Nanomedicine: Implications for Drug and Market Development
by
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- Nanomedicine is the application of nanotechnology, the engineering of tiny machines, to the prevention and treatment of diseases and disorders in the human body.
- Although this discipline is in its infancy, some predict that in 10 – 15 years about one-half of the production of pharmaceuticals will depend on nanotechnology. (M.C. Roco at AAAS meeting 2/14/01)
- The most elementary nanomedical devices will diagnose illness by using nanomachines to monitor the internal chemistry of the body; a more advanced use might be implanted devices to dispense drugs or hormones.
- The most advanced would involve the use of nanorobots as miniature surgeons to repair damaged cells or correct genetic deficiencies.
- When the National Nanotechnology Initiative (NNI) began in February 2000, for the first time since World War II the US was behind in a developing technology. Since that time numerous initiatives in universities and private companies have emerged.
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Introduction to Nanomedicine

When ancient soldiers slashed and cut the enemy exposing the white, glistening bone, some ingenious physician found a unique way to close the wound. While one person held the wound together, another would apply ants or termites. They then pinched off the body of the insect leaving the strong jaws to hold the wound together. We think this is indeed crude. But sometime in the future, a doctor may think a surgeons slashing of cells during an operation primitive and bizarre. Our drugs of today are simple molecular devices that affect specific cells; however, drugs work without direction traveling willy-nilly through the bloodstream until they hit and attach to a target molecule. With nanomedicine, nanorobots will be like targeted miniature surgeons repairing damaged cells and getting inside cells to replace or assist damaged intracellular structures. At the extreme, nanomachines could replicate themselves and correct genetic deficiencies at the DNA level.

To understand nanomedicine, we must look at the body from the perspective of an intricate machine filled with active, molecular structures. Modern medicine affects diseases and disorders in many ways but from the molecular viewpoint, present efforts are as crude as the jaws of the termites. When we gain the perspective of the body as a construction site, building, growing, and healing tissue, we realize how everything is the human body is like a molecular machine. The cell’s genes use the building materials to build biological structures.

The word nanotechnology includes the Greek root “nano” meaning one-billionth of something- whether it is a second, liter, or meter. In scientific nomenclature it is written 10^{-9}. A nanometer is about ten hydrogen atoms wide; red blood cells are several thousand nanometers in diameter. Nanoscience and nanotechnology both refer to a world working on the nanoscale; thus, nanomedicine refers to the application of nanotechnology, the engineering of tiny machines, to the treatment and disease of the human body.

M.C. Roco, National Science Foundation, said that the essence of nanotechonology is working at the atomic and molecular levels to create materials, devices, and systems with totally new properties and functions. (Roco, MC. 2001 *Journal of Nanoparticle Research* 3:5 – 11) It's like building the world atom by atom. He thinks that in 10 to 15 years over half of the pharmaceutical industry will depend on nanotechnology devices.

Although serious investigation into nanotechnology began only about 20 years old, Richard Feynman gave a speech at the American Physical Society on December 29, 1959 that challenged scientists to think small. In his now classic address, "There's Plenty of Room at the Bottom," he asked the question, "What would happen if we could arrange the atoms one by one the way we want?" He also added in the year 2000, when they look back at this age, they will wonder why it was not until 1960 that anyone began to seriously move in this direction. Noria Tamiguchi first used the word "nanotechnology" in 1974. In 1986 Eric Drexler penned *Engines of Creation: The Coming Era of Nanotechnology*, a futuristic book popularizing nanotechnology. Chapter 7 called "Engines of Healing," described how molecular technology could be used to create a state of health not just tackle disease. Scrambled or misarranged atoms cause aging, illness, and injury. Viruses, time, or swerving cars can cause this disorder. Devices that rearrange these errant atoms will correct them. Nanotechnology will bring a fundamental breakthrough in medicine. (This entire book *Engines of Creation* may be read at http://www.foresight.org/EOC)

Current Progress

When in January 2000, President Clinton approved a new $500 million National Nanotechnology Initiative, it was divided into several departments. One major area was for the National Institutes of Health (NIH). For Fiscal Year (FY) 2003 the request for NIH was $43.2 million, $2.4 million over FY 2002 for work in nanomedicine. NIH will receive nanoscience and nanotechnology grant applications under existing and renewed programs, and the individual Institute and Centers manage these programs. Overall nanotechnology program coordination occurs through the NIH Bioengineering Consortium (BECON).

The joint National Cancer Institute NCI-NASA program, "Fundamental Technologies for Development of Biomolecular Sensors," will continue. The purpose of this collaborative interagency program between the National Cancer Institute and NASA is to advance the development of technologies and informatics tools to enable minimally-invasive detection, diagnosis, and management of disease and injury. Using technology platforms, biomolecular sensors can function in the living body to measure, analyze, and manipulate molecular processes.

Training of scientists and engineers to conduct multifaceted nanotechnology research is essential. NIH, through BECON, is re-issuing a program solicitation, "Mentored Quantitative Research Career Development Award," to support career development of investigators with quantitative scientific and engineering backgrounds who have made a commitment to focus their research on biomedical (basic or clinical) or behavioral research. NCI has funded a contract at NASA's Ames laboratory to study how nanotechnology can be used in the detection of cancer cells. NIH is developing several research areas for FY 2003: nanomaterials, nano-imaging, cell biology, molecular and cellular sensing/signaling, and nanomotors.

In-Stat/MDR issued a report “Biological and Chemical Sensors: Watching the Next Generation Evolve” on April 2, 2003 that identified biosensors in blood glucose testing as the biggest market now and in the future even outdistancing sensors for real-time detection of biological and chemical weapons The market in sensors is expected to push revenues from $2.3 billion in 2002 to nearly $4 billion in 2007, an annual growth rate of 11.5 percent.

The Freedonia Group Inc., a research organization, reported that biomedical applications for microelectromechnical systems (MEMS) is projected to grow more than 20 percent a year from $215 million in 2001 through $550 million in 2006 topping $1 billion by 2011.

The Foresight Institute website lists over 200 groups involved in nanomedical research. These are located throughout the world and include research institutions, governmental organizations, and commercial enterprises. New companies are added almost daily.

Nanorobots: They are Coming

In 1920 Czech writer Karel Capek wrote a science fiction comedy called *R.U.R.: Revenge of the Robots*. He first used the word “robotnik” to tell about an army of mechanical slaves, who have no feelings or emotions, that rise up and take control destroying everybody in the world except one. A fanciful tale, it grabs us with the interesting ideas about the scientific unknowns and gave us a term that we understand today- robot. To apply “nano” to “robot” gives us a fresh perspective of unknowns that may soon be reality- with concomitant responsibility.

Robert Freitas, PhD, is a scientist at Zyvex Corporation (Richardson, Texas), a company devoted to exploring the possibilities of nanomedicine. He envisions billions of minute, self-assembling, computerized, mechanical robots swarming to the site of injury and sensing, diagnosing, and activating therapeutic systems. He details work on nanorobots in his book *Nanomedicine, Volume I: Basic Capabilities.* He emphasizes how basic nanostructural materials like engineered enzymes and the many products of biotechnology cannot reach its promise until the development of controlled or programmable medical nanomachines and nanorobots. He has proposed respirocytes, artificial red blood cells, and clottocytes, artificially manufactured platelets. His latest experimentation involves microbivores, artificial phagocytes whose primary function is to destroy microbiological pathogens found in the human bloodstream. He also has proposed vasculoids, a personal appliance to replace human blood.

One of the major problems is that all medical nanorobots used in nanomedicine must be biocompatible. In IMM Reports “Could Medical Nanorobots Be Carcinogenic?” (http://www.imm.org/Reports/Rep033.html) Freitas emphasized how the exploration of carcinogenicity is still in diapers but the information available to date appears optimistic. For example, diamond coatings show low mutagenic capacity on human fibroblasts *in vitro.* Alumina (sapphire) appears to have no mutagenic or carcinogenic effects on cultured human osteoblasts. He cautions that the risk factors must be born in mind when designing these robots as well as any detachable systems that could be poisonous to cells.

When Carlo Montemagmo, Ph.D., Cornell University announced his first bionic machine on November 24, 2000 (*Science* 2000 290:1555-8), molecular machines moved out of the realm of speculation. A flurry of molecular machines have come to the forefront in the last few years, with many still in design as well as experimental stages.

NASA and a group of researchers headed by Dr. James F. Leary, University of Texas Medical Branch, are developing nanoparticles or nanocapsules that could help make exploration of Mars and other long-term exploration of space possible. This project focuses on cancer caused by the high radiation doses that astronauts may experience in space when they leave the protective veil of the magnetic field around the earth. These photons shoot through the body like tiny bullets blasting DNA and leading to cancer. When radiation damages cells, they produce a class of proteins called CD-95 that gravitate to the surface and wave it like a flag to tell other cells of the injury. By implanting nanoparticles that bind to CD-95 markers, scientists can program the particles to find the cells. If radiation damage is serious, the nanoparticles enter the cell and release enzymes that will start the cell's own self-destruction sequence or apoptosis.

Another part of the study involves attaching fluorescent molecules to the nanoparticles. These would light up at certain stages of the process. Astronauts may don a pair of glasses that look inward upon the retina. The flowing of fluorescent nanoparticles on cells through the retina is a measuring instrument. This technology already exists in measuring blood flow changes in the retina caused by various diseases. "Astronauts might wear these glasses to sample what's going on in their bloodstreams. If they need treatment, they have a hypodermic needle with the appropriate nanoparticles," said Dr. Leary. (*UTMB Quart Summer* 2002 4(1)26-7)

DNA Nanotechnology

Tatjana Paunesku and Gayle Woloschak and a team from Northwestern University and Argonne National Laboratory, have created a composite of titanium oxide nanocrystals that attaches to snippets of DNA and then may detach when exposed to light or X-ray. The titanium oxide crystals are less than a few billionth of a meter in diameter and can provide a scaffold for a strand of DNA matching a defective gene within a cell. Insertion into the cell would bind with its “evil twin” to form a double-helix molecule. The crystal then could be exposed to light or X-ray and cut away from the gene.

The researchers said this “Swiss army knife” is not like today’s drugs because ten kinds of good genes can be injected to target either specific or extremely broad destinations. Although the work is at least two years away from testing in a laboratory model, the researchers see the possibility for gene therapy targeting cancer, neurological diseases, as well as carrying enzyme or other proteins. Such nanoparticles could overcome adverse reactions of genetically modified viruses for gene therapy. The work was described in the May 2003 online version of *Nature Materials* and reported at *News.NanoApex*, April 23, 2003.

Quantum dots are nanocrystals that are being proposed for several uses, and many look to be commercially viable. These dots are less than 10 nanometers and are extremely luminous and stable. Predictions of use range from nanoscale transitors to lasers and solar panels.

Researchers at the Burnham Institute and US San Diego have developed programmed nanocrystalline semi-conductor quantum dots (qdots) wrapped in tiny pieces of protein that go home to specific places inside living tissue. These homing peptides using the qdots represent the first successful targeting of an inorganic nanomachine into cancers in live mice. Reporting in Proceeding of the *National Academy of Science (PNAS*) (September 17, 2002, 99,19), Erikki Ruoslahti and colleagues believe that qdots can be successfully introduced into the body without causing blood clotting. The homing peptides directed the qdots to a specific type of cancer. Since qdots can be programmed to emit red or green light, they may be delivered to several different tissues. The destination is determined by the peptide coating that homes in on normal lung tissue, blood vessels feeding tumors, or lymph vessels draining tumor tissue.

Molecular Manufacturing

Eric Drexler, founder of the Foresight Institute, Palo Alto CA, believes the future of generations of nanotechnology relies on arranging atoms effectively. Molecular manufacturing or arranging atoms and the use of molecular assemblers will hold the key to controlling how molecules react and allow scientists to build complex structures. He emphasized how biological molecular machines are programmed in cells with genetic data and can build more molecular machines cheaply. In an essay released on April 23, 2003 and sponsored by the Department of Energy, he stated how molecular manufacturing will bring both great opportunities and great dangers. Nanocomputers will extend desktop power a billion or more. Nanosensors, computers, and tools will bring surgical control to the molecular level enabling a new revolution in medicine.

Zyvek Corporation, the first company dedicated to molecular nanotechnology, announced on April 15, 2003 the release of the $100

Nanomanipulator® System. This system sets up four quadrants of three-dimensional stages that grasp, move, test, and postion molecular samples for electron scanning microscopes (SEMs). A joy stick and illuminated keypad provide the user with a great degree of control.

Drug Delivery

The goal of drug delivery systems is to send medication intact to specifically targeted parts of the body and control the release using a physiological or chemical trigger.

Advectus Biosciences, Inc. focuses on the development and commercialization of a patented nanotechnology process for the delivery of approved cancer fighting drugs across the blood-brain barrier for the treatment of brain tumors. Collaborating with the University of North Carolina, Chapel Hill, the researchers announced on April 3, 2003 the results of stage 3 pre-clinical trials with the nanoparticle-based technology P80DOXNP or Nanocure™. The preclincal trial tested six different types of cancer that metastasized to the brain from patients with colon, breast, renal, and other cancers. The hope is to soon begin Phase I human trials of a large group of brain cancer patients and that Food and Drug Administration (FDA) will put the product on a fast track designation.

Rice University and Lon Wilson have become known for their nanocreation buckyballs, spherical cages containing 60 carbon atoms. Announced on April 23, 2003 researchers at Rice have attached vancomycin, the antibiotic of last resort, to be possibly the first targeted antibiotic. With the recent emergence of vancomycin-resistant bacteria, finding a way to revive vancomycin would be an important find. The investigators founds pairs of the molecules attached with an intermediate molecule, have proven effective at killing these bacteria. Also, by linking antibiotics to a cancer drug, they created targeted compounds that bind only with certain cells like those found in melanoma. They believe also they can create a C-60 vancomycin conjugate that will bind to anthrax while it is still in the spore form. This could be an agent in the war against biological weapons.

Researchers at Cleveland Clinic have developed a procedure that may eliminate many of the 500,000 dreaded bone grafts in the US each year. Bioengineer Shuvo Roy and surgeon George Muschler (Cleveland Clinic) teamed to show that cells grow faster on a micropatterned polymer surface. Muschler hopes to use this technique to grow adult stem cells that will turn into bone. The researchers found that when the polymer polydimethylsiloxane (PDMS) has been molded with tiny bumps 6 microns high and 10 microns wide, cell growth after nine days is about 280 percent better than cell growth on standard glass petri dishes. They also see that once the process is perfected and approved for bone growth, the technology would work for other applications like growing cartilage, tendons, and skin.

Paradigm Shift: BioMEMS

The term lab-on-a-chip is a hot buzz-word with a nano-twist. A pinprick can funnel a tiny droplet of blood into a microscopic maze of fluid circuits, sensors, and filters- all housed on a device no bigger than a credit card. With these devices, doctors will get the results from many basic screenings without having to wait for blood samples to be shipped to a lab for analysis.

BioMEMS applies microdevices to biological and medical problems that many predict will cause a paradigm shift in both diagnostics and therapy. An area that will feel the impact especially is patient monitoring. Miniature implanted devices will offer an avenue to artificial organs, personalized drug therapies, and new techniques to view cellular communication.

Traditional biology focused on a single biomarker in isolation. The genomic revolution has caused a shift in paradigm that has a marked influence on drug and market development. The new systems biology looks at the complex interactions among DNA, mRNA, proteins, protein activations, and pathways. As knowledge increases, classification of disease and the practice of medicine will be defined in terms of molecular medicine.

Many companies are venturing into this field. Aclara Biosciences (Mountain View, CA) has developed a system for assays that focuses on the shift to the new biology of molecular medicine. Their eTag Assay System™ is a high performance device that can study 10s to 100s of genes, proteins, and pathways across thousands of samples. They have developed a novel, proprietary microfluidics technology that will integrate with the eTag System for even greater throughput for automation. This microfluidics platform will have enhanced sensitivity using a single-use plastic LabCard™ devise that gives higher throughput at a lower cost.

Hitachi Ltd. (Tokyo, Japan) on April 3, 2003 announced it has developed a DNA analyzer that can make gene diagnoses using only 1 milliliter of blood. The analyzer can do it for only $10 and in minutes instead of three to seven hours. Using a 150-micron diameter fused silica capillary packed with 100-micron glass beads, the company says it can be on the market in 2005. In the capillary, nanobeads are coated with artificial DNA molecules designed to have complementary base sequences to genes. As the sample passes though the tube, target genes adhere to the complementary strands and are detected by a laser. Several competitors are in the market in Japan. Olympus Optical (Osaka) plans to start mass-producing a DNA chip that could sense the presence of target genes in three minutes at a cost of $424.

STMicroelectronics, a leading semiconductor company, is gearing up for involvement in the medical MEMS or bioMEMS market. It is creating a lab-on-a-chip made with silicon rather than glass. This chip will test small amounts of bodily fluids in seconds. The prototype is fabricated using microfluidics, building on their expertise in inkjet computer chips that combine electronic and fluidic elements. This chip is unique in that it using silicon rather than plastic and glass substrate normally used in DNA detection.

Synthetic Blood International (Kettering, Ohio) has developed an implantable glucose biosensor to monitor blood glucose without the need for finger sticks. Implanted in subcutaneous tissue, it uses an enzyme specific for glucose, and measurement is more accurate than current portable monitoring devices. About the size of a cardiac pacemaker, a digital display provides a read out in a wearable beeper-sized device. Ultimately, the biosensor will link to an implanted insulin pump, thus creating a closed-loop mechanical pancreas.

Specialty Areas- New Wrinkles

Several other areas of investigation are touched by nanomedicine. PowerPaper Ltd., (Tel Aviv, Israel) has created a unique cosmetic patch to enhance cosmetics. Their thin micro-electronic patches use patented, thin, flexible energy cells or tiny batteries that require no metal casing and can be printed directly onto paper, plastics, or other surfaces using standard printing methods. The patch can enhance delivery of cosmetics to treat a variety of cosmetic skin disorders, such as wrinkles and fine lines, dark spots, age spots, skin redness, puffy eyes, and other cosmetic problems.

Edward M. Reifman, a dentist in Encino, California, believes that in the next 10 to 20 years, nanotechnology will put a halt to the genetics behind tooth loss, gum disease, and bone loss in the jaw due to aging. He predicts that pre-programmed artificially made nanomolecules will be delivered with precision by million of molecular circuits to do all kinds of procedures that dentists today do by hand. Long-lasting teeth will be produced from the most durable compounds around- diamond. He predicts a replacement of the entire jaw and teeth with a diamond-like matrix that would be durable and hard.

And at the extreme is the possibility of how the nanoworld may keep one forever- or forever young. Speaking at a cryonics conference, Ralph Merkle and Robert Freitas of Zyvek told the group that nanorobots may one day be designed to repair broken chromosomes. Many of the attendees were members of Alcor, an Arizona based organization that freezes deceased members in liquid nitrogen in hopes they will be brought back to like when medical technology becomes sufficiently advanced. Recently Alcor froze the body of the late Ted Williams, famous baseball player.

Conclusion

Nanotechnology has created new perspectives in the paradigm shift in drug discovery and development. Prior to the genomics revolution with traditional biology the scientist examined a single biomarker in isolation. Now with systems biology complex interactions of DNA, mRNA, proteins, protein activators, and pathways provide a multitude of targets. The challenge is to find the most promising targets from a large number of alternatives.

Robert Freitas said that the full promise of nanomedicine is unlikely to arrive until the development of precisely programmed nanomachine and nanorobots that can deliver the materials safely. Nevertheless, the impact on drug and market development in years to come is presently inconceivable. From cell repair machines to drug delivery and conquest of cancer and even aging, nanoscience is leading us from just treating disease to promoting health. Right now we do not know the outcome and probably many of these things will never reach clinical and practice status. However, if only a few are effective and proven, it will revolutionize the way medicine diseases are treated and even prevented. While we cannot predict details of the results, we can agree with Karl Darrow who said in the *Renaissance of Physics*, "…that which distinguishes ours from all earlier generations is…that we have seen our atoms," and this vision will be a dominant force in the twenty-first century.