the active substances to the target over a relatively long period of time. These mechanisms are of interest above all for cancer treatment, since by the controlled release of the cytostatics exclusively in the tumor tissue the side effects can be reduced and at the same time higher doses of active substance than hitherto arrive at the tissue affected. Cancer treatment based on targeted transport of active substances can moreover take advantage of the EPR (enhanced permeability and retention) effect described in 1986 by Yasuhiro Matsumura and Hiroshi Maeda [16]: the fact that nanoparticles are deposited in tumors to a greater degree than in healthy tissue.

Possible Uses of Nanomedicine

The possible uses of nanotechnology in medicine are based on three pillars [17]:

1. nanomaterials and nanoinstruments which can be used as biosensors, as aids in treatment and as transporters of active substances,

2. knowledge of molecular medicine in the fields of genetics, proteomics and synthetically produced or modified microorganisms,

3. nanotechnologies which can be used for rapid diagnosis and for therapy, for repair of genetic material and for cell surgery, as well as for improving natural physiological functions.

There is hardly any area of medicine which could not benefit from the prospects nanotechnology offers [18]. The list in Figure 2 summarizes the specialist fields of nanomedicine which could become established in the 21st century.

The use of nanomaterials as contrast media in diagnostic *in vivo* procedures enables imaging with an improved three-dimensional view by means of which types of tissue can be differentiated more easily. Thanks to the use of fullerenes and carbon nanotubes the amount of contrast medium required can be reduced significantly [19]. Genes, nucleic acids, proteins, molecules and cell processes can be rendered visible in real time with the aid of quantum dots, i.e. nanoparticles of semiconductor crystals which can be diversely modified electronically and optically [20,21]. Due to the enormous stability and brightness these photoprobes display a luminosity 1,000 times greater than that of conventional contrast media. By imaging methods optimized by nanotechnology (nanoimaging), the presence, position and size of tumors can be determined more accurately than with conventional methods [18].

The hopes and expectations placed on the diagnostic possibilities of nanomedicine revolve around early detection of diseases and genetic dispositions at the molecular level with the aid of simple and inexpensive rapid tests and accurate imaging methods. Research is being undertaken into instruments which are portable and decentralized and which require only the smallest amounts of sample for measurement and diagnosis. The extremely miniaturized lab-on-a-chip technique necessary for this is precise, inexpensive and of little burden to the patient [22,23]. It can be used in the doctor's practice and hospitals and for preventing the spread of infectious diseases.

In the therapy sector it is hoped that nanotechnology applications will optimize existing and develop new medicines and methods for

Nanodiagnostics
- Extending limits of detection by refining currently available molecular diagnostic technologies
- Development of new nanotechnology-based assays
- Nanobiosensors
- Nanoendoscopy
- Nanoimaging

Nanopharmaceuticals
- Nanoparticulate formulations of drugs
- Nanotechnology-based drug discovery
- Nanotechnology-based drug delivery

Regenerative medicine
- Use of nanotechnology for tissue engineering
- Transplantation medicine
- Exosomes from donor dendritic cells for drug-free organ transplants

Nanomedicine specialties

Nanocardiology	Nanomicrobiology
Nanodermatology	Nanonephrology
Nanodentistry	Nanoneurology
Nanogerontology	Nanooncology
Nanohematology	Nanoophthalmology
Nanoimmunology	Nanoorthopedics

Implants
- Bioimplantable sensors that bridge the gap between electronic and neurological circuitry
- Durable rejection-resistant artificial tissues and organs
- Implantations of nanocoated stents in coronary arteries to elute drugs and to prevent reocclusion
- Implantation of nanoelectrodes in the brain for functional neurosurgery
- Implantation of nanopumps for drug delivery

Nanosurgery
- Minimally invasive surgery: miniaturized nanosensors implanted in catheters to provide real-time data
- Nanosurgery by integration of nanoparticles and external energy

Nanorobotic treatments
- Vascular surgery by nanorobots introduced into the vascular system
- Nanorobots for detection and destruction of cancer

Figure 2: Nanomedicine in the 21st century (adapted from Jain 2012 [18]).

preventing, controlling and curing diseases: Synthetically produced vaccines, above all against infectious diseases and autoimmune diseases, medicines which can be taken by simply inhaling and more efficient possible treatments of cardiovascular diseases. Research and development is centered on the 100 year old concept of targeted transport of active substances, realization of which looks to be possible for the first time with the aid of nanotechnology. Biocompatible, spherical nanomaterials (for example polymers, liposomes or micelles) can be used as transport agents. Such vehicles in the hollow interiors of which active substances can be transported and the surfaces of which can be equipped with sensors which detect chemical states or cell types, viruses and other pathogens attach themselves to these and can release the active substances to the target without the surrounding tissue being damaged. These liposomes, which – individually modified for the respective targeted transports – carry differing ligands (for example antibodies, proteins, peptides, carbohydrates etc.) and can have various surface conformations, are increasingly being used (Figure 3) [24,25].

There is intensive research into the possibilities of using such nanocapsules in cancer treatment [26]. The reasons for their suitability are their small dimensions, biocompatibility, robustness (biodegradability), hydrophobic and hydrophilic properties, low toxicity and immunogenicity [24]. In this case the surface of the nanoscale carrier systems is equipped with antibodies which either react to the lower pH of the tumor compared with the surrounding tissue or recognize the tumor cells directly, penetrate into these and release active substances accurately on target and over a relatively long period of time. One particular variant of this method is magnetic drug targeting (MDT): In passive MDT nanoscale metal oxides (iron and gold particles) are bound to the cytostatics and introduced into the organism, where they circulate but are deposited to a not insignificant extent in the organs of the reticuloendothelial system (RES). In active MDT the iron oxide particles [Fe_3O_4] bound to cytostatics are guided into the tumor tissue by applying magnetic fields and are concentrated there. The advantages of this method over conventional chemotherapy, which attacks the entire organism and in which only a small portion of the active substances reaches the tumor tissue, have been demonstrated in animal studies [27,28] and also when used on humans [29]: In active MDT significantly fewer side effects occur, and lower doses of active substances can be used, but directly in the tissue affected in a targeted way and for a longer period of time due to being released in stages.

Another variant of cancer nanotreatment is that of particles which have accumulated in the tumor tissue being heated by hyperthermia or thermoablation methods, whereby not only is the tumor tissue weakened and destroyed, the toxicity of chemotherapeutics is also increased [30]. In the treatment of brain tumors the ferrofluids are injected directly into the tumor and heated there with the aid of alternating magnetic fields. Clinical studies have shown that this method can be used safely on humans [31] and that promising results can be achieved in combination with radiotherapy [32].

In essence, multifunctional nanoparticles have been devised with (a) stealth-like features to evade the immune system and prevent opsonization, (b) protective layers to prevent the degradation of biologic cargo (e.g. proteins, DNA), (c) targeting moieties to improve specificity and tumor accumulation, (d) membrane-permeation moieties to improve cell uptake, (e) imaging agents to assess delivery and dosing, (f) endosome escape mechanisms, target-dependent assembly or disassembly to control drug release, (g) microenvironment sensors (pH, proteases, phospholipases) to trigger drug release and cell uptake, and (h) intracellular targeting moieties to direct drugs to specific intracellular compartments [33]. A challenge to these complex therapeutic systems, however, remains the weighing up of costs and benefits.

Prospects: Future Development of Nanomedicine

In the coming decade nanotechnology and nanobiotechnology applications will gain importance in medicine and medical technology. This trend is already clearly detectable at present: For the first half of

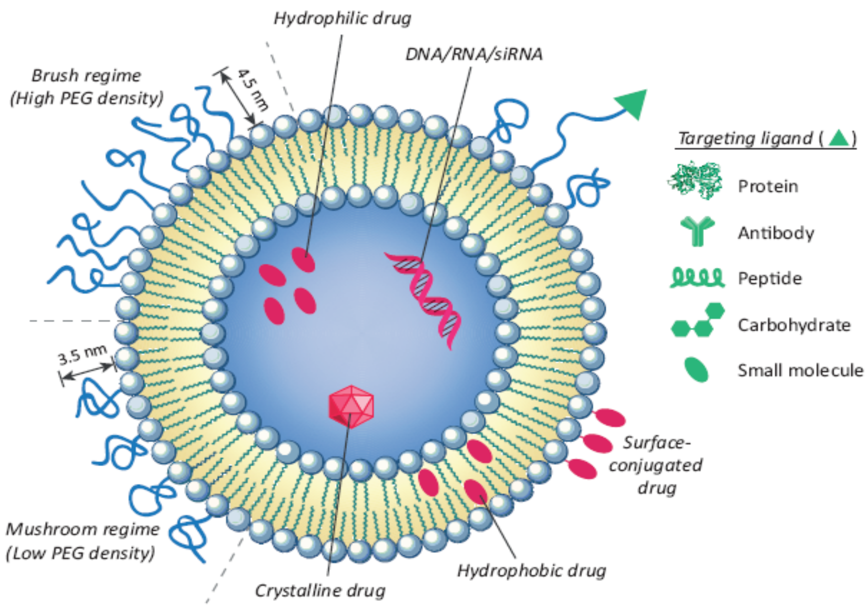

Figure 3: Various liposome structures modified for targeted transport of active substances [24,25]. The polyethylene glycol layer camouflaging the surface (PEG, *blue threads*) can occur in three different conformations depending on the distribution density of the polymer.

this decade (2010-2014) the *Web of Knowledge (Core Collection)* records the titles of 3,438 publications under the key word "nanomedicine" (as against 857 entries for the entire previous decade of 2000-2009). Nanomedicine has the potential to significantly improve the quality of life of patients. Nevertheless, the new possibilities also involve risks and raise sociological and ethical questions which must be analyzed and debated.

Figure 4 shows the four research and development areas which will probably receive the greatest impetus from nanomedicine in the coming decades.

The nanotherapy vision of the future is treatment of patients with individually tailor-made medicines ("personalized medicine") at the molecular level as soon as the disease is in the development stage [34]. The preparation of nanodrugs and the various methods of targeted transport of active substances (drug delivery) will play a prominent role here. With these it could become possible to develop effective and well-tolerated treatments for hitherto incurable diseases.

Nanotechnologies provide methods by which biological information can be acquired easily, quickly and inexpensively and analyzed, and thus enormously increase the possibilities of preventive medicine. Therapy and diagnostics are increasingly becoming fused into the new specialist medical field of theranostics, because the nanotechnology methods and medicines serve diagnostic and therapeutic purposes simultaneously. Examples are the contrast medium which brings with it directly the active substance in the event of a pathological tissue change [35] and carrier systems which circulate preventively in the organism and react to endogenous signals and automatically secrete active substances if needed [36]. The production of nanomaterials which recognize cells and cell constituents, including individual genes, of impaired function and repair them of their own accord in the organism is also being researched [37-39].

Recently, a promising theranostic application has been addressed

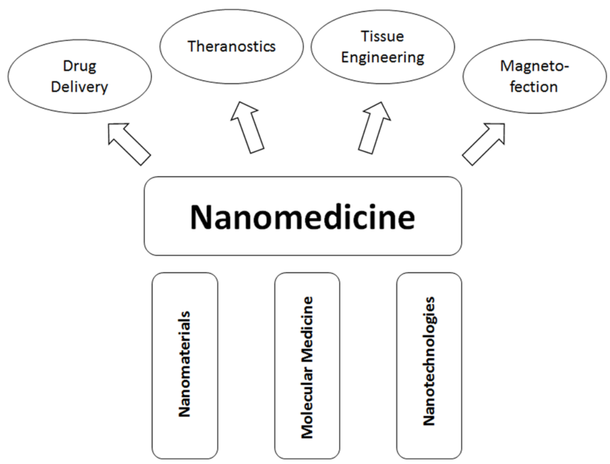

Figure 4: Future development of nanomedicine.

in modulating an on-switch chimeric Antigen Receptor (CAR) against chemotherapy-resistant forms of B cell cancer [40]. By introducing small molecules a switch-on-switch-off mechanism could successfully be established in a draconic engineered T cell therapeutic approach, thus avoiding toxic effects of the cell killer function.

Nanobiotechnology opens up new possibilities above all in the field of regenerative medicine. By stimulation and targeted control of cell growth, damaged or absent tissue – from hair, cartilage and bone, via muscles and organs, through to nerve cells – could be regenerated or produced artificially with the aid of nanomaterials (tissue engineering). Nanoporous carrier materials are already now being used in wound healing and in plastic surgery as matrices along which controlled cell growth takes place [41]. If targeted growth of nerve cells were also to be successful, new possible treatments for hitherto incurable neurological diseases such as Alzheimer's, Parkinson's, epilepsy and multiple sclerosis could be developed. And should targeted manipulation of adult stem cells also be successful, endogenous tissue which causes no rejection reactions could be cultured, and the use of embryonic stem cells could be abandoned.

The fourth area in which nanomedicine will gain importance in the coming years is gene therapy. Intensive research is being conducted into whether and how the various mechanisms of targeted transport of active substances can be used to introduce nucleic acids, DNA fragments and individual genes into tissue and cells by means of non-viral nanoparticles. In a cutting-edge animal study using rats biodegradable, polymeric gene delivery nanoparticles have been shown to effectively kill glioma cells in the brain and extend the survival of the animals [42].

One further possibility is magnetofection in which – as in active MDT – positively charged nanoparticles containing iron are loaded with negatively charged nucleic acids, brought to the target cells with the aid of a magnetic field and due to their appropriately prepared surface structure are sluiced into these. The nucleic acids are released there and the particles are transferred into cell iron metabolism. One advantage of this method, which is also called "magnetic gene targeting" (MGT) and is of interest above all for treatment of cancer and neurodegenerative diseases as well as myocardial infarction [43], is that the target cells are not damaged. An example of this strategy is an innovative gene delivery method that may be applicable in stent angioplasty and thereby contribute to bridge the gap between research and clinical application [44]. The approach established in a rat model uses stents as a platform for magnetically targeted gene delivery, where genes are moved to cells at arterial injury locations avoiding adverse effects to other organs. Novel magnetic nanoparticles protect the transferred genes and help them reach their target in active form.

Nano-based gene therapy is aimed at addition of missing and replacement of defective DNA and therefore intervenes directly in cell processes at the molecular level. Because the possibility of repairing DNA sooner or later will also result in the capability of targeted manipulation of DNA, areas are stumbled into here which make confrontation with ethical and social matters unavoidable. Is only the repair of defective or damaged DNA allowed, or is it also desirable for human sensory and physical capabilities to be optimized without a therapeutic indication existing? and for whom under what circumstances and by whom will the possibility of genetic modification be granted? How will we deal with the body's inadequacies in the future?

Overview of Follow-up Literature

The following recently published books provide a good introduction to nanomedicine: *Handbook of Nanobiomedical Research. Fundamentals, Applications and Recent Developments* by Vladimir Torchilin [45], *Handbook of Materials for Nanomedicine* by Vladimir Torchilin and Mansoor M Amiji [46] and *Nanomedicine. Technologies and Applications* by Thomas J Webster [47].

The books *The Textbook of Nanoneuroscience and Nanoneurosurgery* by Babak Kateb and John D Heiss [14] and *Handbook of Nanotoxicology, Nanomedicine and Stem Cell Use in Toxicology* by Saura C Sahu and Daniel A Casciano [48] are concerned with possible developments in nanomedicine especially in neurosurgery and the toxicological effects of applications within nanomedicine.

A good review of the possible developments in nanomedicine is given by the books *The Clinical Nanomedicine Handbook* by Sara Brenner [49], *Understanding Nanomedicine. An Introductory Textbook* by Rob Burgess [50] and *Selected Topics in Nanomedicine* by Thomas Ming Swi Chang [51].

Conclusion

Nanotechnology and nanobiotechnology applications will change medicine greatly in the coming decades. Early detection of diseases in the molecular stage of development by simple and inexpensive rapid tests and highly accurate imaging methods, optimization of existing and introduction of new, minimally invasive treatment methods for hitherto incurable diseases, development of tailor-made medicines free from side effects, close intermeshing of diagnosis and therapy, culture of bone, tissue and organs with the aid of nanomaterials and adult stem cells will improve healing prospects and the quality of life for the patient and significantly reduce treatment and after-care costs. However, the new prospects opened up by nanomedicine are also associated with risks and social and ethical questions which should not be ignored. Last but not least there is the matter of sharing: When simple and inexpensive diagnosis and therapy are possible, will everyone then benefit from nanomedicine?

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