

## NANOTECHNOLOGY AND DIABETES

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### SUMMARY

*Nanotechnology, engineering and manufacturing at the scale of a nanometer or nano-scale (nanometer =  $10^{-9}$  meter) is a new technology which is already present in many parts of industry and medicine, and the impact of nanotechnology is growing bigger every day. Nanomedicine, the application of nanotechnology to medicine, has already offered some new solutions, and many pharmaceutical companies are trying to develop targeted drug delivery using nanotechnology and already existing drugs. Nanotechnology offers some new solutions in treating diabetes mellitus. Boxes with nanopores that protect transplanted beta cells from the immune system attack, artificial pancreas and artificial beta cell instead of pancreas transplantation, nanospheres as biodegradable polymeric carriers for oral delivery of insulin are just some of them. The abilities of nanomedicine are huge, and nanotechnology could give medicine an entirely new outlook.*

### INTRODUCTION

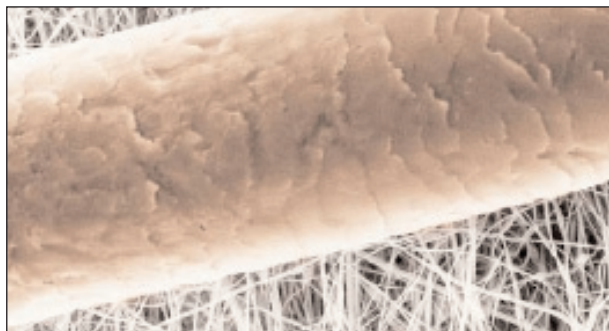
Nanotechnology, nanomedicine, and nanorobotics are terms that still sound like science fiction to most people. Yet, nanotechnology is now already present in

our lives; computer and cell phone industry, plastic industry are making products with nanotechnology-made parts. The impact of nanotechnology on medicine is growing every day.

### NANOTECHNOLOGY

The prefix nano comes from the Greek word *nanos*, which means one-billionth part of something. So, nanotechnology can be described as engineering and manufacturing at the scale of a nanometer or nano-scale (nanometer =  $10^{-9}$  meter). Just to give a sense of how small things are, here are some entities and their average size: atom diameter 0.15 nm, diameter of double strand DNA 2 nm, and cell 1000 nm (Fig. 1).

Figure 1. Nanofibrils behind a human hair for comparison (eSpin Technologies) (1).



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The aim of nano-scientists is to virtually imitate nature. They are trying to construct objects out of their most basic components, atom by atom, the way that nature does. This offers an unprecedented degree of precision and control over the final product. As a fundamental understanding of how nature works at the atomic scale, we can consider nanotechnology as enabling technology; it will enable us to do radical new things in virtually every technological and scientific arena. This all started in 1989, when a group of engineers at IBM company managed to create the smallest-ever company logo; they spelled IBM letters out of individual atoms (2). Since then, nanotechnology has become a part of almost every field of industry. In the year 2003, 18,347 patents related to nanotechnology were issued. The biggest assignee is Genentech, Inc. with 1427 patents, followed by IBM with 293 and Hitachi with 177 patents (3). In the last year, governments and corporations worldwide have ploughed over 4 billion USD into nanotechnology (4). However, despite great investments and hard scientific work, things are actually moving a bit slowly. Most scientists believe that nanotechnology will start seriously influence our lives around the year 2020 (5).

## NANOTECHNOLOGY IN MEDICINE

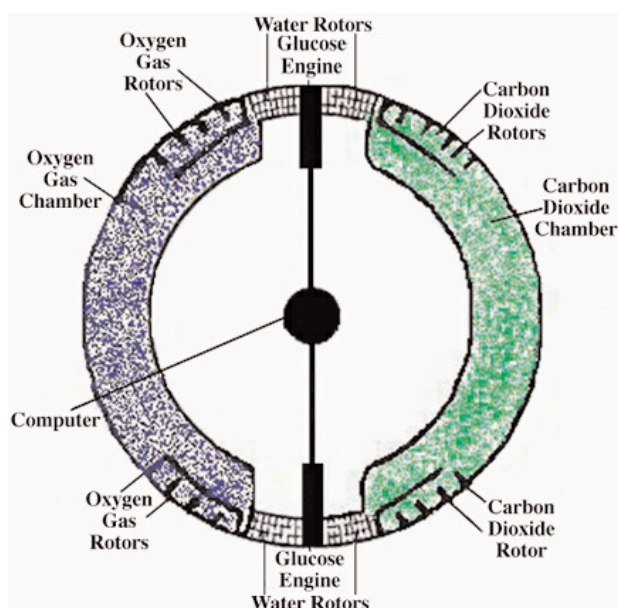
The application of nanotechnology to medicine is called nanomedicine. Nanomedicine subsumes three mutually overlapping and progressively more powerful molecular technologies: nanoscale structured materials and devices; genomics, proteomics and artificial engineered microbes; and medical nanorobots (6).

1) Nanoscale structured materials are parts of nanomedicine with a rapid evolution, because of the impact of pharmaceutical industry. Pharmaceutical companies are trying today to develop targeted drug delivery using nanotechnology and drugs that already exist. The fact is that we do have useful drugs, but in some cases with pure bioavailability. The problem is how to deliver drugs right where we need it. The possibilities are great. For example, researchers are contemplating the possibility of using magnetic nanoparticles containing drugs to be delivered to specific parts of the body by means of magnetic field (7). Drugs can also be attached to nano-ligand, the role of which would be to deliver the drug only to target tissue while at the same time reducing its side effects (8). Some drugs have the problem of poor water

solubility. The NanoSystems company, which is part of the Elan Corporation, has developed a process called nanonization to solve this problem. First, drug crystals are reduced until they become particles of less than 400 nm in diameter. To stabilize the particles and prevent aggregation, a thin layer of polymeric surface modifiers is adsorbed onto crystal surfaces. The outcome is a suspension that functions like a solution, which can be used in various dosage forms, like pills, sprays or creams (9). Medical nanomaterials may also include smart drugs that become active only in specific circumstances. Yoshihisa Suzuki from Kyoto University has designed a novel drug molecule that releases antibiotic only in the presence of an infection. Suzuki bound the molecule of gentamicin to a hydrogel using a newly developed peptide linker. The linker can be cleaved by a proteinase enzyme produced by *Pseudomonas aeruginosa*. Tests on rats have shown that the antibiotic is not released if no *Pseudomonas aeruginosa* bacteria are present. If any bacteria of this type are present, the enzyme produced by the microbes cleaves the linker and gentamicin is released to kill the bacteria. This is highly desirable because the indiscriminate prophylactic use of antibiotics is associated with the emergence of drug-resistant bacterial strains (10).

2) Artificial engineered microbes are already being used to produce human hormones, for example. Human DNA is incorporated in the genome of the bacteria, which then start to produce human hormones, used to cure endocrine diseases.

3) Medical nanorobots are still only a theory, but scientists are working to develop them. Robert A. Freitas has designed an artificial red blood cell called respirocyte, a spherical nanorobot of about the bacterium size. This respirocyte would be made up of 18 billion atoms, precisely arranged in a crystalline structure to form a miniature pressure tank. The tank would hold as many as nine billion oxygen and carbon dioxide molecules. When respirocytes are injected into an individual's bloodstream, sensors on the surface would detect oxygen and carbon dioxide levels in the blood. The sensors would then signal when it is time to load oxygen and unload carbon dioxide, or *vice versa*. Respirocytes could store and transport 200 times more gas than red blood cells. Although still only a theory, respirocyte could become a reality tomorrow (12) (Fig. 2).

Figure 2. **Respirocyte (11).**

## NANOMEDICINE AND DIABETES

Mauro Ferrari from Ohio State University and Tejal Desai from Boston University have created what could be considered one of the earliest therapeutically useful nanomedical devices. They created a tiny silicon box that contains pancreatic beta cells taken from animals. The box is surrounded by a material with a very specific nanopore size (about 20 nanometers in diameter). These pores are big enough to allow for glucose and insulin to pass through them, but small enough to impede the passage of much larger immune system molecules. These boxes can be implanted under the skin of diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need of powerful immunosuppressants that can leave the patient at a serious risk of infection (13).

Another possible permanent solution for diabetic patients could be artificial pancreas. The original idea was first described in 1974. The concept of its work is simple: a sensor electrode repeatedly measures the level of blood glucose; this information feeds into a small computer that energizes an infusion pump, and the needed units of insulin enter the bloodstream from a small reservoir (14). However, the main problem and the reason why most patients refused to have such an artificial organ was its size. Today, it is logical to assume

that nanotechnology can solve the problem. An American company, Medtronic MiniMed, has been working on a device called Long Term Sensor System (LTSS), which links an implantable long-term glucose mini sensor with an implantable insulin mini pump. The main problem is how to develop and refine a sophisticated algorithm to translate glucose levels determined by the sensor into appropriate insulin dosages. Testing of the LTSS to date is promising and MiniMed scientists predict they can bring an artificial pancreas to market by the year 2008 (15). It is not hard to imagine what the artificial pancreas might bring to diabetes patients. Ideally, it would mean nearly normal glycemia, no checking of blood glucose levels, no risk of hyper/hypoglycemia, no (or very few) chronic diabetic complications, no chronic immunosuppression as in islet transplantation, etc. There is no doubt that with its small size, artificial pancreas would be an acceptable solution for every diabetic patient.

Todd Zion from Nanostructure Materials Research Laboratory has developed technology for diabetes treatment called SmartCell. The author says about his technology: "When glucose rises in the bloodstream, it will eat away SmartCell's structure. As the SmartCell protein matrix breaks down, insulin is released. The more glucose is present, the faster matrix will erode." SmartCell technology means that diabetics could stop endlessly checking and rechecking their glucose levels, injecting more insulin as needed, because the drug will handle the chore. An injection a day is all that diabetics will need. No blood testing, no multiple shots. Early round of experiments with lab rats has begun, and the preliminary results are promising (16).

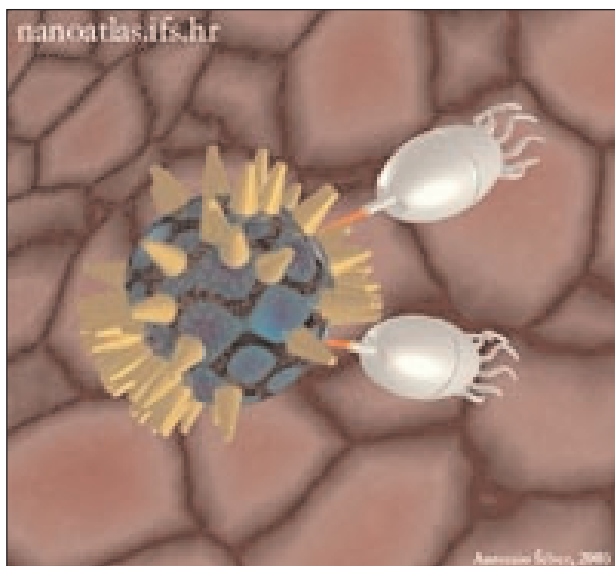
Radwant M.A. and Aboul-Enein H.Y. from Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, used polyethylcyanoacrylate (PECA) nanospheres as biodegradable polymeric carriers for oral delivery of insulin. The administration to streptozotocin-induced diabetic rats showed a very good hypoglycemic effect. Should the effect be proven in human research, it might significantly improve patient compliance (17).

One great alternative for pancreatic tissue transplantation could be so-called artificial beta cell. There are many attempts worldwide to develop such a cell. One possible way to accomplish this is to change certain molecules on the beta cell surface that are normally targets for an immune attack. Another

approach is to insert new genes into naturally occurring cells. The cells can be genetically altered so that they could not only produce insulin, but could also respond to the rise and fall of blood glucose, just as normal pancreatic beta cells do (18). Illani Atwater, Ph.D., from Sansum Medical Research Institute, Santa Barbara, CA, is working on inserting the proinsulin gene into a keratinocyte cell line attached to a glucose sensitive promoter gene, as well as the genes for GLUT2 glucose transporters and glucokinase phosphorylation enzymes (19). No matter which way leads toward the solution, the result will be the same, i.e. artificial beta cell that will produce insulin in response to the rise of blood glucose, and no target for the immune system. So, without immunosuppression, isn't artificial beta cell a better solution than pancreas transplantation?

Scientists are also trying to create a nanorobot which would have insulin departed in inner chambers, and glucose-level sensors on the surface. When blood glucose levels increase, the sensors on the surface would record it and insulin would be released. Yet, this kind of nano-artificial pancreas is still only a theory (20) (Fig. 3).

Figure 3. **Nanobots killing a virus, by Dr. Antonio Siber (21).**



## CONCLUSION

Banting and Best discovered insulin 85 years ago, so thousands and thousands of lives have been saved. Today, diabetic patients can reach old age, but the effort for treatment is enormous. The primary concern of modern diabetology must be the quality of life of diabetic patients.

Not long ago industrial revolution happened, atomic energy was discovered, computer was invented, and internet has become a part of daily living. So it is not hard to imagine that nanotechnology will become an important part of our lives tomorrow. Furthermore, nanotechnology is not science fiction anymore, it is taking place today. Scientists and governments around the world have recognized the possibilities of nanotechnology, and great effort in developing such technology is taking place today. Nanotechnology-created devices are already around us, in industry and in medicine. The abilities of nanomedicine are huge, and nanotechnology could give medicine an entirely new outlook. Imagine, for example, in the near future, your doctor has diagnosed you with diabetes, saying: "Don't worry, it's something like common cold. I'm going to insert a nanorobot into your bloodstream, and the problem is solved".

Nanorobots which have the size of a bacterium are not cleaning atherosclerotic plaques, killing viruses and healing diabetes yet, but the possibility that they will be doing it in a few years is rising every day.

## REFERENCES

1. Nanofibrils behind a human hair for comparison. [electronic resource] [accessed 2005 Mar 4]. Available from:URL: <http://www.biotech.ca/imagenation/nanotech.html>
2. Freitas RA. Say Ah! The Sciences [electronic resource] 2000 Jul/Aug [accessed 2005 Feb 5]. Available from:URL: <http://foresight.org/Nanomedicine/SayAh/index.html>
3. Will you live to see 153?Years!That Is. [electronic resource] [accessed 2005 Mar 4]. Available from:URL: <http://www.nanotech-now.com/products/nanonewsnow/issues/003/003.htm>
4. Harper T. What is nanotechnology? Nanotechnology [electronic resource] 2003; [accessed 2005 Feb 5]. Available from:URL: <http://www.zyvex.com/nanotech/nanotechAndMedicine.html>
5. Merkle R. How long will it take to develop nanotechnology? [electronic resource] [accessed 2005 Mar 4]. Available from:URL: <http://www.zyvex.com/nanotech/howlong.html>
6. Čeka nas duži, kvalitetniji i jednostavniji život. Medicinar [electronic resource] 2003 Dec [accessed 2005 Feb 6]. Available from:URL: <http://medicinar.mef.hr/tekstovi.php?id=39>
7. Nanotechnology-latest. [electronic resource] [accessed 2005 Mar 4]. Available from:URL: <http://www.countrydoctor.co.uk/education/sducation%20-%20Nanotechnology.htm>
8. Drug Delivery Systems – Markets and Applications for Nanotechnology Derived Drug Delivery Systems. [electronic resource] [accessed 2005 Feb 5]. Available from:URL: <http://www.azonano.com/details.asp?ArticleID=1078>
9. Nanocrystal Technology. [electronic resource] [accessed 2006 Jan 10]. Available from:URL: [http://www.elan.com/EDT/drug\\_delivery/nanocrystal\\_technology.asp](http://www.elan.com/EDT/drug_delivery/nanocrystal_technology.asp)
10. Freitas RA. The Future of Nanofabrication and Molecular Scale Devices in Nanomedicine. [electronic resource] [accessed 2005 Feb 5]. Available from:URL: <http://www.rfreitas.com/Nano/FutureNanofabNMed.htm>
11. What are respirocytes? [electronic resource] [accessed 2006 Jan 20]. Available from:URL: <http://dev.nsta.org/evwebs/10955/page2.html>
12. Respirocytes. [electronic resource] [accessed 2006 Jan 20]. Available from:URL: <http://www.foresight.org/nanomedicine/Respirocytes.html>
13. Freitas RA. Current status of Nanomedicine and Medical Nanorobotics [electronic resource] [accessed 2006 Jan 20]. Available from:URL: <http://www.nanomedicine.com/Papers/NMRevMar05.pdf>
14. Hanazaki K, Nosé Y, Brunicardi FCh. Artificial endocrine pancreas. J Am Coll Surg [electronic resource] 2001 Sep [accessed 2006 Jan 20]. Available from:URL: [http://www.sciencedirect.com/science?\\_ob=ArticleURL&\\_u d i = B 6 T 9 1 - 4 3 T F M 1 9 - C&\\_coverDate=09%2F30%2F2001&\\_alid=357932693&\\_rdoc=1&\\_fmt=&\\_orig=search&\\_qd=1&\\_cdi=5101&\\_sort=d&view=c&\\_acct=C000050661&\\_version=1&\\_urlVersion=0&\\_userid=3875467&md5=debe58d619bd36dc9719924e02f208cd](http://www.sciencedirect.com/science?_ob=ArticleURL&_u d i = B 6 T 9 1 - 4 3 T F M 1 9 - C&_coverDate=09%2F30%2F2001&_alid=357932693&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=5101&_sort=d&view=c&_acct=C000050661&_version=1&_urlVersion=0&_userid=3875467&md5=debe58d619bd36dc9719924e02f208cd)
15. JDRF-The next five years. [electronic resource] [accessed 2006 Jan 20]. Available from:URL: <http://www.jdrf.org.au/publications/factsheets/jdrf5years.html>
16. Aaron K. Outsmarting Diabetes. Cornell Engineering Magazine [electronic resource] 2003 FALL [accessed 2005 Apr 20]. Available from:URL: [http://eng-2k-web.engineering.cornell.edu/engrMagazine/magazine.cfm?issue=FALL2003&page\\_number=1&section=feature4](http://eng-2k-web.engineering.cornell.edu/engrMagazine/magazine.cfm?issue=FALL2003&page_number=1&section=feature4)
17. Radwant MA, Aboul Enein HY. The effect of oral absorption enhancers on the *in vivo* performance of insulin-loaded polyethylcyanoacrylate nanospheres in diabetic rats. J Microencapsul [electronic resource] 2002 [accessed 2005 Apr 2]. Available from:URL: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=11837977&query\\_hl=3&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11837977&query_hl=3&itool=pubmed_docsum)
18. Robert S. Dinsmoor: Islet Cell Transplantation: Working toward a Cure. [electronic resource] [accessed 2006 Jan 16]. Available from:URL: [http://www.childrenwithdiabetes.com/d\\_On\\_701.htm](http://www.childrenwithdiabetes.com/d_On_701.htm)

19. Grant 126. Construction of an Artificial Beta-cell. [electronic resource] [accessed 2006 Jan 16]. Available from:URL:  
<http://www.daref.org/research00.html>
20. Freitas RA. The Future of Nanofabrication and Molecular Scale Devices in Nanomedicine. [electronic resource] [accessed 2006 Jan 20]. Available from:URL:  
<http://www.rfreitas.com/Nano/FutureNanofabNMed.htm>
21. Siber A. Nanobots killing a virus. [electronic resource] [accessed 2006 Jan 20]. Available from:URL:  
[http://www.nanotech-now.com/Art\\_Gallery/antonio-siber.htm](http://www.nanotech-now.com/Art_Gallery/antonio-siber.htm)