

# Review Article

## NANOMEDICINE

Moslem Bahadori MD, FCCP<sup>1</sup>, Forouzan Mohammadi<sup>2</sup>

1. Permanent Member, Iranian Academy of Medical Science
2. National Research Institute for Tuberculosis and Lung Disease, Massih Daneshvary Hospital, Tehran

### ABSTRACT

Since its original conception in 1959, by Nobel physicist Richard P Feynman, the notion of nanotechnology and its potential ramifications have not only created fascination, but also intense scientific efforts and scrutiny.

One of the most promising applications of nanotechnology is in the context of medicine. Due to their unique size-dependent properties nanomaterials such as nanoparticles offer the possibility to develop both new therapeutic and diagnostic tools. This applied nanotechnology to medical problems has been proposed as nanomedicine by NIH.

Nanomedicine can offer new concepts that are reviewed. Specific attention is given to the development and basic approach of this new technique and give some principle definition of nanosized-particle and its application in treatment, diagnosis, monitoring and control of biological system. The future of nanomedicine and their applications of diseases of different organs will be reviewed later.

**Key words:** Nanotechnology, Nanomedicine, Nanosized particle, Nanovehicle and Delivery system, Nanotherapy, Nanodiagnosis

In December 2002, the US National Institute of Health (NIH) announced a 4- year program for nanoscience and nanotechnology in medicine (1). Burgeoning interest in the medical application of nanotechnology has led to the emergence of a new field called NANOMEDICINE(2,3).

### Introduction

One of the most promising applications of nanotechnology is in the context of medicine. Advances in nanotechnology research, which involves investigating and manipulating matter at the atomic and molecular (nanometer) levels,

may result in drastic changes in society. One nanometer is one-billionth of a meter, spans 10 atoms (4). In medicine, nanotechnology could produce an array of new products, from novel drugs and devices to nanorobots that travel through the body finding and diagnosing illness. This emerging field of research for medical

\*Address communications to: Professor Moslem Bahadori, National Research Institute for Tuberculosis and Lung Disease, Massih Daneshvary Hospital, Tehran-Iran  
E-mail: Bahadori@AMS.AC.ir

sciences called more attention in the era of nanotechnology. So, the burgeoning interest in the medical applications of nanotechnology has led to the emergence of many applicable research in the field of medical problem solving (5-7). Nanomedicine is a technology dealing with for diagnosing, drug delivery and treating, preventing diseases and preserving and improving human health. Nanomedicine using molecular tools and molecular knowledge of the human body. So it is the application of nanotechnology to medicine. In this part we review briefly the key aspect of nanomedicine with recent advances in this field.

### What is nanomedicine?

Nanomedicine has been defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructure.

The early genesis of the concept of nanomedicine raised from the visionary idea that tiny nanorobots and related machines could be designed, manufactured and introduced into the human body to perform cellular repairs at the molecular level. The first scientist to voice these possibilities was late Nobel Physicist Richard P. Feynman, who worked on the Manhattan Projects at Los Alamos during World War II and later taught at CalTech for most of his professional carrier. In his 1959 prescient talk he proposed using machine tools to make smaller machine tools, these to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level( 8). This prophetic idea was later championed in the popular writing of Drexler ( 9 ) and in technical writing of Freitas in 1990s and 2000s. Feynman was clearly aware of the potential medical applications of the new technology that he was proposing. After discussing his ideas with a colleague, Feynman offered the first known proposal for a nanomedical procedure to cure heart disease, He says it would be interesting in surgery if you could swallow a surgeon. You put the mechanical nano-surgeon inside the blood

vessel and it goes into the heart and looks around. It finds out which valve is faulty one and take a little knife and slice it out (Freitas 2005). Now this dream become true with the experimental nanoneurosurgery reported (Leary et al 2006)

### The principle of nanomedicine

The principle of nanomedicine share with other scientific field of nanotechnology and the basis is summarized below (10-16).

#### Nanosizede particles

Nanotechnology is an area of science devoted to the manipulation of atoms and molecules involving in the structure or functions of the organisms. This technique is looking at the nanometer scale size which retain unique properties ( 7). When the materials are looking at this small size, the chemical and physical property can be significantly appreciated. Since small size means different arrangements and spacing for surface atoms, and these dominate the object's physics and chemistry.

Two principal factors cause the properties of nanomaterials to differ significantly from other materials: increased relative surface area; and quantum effects (2,10). These factors can change or enhance properties such as relativity, strength and electrical characteristics. When particle decrease in size, a greater proportion of atoms are found in the surface compared to those inside. For example, a particle of size 30nm has 5% of its atoms on its surface, at 10nm 20% of its atoms, and at 3nm 50% of its atoms. Thus nanoparticles have a much greater area per unit masse compared with larger particles. This can affect the optical, electrical and magnetic behavior of materials, particularly as the structure of particle size approaches the smaller end of the nanoscale. Materials that exploit these effects include quantum dots and quantum well laser for optoelectronics. If semiconductor particle are made small enough, quantum effects come into play, which limit the energies at which electrons and holes (the absence of an electron) can exist

in the particle. As energy is related to wavelength (or color), this means that the optical properties of the particle can be finely tuned depending on their size. Thus, particles can be made to emit or absorb specific wavelength or color of light, merely by controlling their size.

From the point of nanotechnology there are several tools and assembly to deal with nanomaterials. These include nanomachines and nanoparticles (2,5,7,9)

Tools and nanomachine in nanomedicine are of different nature. Some examples are: nanopore sequencing machine which is an ultra rapid method of sequencing based on pore nanoengineering and assembly; microneedle or micromachined needle and lancet; microchips for drug delivery which is a microfabricated devices that incorporate micrometer-scale pumps, valves and flow channels and allow controlled release of drugs on demand; carbon nanofibers and carbon nanotubes

Nanoparticles also vary and have different biological and medical application; superparamagnetic iron oxide crystals, colloidal gold, quantum dots, dendrimer, polymeric micelles, liposomes and nanospheres are examples of nanoparticles. The sizes of nanoparticles are usually in the range of 1-20nm. These nanoparticles have diagnostic applications in biology and medicine (7). Here two examples of nanoparticles are described. These

Nanoparticles are Quantum dots and dendrimer, with biological and medical application which are adapted from Moghimi et al 2005:

Quantum dots (QD); these are mono-scale crystalline structures made from variety of different compounds, such as cadmium selenide, that can transform the color of light. QDs absorb white light and then re-emit it a couple of nanoseconds later at a specific wavelength. By varying the size and composition of QDs, the emission wavelength can be turned from blue to near infrared. QDs have greater flexibility, when compared to other fluorescent materials, and this makes them suitable for use in building nano-

scale computing applications where light is used to process information. These structures offer new capabilities for multicolor optical coding in gene expression studies, highthroughput screening, and in vivo imaging.

## Dendrimers

These are highly branched macromolecules with controlled near monodisperse three-dimensional architecture emanating from a central core. Polymer growth starts from a central core molecule and growth occurs in an outward direction by a series of polymerization reactions. Hence, precise control over size can be achieved by the extent of polymerization, starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications. Therapeutic and diagnostic agents are usually attached to the surface groups on dendrimers by chemical modification (15,17).

## Nanovehicle and Delivery systems

Numerous engineered constructs and assemblies are developed for the purpose of delivering nanoparticles to their targets. These include polymeric micelles, dendrimers, polymeric, ceramic nanoparticles and others (moghimi et al 2000, Allen et al 2004, Oh et al 2004, James Baker 2006) (12-16). Therapeutic and diagnostic agents can be encapsulated and covalently attached or absorbed on to such nanocarrier. Each nanocarriers according their structure and built up may have hundreds or more receive devices on their surface. Baker for example, used dendrimer as nanovehicle in his experiment on human tumor grown on mice. He used highly branched molecule (dendrimer) which has more than hundreds receiving devices “ hooks “ on its surface. To five or six of these hooks Baker connected folic acid molecules. Because folic acid is a vitamin, most cells in the body have proteins on the surface that bind to it.

But many cancer cells have significantly more of these receptors than normal cells. Baker linked an anticancer drug to other branches of dendrimer, when cancer cells ingest the folic acid; they consume the deadly drug as well (17).

Freitas in his classic paper describes several subjects in medicine which is currently delving in medical problems. Their successful development is almost inevitable and their subsequent use into medical diagnoses, treatment, research and prevention is possible and may occur very soon. Several of 96 research projects are listed and tabled by Robert A Freitas (2).

### **Nanodiagnostics and molecular imaging**

In nanodiagnostics the ultimate goal is to identify disease at the earliest stage possible, ideally at the molecular levels. To achieve this goal we need to find new “smart” probe that signals pathologies at the level of single cell (Pison et al 2006, Mahmood et al 2005, Leary et al 2006, Patel et al 2006) (11,18,19,20). Nanotechnology offers the possibility for probes that are small enough to cross physiological barriers, and to take different measurements in parallel or to integrate several analytical steps from sample preparation to detection into a single miniaturized device. Such a device could contain enough hard wired intelligence and robustness to be used by the patient and deliver a multitude of data to the practitioner. Improvement of microscopic and spectroscopic techniques towards ultra-high spatial resolution, molecular resolution and ultra-high sensitivity will provide a better understanding of the cell’s complex “machinery” in basic research. The resulting progress should pave the way to more innovative and powerful in- vivo diagnostic tools.

### **Targeted drug delivery and controlled release**

Nanotechnology offers advantages that allow a more targeted drug delivery and a more controllable release of a therapeutic compound.

The aim of targeted drug delivery and a controlled release is to better manage drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition of systems in the quest for improved efficacy.

Two aspects drive the progress of nanostructured drug development: drug formulation and route of administration. New drug formulation that takes advantage from material science and nanotechnology give rise for new micro and nanoparticles, micro and nanocapsules, liposomes and micelles, dendrimers, liquid crystals, hydrogels, molecularly imprinted polymers, conjugations of biological molecules and synthetic polymers, and in situ forming implants (21,22).

When a drug is suitably manufactured, encapsulated in nanoparticulate form, it can be delivered to the appropriate site, released in a controlled way and protected from undergoing premature degradation. This results in higher efficacy and dramatically minimize undesirable side effects.

### **Route of administration**

The following route regards for the therapeutic power of nanomedicine. For other purposes such as diagnoses, prevention and others the procedures are similar.

The route of administration is an important as the drug itself for therapeutic success. Nano-based approaches to drug delivery are focused on crossing a particular physical barrier such as blood-brain barrier, or on finding alternative and acceptable routes for the delivery of a new generation of protein-based drugs other than via the gastrointestinal (GI) tract, where degeneration effects can occur.

The peroral route is the most frequently used drug delivery, but many effective new therapeutic agents are protein or peptide-based material which does not easily cross mucosal surface and biological membranes, and they do not resist degradation mechanisms that exist in GI tract. Thus peroral administration need appropriate

protection which nanotechnology may help.

Transdermal delivery avoids problems such as seen with GI tract. It is also suitable for unconscious patients. Limitations include slow penetration rate, lack of dosage flexibility and/or precision and a restriction to relatively low dosage drugs.

Parenteral routes of drug delivery using intravenous, intramuscular or subcutaneous injections are very important but more invasive compared to other routes. It has been possible to deliver peptides and vaccines systematically using the nasal route (Vila et al 2004) (23).

Another important route of drug delivery is through the airways systems (23). Pulmonary delivery using metered dose inhaler system for aerosol, powders or solutions may contain nanostructures such as liposome, micelles, nanoparticles and dendrimers. A pulmonary drug deliveries offers local targeting for the treatment of respiratory diseases and increasingly appear to be a viable option for the delivery of drugs systemically. However, the success of pulmonary delivery of protein-based drugs is diminished by proteases and macrophages in the lung, which reduce their overall bioactivity, and by the barrier between capillary blood and alveolar air.

Targeting mechanisms can make advantage of both, drug formulation and route of administration which can be passive or active. Active targeting involves the chemical 'decorating' of the surface of drug carriers with molecules enabling them to be selectively attached to diseased cells (Baker 2006) The controlled drug release is also important. Controlled release of drugs can be sustained or pulsatile, but pulsatile release is often preferred which it mimics the body's natural release of hormone(11).

The long-term objective of drug delivery systems is the ability to target selected cells and/or receptors within the body, and nanomedicine is critical in reaching these goals.

### **Regenerative Approach**

This interesting part of nanomedicine deals

with regenerative process of damaged tissue. Rather than targeting the symptoms or attempting to delay the progress of diseases, future therapies will be designed to rectify chronic conditions using the body's own healing mechanisms. Besides molecular diagnostics and targeted drug delivery and selected drug release, material science with nanotechnology will enable regenerative medicine (11, 24,25). The focus of regenerative medicine is to work with the body's own repair mechanism as to prevent and treat disabling chronic diseases such as allergies, obstructive lung disease, diabetes mellitus, osteoarthritis, and degenerative disorders of cardiovascular and central nervous systems and to help victims of disabling injuries. A cellular and molecular basis has been established for the development of innovative disease-modifying therapies for in situ tissue regeneration and repair, requiring only minimally invasive surgery. To name some examples of these regenerative medicine; facilitating the regeneration of healthy cartilage in an osteoarthritic joint, re-establishing a physiological release profile in diabetic pancreatic islands, or promoting self-repair mechanisms in areas of the central nervous system and of the heart(26). This 'nanobiomimetic' strategy depends three basic elements: intelligent biomaterials, bioactive signaling molecules, and cells(27).

A major focus of ongoing and future efforts in regenerative medicine will be to effectively exploit the enormous self-repair potential and capacity that has been observed in adult stem cells (28). In this regard, nano-assisted technologies will aid in achieving three main objectives: to identify signaling systems, to develop efficient targeting systems for stem cells therapies, and to monitor single cells after transplantation (Pison 2006).

### **Nanomedicine in the process of application**

Nanomedicine is applied in the process of diagnosing, treating and preventing diseases and traumatic injuries. In many countries the principle

of nanopractice started and even state funded programs began. An example is New York's Alliance for nanomedical technologies. The first 12 doctoral candidates in "nanobiotechnology" began laboratory work at Cornell University in June 2000 (29), and many other universities have started similar programs. In a team headed by Ulrich Pison in Germany, application of nanomedicine for respiratory diseases such as COPD, bronchial asthma, fibrocystic disease, and infectious diseases has been reviewed (11). In a murine model allergic asthma John et al used nanoparticle discovered

p-selectin antagonist with strong anti-inflammatory effects. P-selectin is important for the development and progression of peribronchial inflammation in allergic airway disease (30). A further study for allergic airways hyperreactivity Kumar et al used chitosan/interferon  $\gamma$ -pDNA nanoparticle (31). Randy et al presented the first study of delivering anti-tuberculosis drug through nano vehicle, They concluded that nebulization of nanoparticles-based ATDs forms a sound basis for drug delivery and shortening the course of TB treatment (22). An operating biological nanorobots as a versatile tool in nanomedicine has been proposed by Patel et al (20). Leary et al at the department of Neurological Surgery in University of Southern California in three consequent papers presented targeted nanomedicine in surgery and particularly as a realization of nanoneurosurgery (19).

The National Cancer Institute (NCI) has related program, with the goal of producing nanometer scale multifunctional entities that can diagnose, deliver therapeutic agents, and monitor cancer treatment (7). Piotr Grodzinski, program director of the NCI Alliance for Nanotechnology in cancer, says "it is not an evolutionary technology; it's disruptive technology that can address the problems which former approaches couldn't" (17).

### Conclusion

The ability to produce materials and devices at the molecular levels brings enormous benefits

to medical practice in its all aspect; diagnosing, treating, preventing and research. It will revolutionize the research and practice in medical problems in a very near future. Until now, aside from few clinical approach in human, the researcher in nanomedicine are dealing researches in animal at the level of experimentation and many problems including financial matter, ethical issues and many other questions challenging the daily use of this nanotechnology.

Nanomedicine will generate social and ethical debates regarding issues such as weather implantable nano-devices that constantly monitor for illness compromise privacy rights and risk abuse. In USA, the FDA will face an explosion of applications for novel therapies in the coming years, and a substantial portion of these new therapies will be based on nanomedicine. As nanomedicine come closer to fruition, it will present complex social, financial and ethical issues as well as regulatory issues (4). Similar to metabolomics technology, the field of nanomedical technology is dramatically expanding and NIH plays a laborious efforts to ground techniques and ultimately physicians might be able to create personalized medicine by combinations of novel high through put technologies (32).

It is Scientist and physicians hopes that the society will be able to muster these problems and allow such extraordinary powerful medicine to be deployed for human betterment, indeed with due regard to essential ethical consideration. To hasten development of nanobased therapies, the NCI Alliance has committed \$144.5 million to nanomed-related projects, funding seven centers of excellence for cancer nanotechnology (17).

### References

- 1- National Institute of Health. NIH Roadmap (27 Sept 2004), available at [www.nihroadmap.nih.gov/nanomedicine/index.asp](http://www.nihroadmap.nih.gov/nanomedicine/index.asp)
- 2- Freitas R.A. What is nanomedicine: reprinted from Nanotechnology, Biology, Medicine. Dis Mon 2005 51:325-41
- 3- Nanomedicine: ground for optimism, and a call

for papers. *Lancet* 2003 362: 673

4- Miller J. Beyond biotechnology: FDA regulation of nanomedicine. *The Columbia Science and Technology Law review* 2003 4:1-35

5- Emerich DF, Thanos CG. Nanotechnology and medicine. *Expert Opin Biol Ther* 2003 3: 655-63

6- Freitas RA, Merwle RC. Kinematic self-replacing machine. *Landers Bioscience* 2004 (online)

7- Moghimi SM, Hunter AC, Murray JC. Nanomedicine: current status and future prospects. *FASEB J* 2005 19:311-330

8- Feynman RP. There's plenty of room at the bottom. *Eng Sci ( CalTech)*. 1960 23:22-36

9- Drexler KE. Engines of creation. The coming era of nanotechnology. New York, NY. Anchor Press/doubleday 1986

10- Freitas RA Jr. Nanodentistry. *J Am Dent Assoc*. 2000 131: 1559-66

11- Pison U, Welte T, Giersig M, Groneberg DA. Nanomedicine for respiratory diseases. *Eur J Pharmacol ( e j p )* 2006 533: 341-350

12- Moghimi SM, Hunter AC, Murray J et al. Cellular distribution of nonionic micelles. *Science* 2004 303: 626-7

13- Allen TM, Gullis PR. Drug delivery systems; entering the mainstream. *Science* 2004 303:1818-22

14- Oh KT, Bronich TK, Kabanov AV. Micellar formulations for drug delivery based on mixtures of hydrophobic and hydrophilic pluronic block copolymers. *J control release* 2004 94:411-22

15- Baker JR jr, Bielinska AU, Kukowaska-Latallo JF. Dendrimer-mediated cell transfection in vitro. *Methods Mol Biol*. 2004 245:67-82

16- Shi X, Wang S, Baker JR Jr et al. Encapsulation of submicrometer-sized

2-methoxyestradiol crystals into polymer multilayer capsule for biological applications. *Mol Pharm*. 2006 3: 144-51

17- Kevein Bullis Therapeutics Nanomedicine .Technology Review (MIT). March/April 2006 pp58-59

18- Mahmood U, Josephson L. Molecular MR imaging probe. *Proc IEEE*. 2005 93: 800-808

19- Leary SP, Liu CY, Apuzzo ML. Toward the emergence of nanoneurosurgery: part II- and part III Nanomedicine: diagnostics and imaging at the nanoscale

level. *Neurosurgery*. 2006 58:805-23. and 1009-1026

20- Patel G M, Patel G C, Patel R B, et al. Nanorobot: a versatile tool in nanomedicine. *J Drug Target* 2006 14: 63-67

21- Akerman ME, Chan WC, Laakonen P, Bhatia SN et al. Nanocrystal targeting in vivo. *Proc Natl Acad Sci USA* 2002 99: 12617-21

22- Randey R, Sharma A, Zahoor A et al. Poly(Di-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. *J Antimicrob Chemother*. 2003 52: 981-6

23- Vila A, Sanchez A, Evora C et al. PEG-PLA nanoparticles as carrier for nasal vaccine delivery. *J Aerosol Med*. 2004 17: 174-85

24- Zaret K. Regenerative medicine; self-help for insulin cells. *Nature*. 2004 429: 30-31

25- Aldhous P. Regenerative medicine – a world of difference. *Nature* 2001 414:838-40

26- Petit-Zeman S. Regenerative medicine. *Nat Biotechnol*. 2001 19: 201-206

27- Corraera-Duarte MA, Wagner N, Rojas-Chapana J, et al. Fabrication and biocompatibility of carbon monotube-based 3D network as scaffolds for cell seeding and growth. *Nano Lett*. 2004 4: 2233-2236

28- Nakashima K, Colamarino S, Gage FH. Embryonic stem cells: staying plastic on plastic. *Nat Med* 2004 10: 23-24

29- Alliance for Nanomedical Technologies home page. Available at [www.research.cornel.edu/anmt](http://www.research.cornel.edu/anmt).

30- John A E, Lukacs N W, Berlin A A et al. Discovery of a potent nanoparticle p-selectin antagonist with anti-inflammatory effects in allergic airway disease. *FASEB J*. 2003 17: 2296-2298

31- Kumar M, Kong X, Behera A K, et al. Chitosan IFN- gamma-pDNA nanoparticle (CIN) therapy for allergic asthma. *Genet Vaccines Ther* 2003 1: 3

32- Bahadori M, Mohammadi F. Metabolomics in medicine. *Tanaffos (Respiration)*; 2005 4 ( 16); 13-22