

NANOBIOTECHNOLOGY

FULFILLING THE PROMISE OF NANOMEDICINE

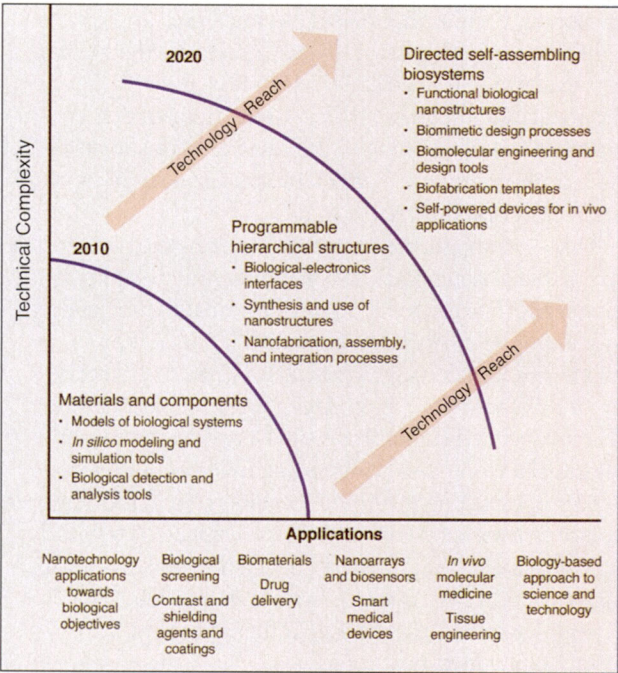
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Leveraging nanotechnology in the life sciences industry has given scientists the potential to transform the world of medicine. Here are some of the remarkable developments being brought to fruition.

The potential of nanotechnology is seemingly endless, promising everything from self-cleaning windows and textiles to nanomachines that generate proteins (according to the blueprint provided by DNA) to create nanoscale, ordered structures for electronic components). As a result, nanotechnology, especially in the life sciences, has been a key driver of research activity and investor interest from governments and industry. In fact, last year, the government poured \$18.3 billion into nanotechnology-related R&D.

The nanosize range refers to anything smaller than 100 nm. The significant point is that at the nanoscale, materials have strikingly different properties vs. their macroscale counterparts. Nanoscience investigates the effects of these properties on materials, people or the environment, while nanotechnologies aim to exploit these properties to create novel structures, devices and systems for different industries.

The application of nanotechnology to biomedical and pharmaceutical sciences — what is now referred to as nanobiotechnology — allows the creation of materials and devices that interact with the body at sub-cellular scales with a high degree of specificity. According to Andrew Broderick, senior consultant at SRI Consulting Business Intelligence, nanobiotechnology's greatest impact has been in the use of nanomaterials, offering improved performance benefits for medical-device coatings, diagnostic contrast agents, analytical components in nanoscale biodetection devices, and advanced drug-delivery systems. So unprecedented is this growth in nanobiotechnology R&D that the collective, monumental effort has been assigned its own moniker — nanomedicine. "It will bring significant advances in the diagnosis and treatment of disease. However, converting research ideas into profitable products will prove to be challenging for industry players," Broderick predicts.



■ Figure 1. The commercial applications of nanobiotechnology will gradually come to fruition. SRI Consulting Business Intelligence.

Technical and market uncertainties, such as regulatory and standards frameworks, are likely to temper the pace of development and lengthen the time frame in which opportunities arise, according to Broderick (Figure 1). "For now, the most important business impact of nanotechnology is that it has encouraged people to identify new opportunities unique to the nanoscale and assess the potential for cross-linking with other technologies to offer breakthrough solutions in various application areas."

Some of the early wins in nanobio are expected in the field of diagnostics. Companies working in this area include Nanosphere Fluorescent and Invitrogen, which acquired Quantum Dot last October, as well as the BioPixels unit of BioCrystal Ltd. to support its Molecular

Probes business. Certain micron-scale technologies that have proven their value in the marketplace (e.g., microarray platforms of Caliper Technologies, Affymetrix and Nanogen) and are regarded as platforms for nanoscale bioanalysis are being honed to improve sensitivity and molecular recognition. Polyprobe has patented self-assembling DNA dendrimers that function as hybridization agents for the detection of nucleic acid sequences.

There are also entrants into the established microarray market that use atomic force microscope tips to detect much smaller amounts of material (e.g., BioForce Nanosciences and NanoInk) for which amplification is not feasible.

Drug delivery applications will provide a solution to solubility problems, as well as offer intracellular delivery possibilities. The use of nanotechnology in implantable devices is also attracting the attention of industry leaders, as nanoscale architecture presents a more size-appropriate interface to biological systems. Companies developing such systems include iMEDD, which is etching nanopores into implantable drug-delivery devices for controlled release of therapeutics, as well as cardiovascular medical products provider Guidant and insulin pump manufacturer Medtronic.

Also being sought are sustainable power sources for implantable nanodevices. A \$6.5 million multidisciplinary national effort is underway to develop a nano-size battery that will power an artificial retina developed at the Doheny Eye Center, Univ. of Southern Calif. to correct certain forms of macular degeneration. Meanwhile, biomimics, namely biological implants such as joint replacements and artificial blood vessels, are being explored under the auspices of tissue engineering. Late bloomers in the marketplace will comprise nanorobots or "nanobots" (e.g., cellular components that can be engineered to generate proteins, enzymes or energy, or even to detoxify blood) could carry out integrated diagnosis and therapies by refined and minimally invasive procedures.

Universal to each step in this process is the need for funding and support. Government funds often provide the early-stage investment in these high-risk, high-payoff technologies, but venture capital will bring them to fruition. A case in point is the U.S. National Institutes of Health's \$43 million grant package to build four nanomedicine R&D centers under the "New Pathways to Discovery" Program. Moreover the National Cancer Institute committed \$144 million to nanotechnology research in October 2004, and 40% of nanotech venture capital since 1998 has gone to life sciences start-ups.

One driver for these investments, say various analysts, is the looming expiration of patents protecting the first-generation therapeutic protein drugs — blockbusters such as insulin, human growth hormone and erythropoietin — coupled with the prospects of stiff competition that these

pioneers are potentially facing from biogeneric companies in terms of production processes and drug applications.

Enter nanoparticles — entities that can be engineered into drug formulations to overcome many of the problems encountered with tailor-made pharmaceuticals and biopharmaceuticals, namely poor solubility, limited chemical stability *in vitro* and *in vivo* (after administration), poor bioavailability and potentially strong side-effects. It's no wonder why pharmaceutical companies are turning to nanotechnology for ways to improve the clinical performance of their first-generation therapeutics — and to protect their intellectual property.

Nanoparticles in therapeutics

Nanoparticulate carriers (such as drug nanocrystals and nanostructured lipid carriers (NLC)) are one way to overcome drug delivery problems. Flamel Technologies of Lyon, France, is leveraging its Medusa drug-encapsulation platform to create a self-assembled, polyamino acid nanoparticle system that binds the drug in a lattice of protein and carrier. Upon injection, the lattice disintegrates, delivering the drug gradually over time. Flamel has teamed up with Bristol Myers Squibb to develop and market an injectable form of Medusa-based human insulin called Basulin, which maintains good insulin blood levels for 24 h.

Nanoprobes' 1.4-nm gold clusters (Nanogold) incorporate an organic shell and spacer arms that allow binding to biomolecules, such as thiol- or amine-containing peptides and proteins. The nanogold particles covalently attach to peptides, while their colloidal gold component enables scientists to visualize molecules, tissues and other structures nonradioactively for *in situ* hybridization, gel staining, peptide or RNA labeling.

Some nanostructures, such as fullerenes, are drug candidates themselves, as they allow precise grafting of active chemical groups in three-dimensional orientations. C-Sixty discovered that C60 fullerene (clusters of C60 carbon atoms), which the firm modified to enhance bioavailability and solubility, is a powerful antioxidant. The company recently entered into an agreement with Merck & Co. to explore the buckyballs' ability to treat or reverse the results of oxidative damage in the body, which are characteristic of neurodegenerative diseases such as multiple sclerosis and Parkinson's disease. "The overall size of modified fullerenes appears to be small enough to cross the brain blood barrier (BBB)," says C-Sixty president Russ Lebovitz, adding that human trials are at least two years away.

Drugs with a sense of direction

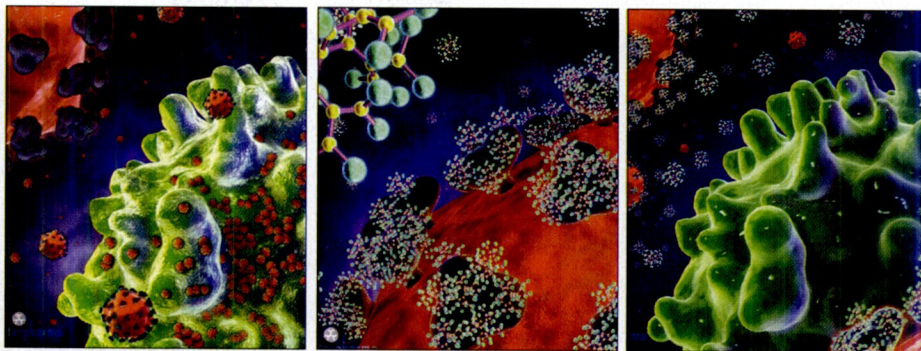
Apart from offering a solution to solubility problems, nanobiotechnology provides targeted or "smart" delivery possibilities. The PathFinder tech-

nology, an innovation of Rainer Müller at Free Univ. of Berlin, Germany, is based on the identification of naturally occurring mechanisms for the localization of material (e.g., proteins) in different parts of the body and uses these principles for the controlled production of site-specific nanoparticulate carriers. These carriers adsorb the targeting molecule (or "pathfinders") from the blood stream. The adsorbed entity determines the cells to which the nanoparticles travel.

Müller identified apolipoprotein E (aE) as a protein that was preferentially absorbed by the brain. He designed a nanocrystal with the physico-chemical surface properties needed to adsorb aE from the blood, and incorporated atovaquone, a drug used to treat Lyme disease, into the crystal. After intravenous injection, the particles "accumulated to a sufficiently therapeutic level in the BBB," says Müller. A U.S. patent has been granted (Radtke and Müller, 2001b), and the European patent is in the process of being issued.

Dendrimers — highly branched polymeric macromolecules structured as concentric shells — also have a surface chemistry that can be modified to hold therapeutic drugs or molecules for tissue-specific recognition. Dendritic NanoTechnologies (DNT) is preparing for FDA Phase I clinical trials to demonstrate the ability of its Starburst and Priostar dendrimers to deliver precise quantities of drugs or contrasting agents to specific locations within the human body. In 2005, Dow transferred its entire dendrimer-related patent portfolio — nearly 200 patents — to DNT (which already holds 30 dendrimer-related patents), in exchange for a major equity stake in the company.

Meanwhile, Starpharma Holdings Ltd., which has a 42% equity interest in DNT, works with modified dendrimers that exhibit "polyvalency," or affinity to multiple regions on a target. The company's VivaGel (SPL7013 gel) — the first dendrimer-based application submitted to the FDA for regulatory approval — is a topical vaginal microbicide that prevents the transmission of HIV and various



■ Figure 2 (left). The HIV virus (red and purple) infects human T-cells (green) by attaching to receptors on the surface of the T-cell. The infected cell causes the replication of new virions, which are released from the cell via budding. This causes cell destruction and leads to a loss of immune function that is typical of HIV infection.

■ Figure 3 (center). The active ingredient of VivaGel is a dendrimer (blue molecule) called SPL7013. Its internal scaffold (pink) enables the polyvalent presentation of surface groups (blue) that give VivaGel activity against HIV and the herpes virus.

■ Figure 4 (right). The active dendrimer (blue), binds to the active surface protein of HIV, called gp120, thereby blocking infection of human cells (green).

Images are courtesy of StarPharma Holdings Ltd.

sexually communicable diseases. Unlike other nanoparticles, SPL7013 exploits the mechanical properties of the dendrimer as the basis, rather than the vehicle, for therapeutics. The gel contains an anionic poly(amidoamine) (PAMAM) dendrimer that binds with the HIV surface protein gp120, thus interfering with the fusion of the HIV molecule with human T-cells (Figures 2–4). Last month, the FDA granted "fast track" status to VivaGel — a designation that allows a given New Drug Application to move more quickly through the regulatory-approval process. VivaGel is now entering Phase II clinical trials.

The highly branched, yet compact PAMAMs (2–13 nm in dia.) form the basis of a targeted anti-cancer drug-delivery platform designed by Univ. of Michigan's James Baker, Jr. His G5 dendrimer, with a diameter of 5 nm and enough surface area to attach as many as 110 targeting, therapeutic and/or imaging molecules, has been used to ferry the anti-cancer drug methotrexate into cancer cells using folate as the targeting molecule. Folate targets folic acid receptor that many cancer cells overexpress.

When tested in laboratory mice that had received injections of human epithelial cancer cells, these methotrexate-loaded dendrimers were 10 times more effective than the drug alone at delaying tumor growth and was less toxic to the mice than the anti-cancer drug alone. Baker has launched a company, Avidimer Therapeutics (formerly NanoCure Corp.), through which he hopes to begin human trials over the next few years.

Acknowledgments

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Visit www.aiche.org/cep for a comprehensive set of tables describing the technology platforms of nanotechnology companies working in the life science industries