NANOMEDICINE AND MEDICAL NANOROBOTICS

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Keywords: Assembly, Nanomaterials, Nanomedicine, Nanorobot, Nanorobotics, Nanotechnology

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Summary

Nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.

In the relatively near term, nanomedicine can address many important medical problems by using nanoscale-structured materials and simple nanodevices that can be manufactured today, including the interaction of nanostructured materials with biological systems.

In the mid-term, biotechnology will make possible even more remarkable advances in molecular medicine and biobotics, including microbiological biorobots or engineered organisms. In the longer term, perhaps 10-20 years from today, the earliest molecular machine systems and nanorobots may join the medical armamentarium, finally giving physicians the most potent tools imaginable to conquer human disease, ill-health, and aging.
1. Nanotechnology and Nanomedicine


In December 2002 the U.S. National Institutes of Health announced a 4-year program for nanoscience and nanotechnology in medicine. Burgeoning interest in the medical applications of nanotechnology has led to the emergence of a new field called nanomedicine. Most broadly, nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. The NIH Roadmap’s new Nanomedicine Initiatives, first released in late 2003, “envision that this cutting-edge area of research will begin yielding medical benefits as early as 10 years from now” and will begin with “establishing a handful of Nanomedicine Centers...staffed by a highly interdisciplinary scientific crew including biologists, physicians, mathematicians, engineers and computer scientists...gathering extensive information about how molecular machines are built” who will also develop “a new kind of vocabulary – lexicon – to define biological parts and processes in engineering terms”. Even state-funded programs have begun, such as New York’s Alliance for Nanomedical Technologies.

In the relatively near term, over the next 5 years, nanomedicine can address many important medical problems by using nanoscale-structured materials and simple nanodevices that can be manufactured today (Section 2). This includes the interaction of nanostructured materials with biological systems. Over the next 5-10 years, biotechnology will make possible even more remarkable advances in molecular medicine and biobotics – microbiological robots or engineered organisms (Section 3). In the longer term, perhaps 10-20 years from today, the earliest molecular machine systems and nanorobots may join the medical armamentarium, finally giving physicians the most potent tools imaginable to conquer human disease, ill-health, and aging (Section 4).

2. Medical Nanomaterials and Nanodevices

2.1. Nanopores

Perhaps one of the simplest medical nanomaterials is a surface perforated with holes, or nanopores. In 1997 Desai and Ferrari created what could be considered one of the earliest therapeutically useful nanomedical devices, employing bulk micromachining to fabricate tiny cell-containing chambers within single crystalline silicon wafers. The chambers interface with the surrounding biological environment through polycrystalline silicon filter membranes which are micromachined to present a high density of uniform
nanopores as small as 20 nanometers in diameter. These pores are large enough to allow small molecules such as oxygen, glucose, and insulin to pass, but are small enough to impede the passage of much larger immune system molecules such as immunoglobulins and graft-borne virus particles. Safely ensconced behind this artificial barrier, immunoisolated encapsulated rat pancreatic cells may receive nutrients and remain healthy for weeks, secreting insulin back out through the pores while the immune system remains unaware of the foreign cells which it would normally attack and reject. Microcapsules containing replacement islets of Langerhans cells – most likely easily-harvested piglet islet cells – could be implanted beneath the skin of some diabetes patients. This could temporarily restore the body’s delicate glucose control feedback loop without the need for powerful immunosuppressants that can leave the patient at serious risk for infection. Supplying encapsulated new cells to the body could also be a valuable way to treat other enzyme or hormone deficiency diseases, including encapsulated neurons which could be implanted in the brain and then be electrically stimulated to release neurotransmitters, possibly as part of a future treatment for Alzheimer’s or Parkinson’s diseases.

The flow of materials through nanopores can also be externally regulated. The first artificial voltage-gated molecular nanosieve was fabricated by Martin and colleagues in 1995. Martin’s membrane contains an array of cylindrical gold nanotubes with inside diameters as small as 1.6 nanometers. When the tubules are positively charged, positive ions are excluded and only negative ions are transported through the membrane. When the membrane receives a negative voltage, only positive ions can pass. Future similar nanodevices may combine voltage gating with pore size, shape, and charge constraints to achieve precise control of ion transport with significant molecular specificity. Martin’s recent efforts have been directed at immobilizing biochemical molecular-recognition agents such as enzymes, antibodies, other proteins and DNA inside the nanotubes as active biological nanosensors, to perform drug separations, and to allow selected biocatalysis. Others are investigating synthetic nanopore ion pumps, voltage-gated nanopores embedded in artificial membranes, and an ion channel switch biosensor that detects changes in chemical concentration of ~10⁻¹⁸. Molecular dynamics theoretical studies of viscosity and diffusion through nanopores are in progress.

Finally, Daniel Branton’s team at Harvard University has conducted an ongoing series of experiments using an electric field to drive a variety of RNA and DNA polymers through the central nanopore of an alpha-hemolysin protein channel mounted in a lipid bilayer similar to the outer membrane of a living cell. By 1998, Branton had shown that the nanopore could be used to rapidly discriminate between pyrimidine and purine segments (the two types of nucleotide bases) along a single RNA molecule. In 2000, the scientists demonstrated the ability to distinguish between DNA chains of similar length and composition that differ only in base pair sequence. Current research is directed toward reliably fabricating pores with specific diameters and repeatable geometries at high precision, understanding the unzipping of double-stranded DNA as one strand is pulled through the pore and the recognition of folded DNA molecules passing through the pore, experiments with new 3-10 nm silicon-nitride nanopores, and investigating the benefits of adding electrically conducting electrodes to pores to improve longitudinal resolution “possibly to the single-base level for DNA”. Nanopore-based DNA-sequencing devices could allow per-pore read rates potentially up to 1000
bases per second, possibly eventually providing a low-cost high-throughput method for very rapid genome sequencing.

2.2. Artificial Binding Sites and Molecular Imprinting

Another early goal of nanomedicine is to study how biological molecular receptors work, and then to build artificial binding sites on a made-to-order basis to achieve specific medical results. Molecular imprinting is an existing technique in which a cocktail of functionalized monomers interacts reversibly with a target molecule using only noncovalent forces. The complex is then cross-linked and polymerized in a casting procedure, leaving behind a polymer with recognition sites complementary to the target molecule in both shape and functionality. Each such site constitutes an induced molecular “memory,” capable of selectively binding the target species. In one experiment involving an amino acid derivative target, one artificial binding site per (3.8 nm) polymer block was created. Chiral separations, enzymatic transition state activity, and high receptor affinities have been demonstrated.

Molecularly imprinted polymers could be medically useful in clinical applications such as controlled drug release, drug monitoring devices, quick biochemical separations and assays, recognition elements in biosensors and chemosensors, and biological and receptor mimics including artificial antibodies (plastibodies) or biomimicking enzymes (plastizymes). But molecularly imprinted polymers have limitations, such as incomplete template removal, broad guest affinities and selectivities, and slow mass transfer. Imprinting inside dendrimers (Section 2.7) may allow quantitative template removal, nearly homogeneous binding sites, solubility in common organic solvents, and amenability to the incorporation of other functional groups.

2.3. Quantum Dots and Nanocrystals

Fluorescent tags are commonplace in medicine and biology, found in everything from HIV tests to experiments that image the inner functions of cells. But different dye molecules must be used for each color, color-matched lasers are needed to get each dye to fluoresce, and dye colors tend to bleed together and fade quickly after one use. “Quantum dot” nanocrystals have none of these shortcomings. These dots are tiny particles measuring only a few nanometers across, about the same size as a protein molecule or a short sequence of DNA. They come in a nearly unlimited palette of sharply-defined colors which can be customized by changing particle size or composition. Particles can be excited to fluorescence with white light, can be linked to biomolecules to form long-lived sensitive probes to identify specific compounds up to a thousand times brighter than conventional dyes used in many biological tests, and can track biological events by simultaneously tagging each biological component (e.g., different proteins or DNA sequences) with nanodots of a specific color.

Quantum Dot Corp. (www.qdots.com), the manufacturer, believes this kind of flexibility could offer a cheap and easy way to screen a blood sample for the presence of a number of different viruses at the same time. It could also give physicians a fast diagnostic tool to detect, say, the presence of a particular set of proteins that strongly indicates a person is having a heart attack or to detect known cellular cancer markers.
On the research front, the ability to simultaneously tag multiple biomolecules both on and inside cells could allow scientists to watch the complex cellular changes and events associated with disease, providing valuable clues for the development of future pharmaceuticals and therapeutics. Quantum dots are useful for studying genes, proteins and drug targets in single cells, tissue specimens, and living animals. Quantum dots are being investigated as chemical sensors, for cancer cell detection, gene expression studies, gene mapping and DNA microarray analysis, immunocytochemical probes, intracellular organelle markers, live cell labeling, medical diagnostics and drug screening, SNP (Single Nucleotide Polymorphism) genotyping, vascular imaging and many other applications. Quantum dot physics has been studied theoretically and computationally using time-dependent density functional theory and other methods.

Researchers from Northwestern University and Argonne National Laboratory have created a hybrid “nanodevice” composed of 4.5-nm nanocrystals of biocompatible titanium dioxide semiconductor covalently attached with snippets of oligonucleotide DNA. Experiments showed that these nanocomposites not only retain the intrinsic photocatalytic capacity of TiO₂ and the bioactivity of the oligonucleotide DNA, but more importantly also possess the unique property of a light-inducible nucleic acid endonuclease (separating when exposed to light or x-rays). For example, researchers would attach to the semiconductor scaffolding a strand of DNA that matches a defective gene within a cell, then introduce the nanoparticle into the cell nucleus where the attached DNA binds with its defective complementary DNA strand, whereupon exposure of the bound nanoparticle to light or x-rays snips off the defective gene. Other molecules besides oligonucleotides can be attached to the titanium dioxide scaffolding, such as navigational peptides or proteins, which, like viral vectors, can help the nanoparticles home in on the cell nucleus. This simple nanocrystal nanodevice might one day be used to target defective genes that play a role in cancer, neurological disease and other conditions, though testing in a laboratory model is at least two years away.

2.4. Fullerenes and Nanotubes

Soluble derivatives of fullerenes such as C₆₀ have shown great utility as pharmaceutical agents. These derivatives, many already in clinical trials (www.csixty.com), have good biocompatibility and low toxicity even at relatively high dosages. Fullerene compounds may serve as antiviral agents (most notably against HIV, where they have also been investigated computationally), antibacterial agents (E. coli, Streptococcus, Mycobacterium tuberculosis, etc.), photodynamic antitumor and anticancer therapies, antioxidants and anti-apoptosis agents which may include treatments for amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease) and Parkinson’s disease. Single-walled and multi-walled carbon nanotubes are being investigated as biosensors, for example to detect glucose, ethanol, hydrogen peroxide, selected proteins such as immunoglobulins, and as an electrochemical DNA hybridization biosensor.

2.5. Nanoshells and Magnetic Nanoprobes

Halas and West at Rice University in Houston have developed a platform for nanoscale drug delivery called the nanoshell. Unlike carbon fullerenes, the slightly larger nanoshells are dielectric-metal nanospheres with a core of silica and a gold coating,
whose optical resonance is a function of the relative size of the constituent layers. The nanoshells are embedded in a drug-containing tumor-targeted hydrogel polymer and injected into the body. The shells circulate through the body until they accumulate near tumor cells. When heated with an infrared laser, the nanoshells (each slightly larger than a polio virus) selectively absorb the IR frequencies, melt the polymer and release their drug payload at a specific site. Nanoshells offer advantages over traditional cancer treatments: earlier detection, more detailed imaging, fast noninvasive imaging, and integrated detection and treatment. This technique could also prove useful in treating diabetes. Instead of taking an injection of insulin, a patient would use a ballpoint-pen-size infrared laser to heat the skin where the nanoshell polymer had been injected. The heat from nanoshells would cause the polymer to release a pulse of insulin. Unlike injections, which are taken several times a day, the nanoshell-polymer system could remain in the body for months.

Nanospectra Biosciences (www.nanospectra.com), a private company started by Halas and West, is developing commercial applications of nanoshell technology. Nanospectra is conducting animal studies at the MD Anderson Cancer Center at the University of Texas, specifically targeting micrometastases, tiny aggregates of cancer cells too small for surgeons to find and remove with a scalpel. The company hopes to start clinical trials for the cancer treatment by 2004 and for the insulin-delivery system by 2006. In mid-2003, Rice researchers announced the development of a point-of-care whole blood immunoassay using antibody-nanoparticle conjugates of gold nanoshells. Varying the thickness of the metal shell allows precise tuning of the color of light to which the nanoshells respond; near-infrared light penetrates whole blood very well, so it is an optimal wavelength for whole blood immunoassay. Successful detection of sub-nanogram-per-milliliter quantities of immunoglobulins was achieved in saline, serum, and whole blood in 10-30 minutes.

An alternative approach pursued by Triton BioSystems (www.tritonbiosystems.com) is to bond iron nanoparticles and monoclonal antibodies into nanobioprobes about 40 nanometers long. The chemically inert probes are injected and circulate inside the body, whereupon the antibodies selectively bind to tumor cell membranes. Once the tumor (whether visible or micrometastases) is covered with bioprobes after several hours, a magnetic field generated from a portable alternating magnetic field machine (similar to a miniaturized MRI machine) heats the iron particles to more than 170 degrees, killing the tumor cells in a few seconds. Once the cells are destroyed, the body’s excretion system removes cellular residue and nanoparticles alike. Test subjects feel no pain from the heat generated. Triton BioSystems plans to start designing human tests and ask the FDA for permission to begin human clinical trials in 2006.

Mirkin’s group at Northwestern University uses magnetic microparticle probes coated with target protein-binding antibodies plus 13-nm nanoparticle probes with a similar coating but including a unique hybridized “bar-code” DNA sequence as an ultrasensitive method for detecting protein analytes such as prostate-specific antigen (PSA). After the target protein in the test sample is captured by the microparticles, magnetic separation of the complexed microparticle probes and PSA is followed by dehybridization of the bar-code oligonucleotides on the nanoparticle probe surface, allowing the determination of the presence of PSA by identifying the bar-code sequence.
released from the nanoparticle probe. Using polymerase chain reaction on the oligonucleotide bar codes allows PSA to be detected at 3 attomolar concentration, about a million times more sensitive than comparable clinically accepted conventional assays for detecting the same protein target.

### 2.6. Targeted Nanoparticles and Smart Drugs

Multisegment gold/nickel nanorods are being explored by Leong’s group at Johns Hopkins School of Medicine as tissue-targeted carriers for gene delivery into cells that “can simultaneously bind compacted DNA plasmids and targeting ligands in a spatially defined manner” and allow “precise control of composition, size and multifunctionality of the gene-delivery system.” The nanorods are electrodeposited into the cylindrical 100 nm diameter pores of an alumina membrane, joining a 100 nm length gold segment and a 100 nm length nickel segment. After the alumina template is etched away, the nanorods are functionalized by attaching DNA plasmids to the nickel segments and transferrin, a cell-targeting protein, to the gold segments, using molecular linkages that selectively bind to only one metal and thus impart biofunctionality to the nanorods in a spatially defined manner. Leong notes that extra segments could be added to the nanorods, for example to bind additional biofunctionalities such as an endosomolytic agent, or magnetic segments could be added to allow manipulating the nanorods with an external magnetic field.

Targeted radioimmunotherapeutic agents include the FDA-approved “cancer smart bombs” that deliver tumor-killing radioactive yttrium (Zevalin) or iodine (Bexxar) attached to a lymphoma-targeted (anti-CD20) antibody. Other antibody-linked agents are being investigated such as the alpha-emitting actinium-based “nanogenerator” molecules that use internalizing monoclonal antibodies to penetrate the cell and have been shown, in vitro, to specifically kill leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels, with promising preliminary results against advanced ovarian cancer in mice. However, drug specificity is still no better than the targeting accuracy of the chosen antibody, and there is significant mistargeting, leading to unwanted side effects.

Enzyme-activated drugs, first developed in the 1980s and still under active investigation, separate the targeting and activation functions. For instance, an antibody-directed enzyme-triggered prodrug cancer therapy is being developed by researchers at the University of Gottingen in Germany. This targeted drug molecule turns lethal only when it reaches cancer cells while remaining harmless inside healthy cells. In tests, mice previously implanted with human tumors are given an activating targeted enzyme that sticks only to human tumor cells, mostly ignoring healthy mouse cells. Then the antitumor molecule is injected. In its activated state, this fungal-derived antibiotic molecule is a highly-strained ring of three carbon atoms that is apt to burst open, becoming a reactive molecule that wreaks havoc among the nucleic acid molecules essential for normal cell function. But the molecule is injected as a prodrug – an antibiotic lacking the strained ring and with a sugar safety-catch. Once the sugar is clipped off by the previously positioned targeted enzyme, the drug molecule rearranges itself into a three-atom ring, becoming lethally active. Notes chemist Philip Ball: “The selectivity of the damage still depends on antibody’s ability to hook onto the right cells,
and on the absence of other enzymes in the body that also activate the prodrug.”

A further improvement in enzyme-activated drugs are “smart drugs” that become medically active only in specific circumstances and in an inherently localized manner. Yoshihisa Suzuki at Kyoto University has designed a novel drug molecule that releases antibiotic only in the presence of an infection. Suzuki started with the common antibiotic molecule gentamicin and bound it to a hydrogel using a newly developed peptide linker. The linker can be cleaved by a proteinase enzyme manufactured by *Pseudomonas aeruginosa*, a Gram-negative bacillus that causes inflammation and urinary tract infection, folliculitis, and otitis externa in humans. Tests on rats show that when the hydrogel is applied to a wound site, the antibiotic is not released if no *P. aeruginosa* bacteria are present. But if any bacteria of this type are present, then the proteolytic enzyme that the microbes naturally produce cleaves the linker and the gentamicin is released, killing the bacteria. “If the proteinase specific to each bacterium [species] can be used for the signal,” wrote Suzuki, “different spectra of antibiotics could be released from the same dressing material, depending on the strain of bacterium.” In subsequent work an alternative antibiotic release system triggered by thrombin activity, which accompanies *Staphylococcus aureus* wound infections, was successfully tested as a high-specificity stimulus-responsive controlled drug release system. Other stimulus-responsive “smart” hydrogels are being studied, including a hydrogel-composite membrane co-loaded with insulin and glucose oxidase enzyme that exhibits a twofold increase in insulin release rate when immersed in glucose solution, demonstrating “chemically stimulated controlled release” and “the potential of such systems to function as a chemically-synthesized artificial pancreas.

Nanoparticles with an even greater range of action are being developed by Raoul Kopelman’s group at the University of Michigan. Their current goal is the development of novel molecular nanodevices for the early detection and therapy of brain cancer, using silica-coated iron oxide nanoparticles with a biocompatible polyethylene glycol coating. The minuscule size of the particles – 20-200 nanometers – should allow them to penetrate into areas of the brain that would otherwise be severely damaged by invasive surgery. The particles are attached to a cancer cell antibody or other tracer molecule that adheres to cancer cells, and are affixed with a nanopacket of contrast agent that makes the particles highly visible during magnetic resonance imaging (MRI). The particles also enhance the killing effect during the subsequent laser irradiation of brain tissue, concentrating the destructive effect only on sick cells unlike traditional chemotherapy and radiation which kills cancerous cells but also destroys healthy cells. Nanoparticles allow MRI to see a few small brain tumor cells as small as 50 microns – depending on the cancer type, tumor cells can range from 5-50 microns each and may grow in locations separate from the tumor site, hence are sometimes not visible to surgeons. Fei Yan, a postdoc in Kopelman’s lab, is working on these nanodevices, called the Dynamic Nano-Platform (Figure 1), now being commercialized as therapeutic “nanosomes” under license to Molecular Therapeutics (www.moleculartherapeutics.com). According to the company, “the nanosome platform provides the core technology with interchangeable components that provide ultimate flexibility in targeting, imaging and treatment of cancer and cardiovascular disease indications.”
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Biographical Sketch

Robert A. Freitas Jr. is Senior Research Fellow at the Institute for Molecular Manufacturing (IMM) in Palo Alto, California, and was a Research Scientist at Zyvex Corp. (Richardson, Texas), the first molecular nanotechnology company, during 2000-2004. He received B.S. degrees in Physics and Psychology from Harvey Mudd College in 1974 and a J.D. from University of Santa Clara in 1979. Freitas co-edited the 1980 NASA feasibility analysis of self-replicating space factories and in 1996 authored the first detailed technical design study of a medical nanorobot ever published in a peer-reviewed mainstream biomedical journal. More recently, Freitas is the author of Nanomedicine, the first book-length technical discussion of the potential medical applications of molecular nanotechnology and medical nanorobotics; the first two volumes of this 4-volume series were published in 1999 and 2003 by Landes Bioscience. His research interests include: nanomedicine, medical nanorobotics design, molecular machine systems, diamond mechanosynthesis (theory and experimental pathways), molecular assemblers and nanofactories, and self-replication in machine and factory systems. He has published 32 refereed journal publications and several contributed book chapters, and most recently co-authored Kinematic Self-Replicating Machines (2004), another first-of-its-kind technical treatise.