INSTITUTE OF PHYSICS PUBLISHING NANOTECHNOLOGY

Nanotechnology **13** (2002) R9–R13 PII: S0957-4484(02)38410-1

Tutorial

Nanomedicine: destination or journey?

C A Haberzettl

TechnoMed Strategic Partners, Inc.,1988 Coventryville Rd, Pottstown, PA 19465, USA

Received 19 June 2002
Published 4 July 2002
Online at stacks.iop.org/Nano/13/R9

Abstract
Nanomedicine in a broad sense is the application of nano-scale technologies to the practice of medicine. The creation of nanodevices such as nanobots capable of performing therapeutic functions *in vivo* is a destination within the emerging field of nanomedicine. On the journey to that destination, significant technological advances across multiple scientific disciplines continue to be proposed, validated and commercialized. Advances in delivering therapy, miniaturization of analytical tools, improved computational and memory capabilities and developments in remote communications will be integrated allowing for the development of such nanobots. Nanomedicine is both a destination and a journey. The journey will cross new frontiers, uncover new knowledge and bring new horizons to the understanding and practice of medicine.

1. Background/introduction

Nanotechnology has been defined as being 'concerned with materials and systems whose structures and components exhibit novel and significantly improved physical, chemical and biological properties, phenomena and processes due to their nanoscale size' (National Nanotechnology Initiative 2000). A nanometre (nm) is one billionth of a metre or one thousandth of a millimetre (mm). One of the unique characteristics of nanotechnology is that its success depends on the cross-fertilization and co-operation among several traditionally 'stand-alone' scientific disciplines. Nanotechnology is actively being pursued in many technical fields including aerospace, information management (computers), communications, electronics, materials sciences and medicine.

This discussion focuses on the application of nanotechnology to medicine, i.e. nanomedicine, with its promise of improved therapy and diagnostics. Advances in both diagnostic tools and the development and administration of therapeutics may soon come together for the creation of nanoscale devices known as nanorobots or more simply, nanobots. These nanobots have the potential to serve as vehicles for delivery of therapeutic agents, detectors or guardians against early disease and perhaps repair of metabolic or genetic defects.

2. Why nanobots?

Robots perform tasks too dangerous, tedious or delicate for humans. The robot is programmed to perform specific functions and is remote controlled. Taking these principles and shrinking them down to the nanoscale results in the concept of nanobots. Such devices were first described by Drexler (1986) in his book, *Engines of Creation*. Drexler described the 'bottom-up' approach to manufacturing large-scale materials (atom by atom) using nanobots capable of self-replication (i.e. assemblers). While nanodevices capable of performing specific functions at nanoscale are currently being developed and tested, the aspect of self-replication for large-scale manufacturing is further out on the horizon. Nanobots or smart nanodevices applied to medicine would be able to seek out a target within the body (for example a cancer cell or an invading virus) and perform some function to 'fix' the target. The 'fix' delivered by the nanobot may be that of releasing a drug in a localized area, thus minimizing the potential side effects of generalized drug therapy, or it may bind to a target and prevent it from further activity thus, for example, preventing a virus from infecting a cell. As the technology becomes more sophisticated, gene replacement could occur or new tissue could be seeded for tissue regeneration. Perhaps new types of 'nanosurgery' will ultimately be developed.

If nanobots are to become a reality, it is necessary to develop various components which would be assembled into highly sophisticated devices. In the near term, development

of the various components will occur in mostly independent parallel tracks. With time, the tracks will begin to cross over, eventually intertwining, allowing for the creation of nanobots. Such components might include:

- architecture or structure to carry the payload;
- targeting mechanisms to guide the nanobot to the desired site of action;
- a payload which would vary depending on the intended function of the nanobot:
  - could be as simple as a therapeutic agent or a naturally occurring substance like a gene, hormone or a protein,
  - could be more complex, containing various elements intended to create some molecule or structure *in situ*, release the cargo and leave the scene,
  - could perform some tactical activity;
- on-board communications/operating systems such as sensors, motors or various manipulators;
- computational/information processing and memory capabilities;
- control mechanism:
  - guidance,
  - self-elimination or retrieval.

2.1. Architecture

The journey toward creating nanobots begins with the development of molecular architectures and is well under way in laboratories around the world. These architectures are in various stages of development and validation from newly proposed structures through those with demonstrated clinical utility in animal models followed by human clinical studies and regulatory approval for market. Thus, one near-term focus of nanotechnology in medicine is the area of drug delivery. FDA approval for several products has already been achieved.

Along the journey toward developing nanobots many technological advances have already occurred and many continue to be reported and validated. Drugs are being encapsulated in a variety of nanoparticles to enhance effectiveness and decrease side effects or to overcome solubility and toxicity issues. Imagine what could happen to drug development pipelines if solubility issues could be overcome and toxicity could be decreased by targeting drug delivery. In animal studies, Advectus Life Sciences (using technology licensed from NanoPharm AG) has shown that nanoparticle-stabilized doxorubicin is capable of crossing the blood–brain barrier for intended treatment of glioblastoma. Copernicus Therapeutics is testing nanoparticle-based gene therapy in phase I clinical trials. American Pharmaceutical Partners is testing stabilized nanoparticles in phase III clinical trials for metastatic breast cancer. BioSante Pharmaceuticals has developed a calcium phosphate based nanoparticle platform for treatment of glaucoma (eye drops), administration of oral insulin and enhancement of vaccines. NUCREST Pharmaceuticals, through Smith and Nephew, is marketing Silcrest, a burn and wound dressing based on nanocrystalline silver. Novavax has received FDA approval for Estrasorb (cream), a nanoparticle-based delivery system for ethanol soluble drugs, for the treatment of hot flashes. Orthovita has received FDA approval for VITOSS, a nanoparticle-based scaffold for bone growth, for use in orthopaedic surgery.

Although several categories of architecture are described below, numerous variations and unique structures are continuously being reported.

Buckyballs, fullerenes, nanotubes. Originally described in 1985, buckyball is the short name for a molecule composed of 60 atoms of carbon arranged in a hollow sphere resembling the geodesic dome. This new C60 structure was officially named buckminsterfullerene in honour of the architect, Buckminster Fuller, who designed the geodesic dome. The significance of buckyballs did not go unnoticed by the Nobel Committee when Richard Smalley and his colleagues (Robert Curl and Sir Harold Kroto) were awarded the Nobel Prize in chemistry in 1996. Over time, a series of unique carbon-only molecules with cage-like structures has been developed containing varying numbers of carbon atoms arranged in pentagons and hexagons collectively called fullerenes. Perhaps one of the most studied fullerene structures is the carbon nanotube. Carbon nanotubes can be produced in single-walled or multi-walled (nanotubes within nanotubes) forms having remarkable strength and unique electrical properties making them insulating, semiconducting or conducting depending on their structure. More broadly, nanotubes can be made of materials other than carbon if they have a propensity to form graphite-like sheets (e.g. boron nitride, BN). These architectures are inert, nontoxic and because of their small size, are capable of interacting with cells, proteins and microbes. Their hollow internal structure and ability to be functionalized allows them to carry a payload such as a therapeutic agent.

Dendrimers. Another type of architecture is the class of dendrimers, polymerized macromolecular structures consisting of many branches which repeatedly divide into additional branches forming a dense spherical structure with a central core. The surface of the structure can be functionalized for various applications. The synthesis of the dendrimer can be 'directed' such that it is possible to create internal cavities or channels within the sphere which are capable of carrying a wide range of molecules.

Other architectures. In addition to nanotubes, various nanoparticles and nanocrystals are being investigated as drug delivery mechanisms. Ready-made viruses, emptied of their genetic material may also be useful as delivery mechanisms for therapeutic agents.

New methods of encapsulation are being developed which allow functional cells to be encapsulated for protection from the immune system while allowing the encapsulated cells to deliver hormones, *in vivo*, for the treatment of diabetes. This work by Dr Tejal Desai has successfully advanced through pre-clinical studies and apparently will be commercialized by iMEDD

2.2. Targeting mechanisms

Continuing on the journey toward developing nanobots, successful drug delivery architectures will be enhanced by allowing them to target a particular tissue or organ. The most likely mechanisms to be employed are based on antigen/antibody interactions or binding of target molecules

to membrane-bound receptors. Further along in the nanobot journey will be the incorporation of more sophisticated targeting mechanisms which may include the potential for detection of physiological changes in the nanobot's environment which triggers the desired action. Such mechanisms will likely include the use of nanoscale biosensors and other sensing or detection mechanisms. A discussion of such devices and diagnostic tools is beyond the scope of this paper.

Memorial Sloan Kettering has developed molecular nanogenerators which have successfully been tested in preclinical studies. These nanodevice generators use antibodies to target a tumour and directly deliver radiation for targeted radiation therapy. Phase I clinical studies are planned for the Fall 2002 pending FDA approval.

Space travel presents unique medical issues and potential solutions. During space travel, astronauts may be exposed to high levels of radiation once outside the earth's protective atmosphere. NASA is developing a version of the nanobot which will seek out radiation damaged cells based on the expression of the CD95 molecule. If the damage is repairable, the nanobot will 'enhance' the activity of DNA repair enzymes or trigger apotosis if the cell cannot be repaired.

2.3. Payload

As noted above, nanoparticles are currently being investigated as drug delivery mechanisms. Nanoparticle formulations may function to overcome solubility or stability issues for the drug, limitations on route of administration (e.g. breakdown of orally administered drugs), bio-compartmentalization (e.g. blood–brain barrier) or side effects of generalized drug administration (e.g. chemotherapy).

In the near term, the simplest payload is a currently available therapeutic agent formulated into a nanoarchitecture. Some examples of diseases where nanoparticle formulations are being investigated include: cancer, pacletaxel (active ingredient in taxol); diabetes, orally administered insulin; HIV; sexually transmitted diseases (STD); malaria and hepatitis B.

A more complex payload would be a functional cell. Tejal Desai, currently at Boston University, and colleagues have developed a method of encapsulating hormone producing cells within a nanoarchitecture having well defined and controlled pore size. These structures allow the hormone (e.g. insulin) produced by the encapsulated cells to be released into the circulation while protecting the encapsulated cell from detection and destruction by the immune system.

Payloads could include scaffolds on which new tissue could grow, *in vivo*, from existing components or the scaffold could serve to 'seed' new tissue growth. Implantate AG is developing Ostim, a nanoparticle-based substitute for bone. Orthovita has developed VITOSS, a nanoparticle-based scaffold for bone growth.

Combining therapeutic agents with targeted nanoparticles, the payload could be used to enhance or inhibit a physiological or biochemical process. For example, the National Cancer Institute (NCI) Unconventional Innovations Program has provided funds to Gregory Lanza and colleagues at Washington University (St Louis, MO) to investigate the use of nanoparticles that target capillary cells to prevent angiogenesis (the growth of blood vessels needed to support growth of tumours).

2.4. Communications/operating systems

One of the parallel tracks on the journey to the creation of nanobots is the development of diagnostic tools. In the *in vitro* world, diagnostic technology continues to evolve on the nanoscale and new technologies are emerging. The journey toward developing nanobots cannot be achieved without incorporation of the advances in diagnostics. These advances will allow for more diverse targeting mechanisms than those described above. Beyond the current focus on enhancing drug/therapy delivery lies the goal of having nanobots perform or orchestrate specific functions based on their ability to detect a 'signal', respond to the signal and cause/implement a physiological change. The nanobot must be able to process information and communicate its activities to the control centre. Entering this part of the journey, venture capital interest is scarce, concepts are yet to be proved or disproved and the notion of science fiction looms in the background where sceptics will play and nano-hype is born.

Yet, there are roadmaps. One can read the works of Freitas (1999) with eloquent descriptions of the theory making nanobots possible. Or, one can look at any number of tiny viruses which nature has created. Viruses have remarkable architecture, are quite capable of finding a target cell to infect, carry a payload of enzymes for reproduction and orchestrate a number of physiological effects.

2.5. Computational/memory capability: information processing

Molecular electronics focuses on using organic molecules (e.g. carbon nanotubes) to create wires, switches, transistors, logic circuits and ultimately molecular computers. The goal is to replace or supplement silicon with nanomaterials in order to continue growth in computational and memory capacity of computers. Some recent advances are described below to illustrate accomplishments along this parallel track of developing molecular computers which may serve as components of nanobots.

Weiss and Tour's team (Donhauser *et al* 2001) were the first to demonstrate that a single molecule could serve as a functional switch. The ON/OFF switching ability of phenylene ethylene oligomers (in a matrix of alkanethiolate monolayers) appears to be related to conformational changes in the molecules and the rate of switching can be controlled by the composition of the matrix. The ability to control the rate of switching imparts memory characteristics and the reversibility of the switching provides the capability to 'write-over' the memory.

Devices, such as switches, need to be linked together to form working circuits. Work in this area continues in both academic and industrial settings. For example, Hewlett-Packard was granted patent approval (July 2001) for a process to 'wire' such components together using 'markers' that allow signals to be routed to the device. Such a process would overcome the difficulties of matching the small size of molecular devices with the much larger diameter of traditional wires. The intent is to create integrated circuits with molecular rather than semiconductor components, thus supplementing or replacing silicone. Another approach is under investigation at California NanoSytems Institute at UCLA. The goal here is to

use carbon nanotubes as the 'wires' to connect the molecular switches. In the interim, this group had created circuits using molecular switches on a grid of typical lithographic wires.

IBM reported using carbon nanotubes to create a single-molecule logic circuit where the carbon nanotube functions as a voltage inverter (an electronic circuit that converts ON or '0' to OFF or '1' and vice versa) creating a NOT gate for computer logic. Also working with carbon nanotubes, Weiss and Tour (2001a) demonstrated the creation of functionalized nanotubes. In some cases, the functional groups attached to the carbon nanotubes demonstrated both switching and memory characteristics.

In the autumn of 2001, organic transistors with a single-molecule channel length were also reported by researchers at Bell Laboratories (Schon *et al* 2001). These transistors act to amplify electronic signals and serve as electronic switches. Such molecular transistors were used to create a voltage inverter creating a NOT gate. By year end (2001a) these investigators reported fabricating molecular-scale transistors that can be individually controlled.

Researchers at Harvard (Lieber 2001) reported the assembly of functional devices in solution using electronically defined semiconductor nanowire building blocks. The junctions can be assembled to possess controlled characteristics and can create integrated nanoscale field-effect transistor arrays with nanowires serving as both conducting channels and logic gates. Various logic gates have been configured and utilized for basic computations.

In May, 2002, IBM reported carbon nanotube transistors with a twofold increase in transconductance per unit compared with silicon transistor prototypes, thus coming one step closer to the potential for the commercialization of carbon nanotubes for computing applications.

2.6. Control mechanisms

The ultimate fate of nanobots within the body remains an issue to be addressed and should be considered early the development of nanobots. On the positive end of the scale, such nanodevices could be eliminated from the body through natural mechanisms of metabolism and excretion. Developing architecture which is biodegradable or composed of naturally occurring substances (e.g. calcium phosphate based nanoparticles developed by Orthovita) would, intuitively, favour 'safe' nanobots. Alternatively, nanobots could have 'homing' devices which would allow them to be collected and removed after performing the desired function. In the mid-range of the scale, nanobots could continue to function in the body without the need for removal or destruction. Consider, for example, the encapsulated hormone producing cell used to treat a chronic disease like diabetes. On the negative end of the scale, nanobots potentially could physically 'clog' the system resulting in negative outcomes. Some believe nanobots could become 'out of control' in the absence of feedback mechanisms to control their function.

While still in the early phases of the journey toward creating nanobots, it is difficult to predict the degree to which control mechanisms will be needed. Perhaps traditional LD50 determinations on nanobot formulations will yield surprising results.

Table 1. NanoMedicine Timescale.

Enablers	Challenges
Available funding—multiple sources	Safety questions
Increasing multidisciplinary approach to technology	New science
Global scope of R and D	Patent landscape
Scientific curiosity, new knowledge	Ethical and moral considerations
New analytical tools	
Patent landscape	
Computers and software simulations	
Convergence of scientific disciplines	

3. Timescale

A plethora of predictions exist relating to nanomedicine and the destination of commercializing nanobots. It is the intent of this discussion to demonstrate that the journey has already begun and both research and commercialization milestones have already been achieved. Continuing the journey will provide new knowledge and reaching the destination will open new horizons, define new destinations and initiate new journeys.

Some enablers and challenges listed in table 1 will influence the rate at which the journey continues. The curiosity of the human spirit will fuel progress. The practical aspects of commercialization will keep the tide of nano-hype in check.

> *'The mind oriented to the future is constructive, creative and organizing. It sees the world as one great workshop, and the present as no more than material for the future, for the thing that is yet destined to be.'*
> H G Wells 1902

4. Conclusions

Nanomedicine is both a destination and a journey. If one focuses on the destination of tiny robots able to perform medical procedures, one might become bored like a child on a trip: 'are we there yet?', doubting the destination will ever be reached. If one focuses on the journey, the discoveries and advances in the great workshop of science can only be awesome, inspiring and challenging. The journey will cross new frontiers, uncover new knowledge and bring new horizons to the understanding and practice of medicine.

References

Berkeley Lab Research Review (Fall 2001) http://www.lbl.gov/science-articles/research-review/magazine/2001/fall/index.html

Donhauser Z J 2001 Conductance switching in single molecules through conformational changes *Science* **292** 2303

Drexler K E 1986 *Engines of Creation: The Coming Era of Nanotechnology* (NY: Anchor Press/Doubleday)

Feynman R P 1959 *There is Plenty of Room at the Bottom. An Invitation to Enter a New Era of Physics* http://www.nanomedicine.com

Freitas R A 1999 *Nanomedicine* (Georgetown, TX: Landes Bioscience) http://www.nanomedicine.com

Lieber C 2001 Carbon nanotubes, electronic devices *Science* **294** 5546

National Nanotechnology Initiative 2000 *Leading to the Next Industrial Revolution. A Report by the Interagency Working Group on Nanoscience, Engineering and Technology* (Washington, DC: Committee on Technology, National Science and Technology Council) http://www/nano.gov

Schon J H, Bao Z and Meng H 2001 Self-assembled organic field-effect transistors *Nature* **413** 713

Schon H, Bao Z and Meng H 2001a Addressable transistors *Science* **294** 2138

Weiss P S and Tour J M 2001a *J. Am. Chem. Soc.* **123** 6536