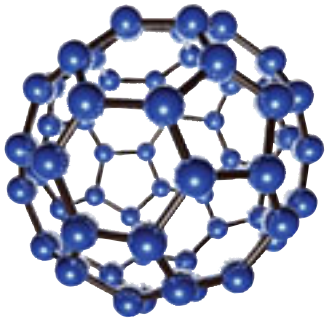
Good things in small packages

Nanotech advances are producing mega-results in drug delivery.

BY RANDALL C. WILLIS



Whether it costs $500 million or $1.5 billion to get a drug to market, the fact remains that a good portion of this exorbitant price tag results from drugs failing late in clinical trials or during the postmarket follow-up (Phase IV). For all of the technical advances that allow researchers to identify greater numbers of lead compounds, pharmaceutical specialists are still challenged by getting the right compound to the right spot in the human body where it can have the maximum effect.

Most drugs are delivered to patients using a systemic approach, the belief being that if you flood the body with enough active compound, some of it will find the affected organ, tissue, or cell. For example, anticancer drugs targeting actively dividing cells don't inherently differentiate between tumor and healthy growing tissue. In homage to a Monty Python skit, if you blow up enough bushes, you will eventually find the one in which someone is hiding.

To address this problem, and mitigate some of the costs associated with drug failure, pharmaceutical scientists expend much effort in finding ways to selectively target therapeutics. In some cases, they conjugate the active ingredient to antibodies against specific cell-type markers in the belief that the hybrid molecule will find its way to and bind the disease tissue specifically. Other researchers try to identify and target metabolic pathway entry points specific to a given disease. But even these targeted-delivery mechanisms typically can only deliver one drug molecule per interaction.

Thinking small

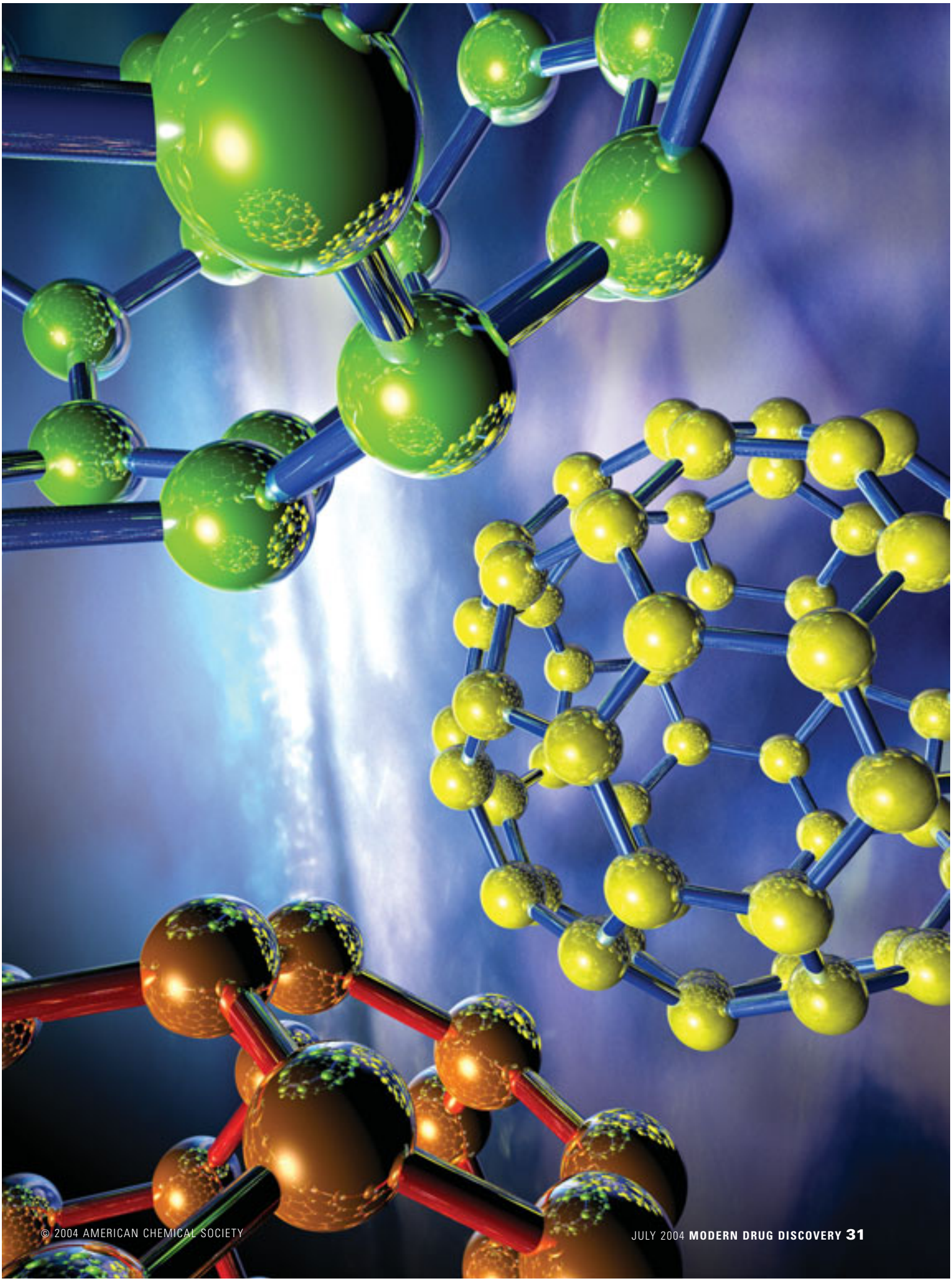
In looking to address these challenges, numerous drug developers are turning to nanotechnology. Coming in many shapes and sizes—although most carriers are less than 100 nm in diameter—nanotech drug delivery systems (nanoDDSs) provide methods for targeting and releasing large quantities of therapeutic compounds in very defined regions. By no means a panacea for all pharmacokinetic difficulties, these vehicles have the potential to eliminate or at least ameliorate many problems associated with drug distribution.

Because many drugs have a hydrophobic component, they often suffer from problems of precipitation in high concentration, and there are many examples of toxicity issues with excipients designed to prevent drug aggregation. To combat this problem, many nanoDDSs provide both hydrophobic and hydrophilic environments, which facilitate drug solubility.

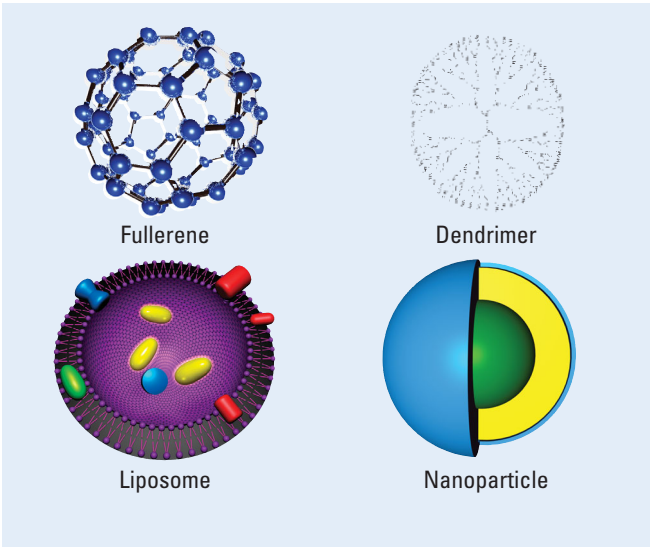
Alternatively, many drugs suffer from rapid breakdown and/or clearance in vivo. By encapsulating or otherwise protecting such compounds from harsh environments, nanoDDSs increase their bioavailability and thereby allow clinicians to prescribe lower doses. Likewise, several studies have shown that nanoparticle encapsulation greatly inhibits renal clearance of drugs.

One problem with many cytotoxic drugs is secondary tissue damage caused by inadvertent drug leakage through vascular walls (extravasation). By regulating drug release using biodegradable polymer matrices in nanoDDSs, however, researchers can reduce or limit the chances of this problem occurring. Similarly, the particulate nature of most nanoDDSs reduces the effective distribution volume and thus the likelihood of side effects.

Finally, unlike the targeting mechanisms already described, where the ratio of drug molecule to targeting partner is approx-



imately 1, many nanoDDSs can carry hundreds or thousands of drug molecules. Thus, rather than simply providing a slow, progressive flow of active ingredients to disease tissue, nanoDDSs have the potential to deposit repeated significant drug doses over a short time.



Nanotech drug delivery systems come in all shapes and sizes.

Drugs in particular

With recent advances in polymer and surface-conjugation chemistries, as well as microfabrication methods, perhaps the greatest focus in drug delivery technology is in the design and application of nanoparticles. Ranging from simple metal- or ceramic-core structures to complex lipid–polymer matrices, these submicron formulations are being functionalized in numerous ways to act as therapeutic vehicles for a variety of conditions.

For example, NanoMed Pharmaceuticals (*www.nanomedpharm.com*) is focusing its efforts on delivering drugs to the brain and immune system using its Nanotemplate Engineering technology platform. According to company co-founder, president, and CEO Stephen Benoit, NanoMed scientists can manufacture stable nanoparticles with neutral, cationic, or anionic surface chemistries in minutes using pharmaceutically acceptable materials, such as long-chain alcohols, phospholipids, or polymeric surfactants. They can then encapsulate or adsorb various molecules onto these beads and target specific tissues or cells using pre- or postincorporation of cell-specific ligands.

In targeting central nervous system (CNS) disorders, however, NanoMed researchers face the daunting challenge of the blood–brain barrier (BBB).

"To effectively treat and ultimately cure CNS conditions, such as brain cancer, stroke, and Alzheimer's and Parkinson's diseases, a drug needs to be able to cross the BBB," Benoit explains. "About 95% of today's therapeutics cannot do this, however, and must be delivered invasively via direct injection into the brain or cerebrospinal fluid, or be released from a device that has been implanted into the brain."

Using the company's technology, however, Benoit says NanoMed scientists can manufacture nanoparticles that mask a drug's BBB-limiting characteristics; enable targeted delivery via BBB transporters; and provide a sustained release in brain tissue, which could reduce dosage frequency, peripheral toxicity, and adverse effects.

"Initially, NanoMed is focusing on the development of paclitaxel NP to treat primary and metastatic brain tumors," Benoit relates. "Paclitaxel, an approved chemotherapeutic agent, has been shown to be effective in treating brain cancers in multiple independent animal and human studies wherein the BBB was bypassed or saturated following administration of an atypical dose. At standard therapeutic doses, however, paclitaxel is severely limited from getting into the brain by the P-glycoprotein efflux pump."

Thus, Benoit suggests, by effectively surmounting the BBB, paclitaxel NP allows clinicians to prescribe lower (and thereby safer) drug doses and still maintain efficacy.

Another company with nanoparticle expertise is Germany's NanoDel Technologies (*www.nanopharm.de*). Using the NanoDel system, scientists can either adsorb a drug to the surface of poly(butyl cyanoacrylate) particles or incorporate it directly into the particle during the polymerization process. They then coat the coformulation with a surfactant, such as polysorbate 80, to facilitate shelf life and biodistribution. According to company CEO Karim Balan, NanoDel does not know what prompts cells to take up the nanoparticles, but he speculates the reaction is likely mediated through receptor endocytosis.

"We believe that apolipoprotein E and/or B quickly adsorbs on the surface of polysorbate-coated nanoparticles in human plasma," Balan explains. "Apo B and E are known to bind lipoprotein (e.g., LDL) receptors on the surface of cells, which have been identified in rat and monkey brains and in brain capillary epithelia. Thus, the polysorbate 80-coated nanoparticles seem to mimic lipoprotein particles that interact with members of the LDL receptor family."

Although the company has only experimented in animal models to date, it has seen good results with a variety of analgesic, antiepileptic, and neuromodulatory drugs, both in proving that the nanoparticles get to the right cells and in modifying test subject behavior. Similarly, NanoDel has seen positive results with doxorubicin nanoparticles, which it used to successfully treat transplanted brain tumors in rats.

NanoDel has no therapeutic pipeline per se, deciding to focus its efforts instead on developing new nanoparticle polymers, but it licenses its technology to pharmaceutical and biotechnology companies and is looking to initiate co-development efforts.

Oil and water

Whereas NanoMed and other companies are striving to design nanoparticle systems where the active ingredient is encapsulated or surface-bound, other companies are formulating particle systems where drug molecules are part of the bead's construction material. Because therapeutically active compounds tend to be lipophilic or have a lipophilic component, this second population of nanoparticles tends to be an oil–water emulsion.

For example, scientists at Kereos (*www.kereos.com*) are developing particles comprising one or more perfluorocarbons, which provide a biologically inert substrate, surrounded by a lipid surfactant layer. According to company CEO Robert Beardsley, the lipid layer provides a noncovalent anchor for lipophilic derivatives of various biomarker ligands, such as small molecules and antibodies, or for a large payload of lipophilic or lipophilic-derivatized agents.

"With each emulsion particle bearing from 10 to a few hundred targeting ligands, multiple binding interactions with the cell-surface biomarkers provide exceptional selectivity and avidity," Beardsley explains. "The real key, however, is the fact that each particle can carry as many as 100,000 payload molecules and yet be very specifically targeted to the disease site. This thousandfold amplification is what allows these products to address medical needs that have frustrated other methods."

Kereos is focusing on the application of its nanoparticle system as medical imaging agents, particularly for magnetic resonance imaging (MRI), and as drug delivery vehicles for the diagnosis and treatment of cardiovascular disease and cancer. In theory, the same target ligands that find a tumor and deliver large doses of MRI contrast agents for early cancer detection could be subsequently used to target the offending tissue with chemotherapeutic agents.

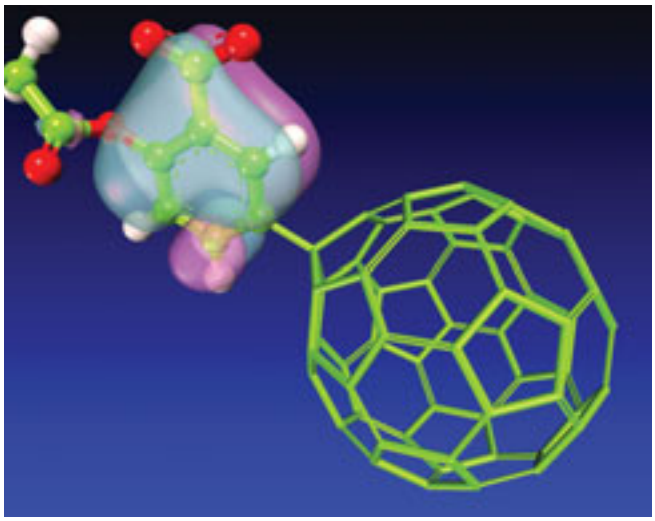
"In cardiovascular disease, one of the shortcomings of current treatments is the inability to detect or directly treat unstable atherosclerotic plaque, a root cause of a majority of heart attacks," Beardsley says. "With Bristol-Myers Squibb Medical Imaging, we've partnered our first product to image unstable plaque."

On the therapeutic front, Kereos has developed a ligand-targeted emulsion formulation of an approved chemotherapeutic agent against solid tumors, which should enter clinical trials in 2006. Likewise, the company has seen very promising results in animal models with a product targeting unstable plaque, and hopes to begin clinical trials in 2007.

Fulsome fullerenes

Starting with what is arguably the canonical nanostructure, researchers at C Sixty (*www.csixty.com*) are using fullerenes less as drug delivery devices and more as actual therapeutic macromolecules. According to Russ Lebovitz, company vice president of research and business development, these soccer-ball-like structures, ranging in composition from 20 to 84 carbon atoms, are strong antioxidants, capable of scavenging a variety of free radicals associated with medical conditions such as neurodegenerative disease, stroke, and diabetes. Often reactive oxygen species, free radicals use their unpaired electrons to break chemical bonds in critical molecules, such as nucleic acids, thereby triggering cell damage and possible apoptosis. C Sixty researchers believe fullerenes interrupt this process by acting as a "radical sponge," essentially absorbing the potentially damaging electrons.

ILLUSTRATION: ACCELRYS



Buckyaspirin

In their natural form, however, fullerenes are insoluble. Thus, C Sixty's drug development platform focuses on devising methods to add chemical functional groups and thereby improve compound solubility and targeting. Initially, the company modified its fullerenes with malonic acid moieties, creating a compound it called C3, which showed strong activity in animal models of neurodegenerative diseases. Later, lead compounds relied on adding large branched structures called dendrimers to facilitate water solubility, and, more recently, company researchers have explored using peptides and antibodies as targeting mechanisms. According to Lebovitz, this effort is resulting in lead compounds that essentially function like small-molecule drugs in terms of biodistribution and pharmacokinetic behavior.

"Our products are all in the preclinical testing phase," Lebovitz says. "And we have licensed one of our compounds to Merck for preclinical evaluation."

Liposome-like systems

An increasingly popular drug delivery method is the use of liposomes—small spheres composed of a lipid layer surrounding an active pharmaceutical ingredient. As recently described in *Modern Drug Discovery* (January 2004, pp 36–39), several companies have made significant progress in using these macromolecular complexes to tackle everything from cancer to infectious disease. But whereas these companies are relying on artificial liposomal constructs, companies like California-based Anosys (*www.anosys.com*) have turned to biology for clues about liposome-like delivery vehicles.

Most cells in the body use small vesicles called exosomes to transmit important signals from one cell to another. In the immune system, dendritic cells receive antigens from tumors or infecting viruses and incorporate them into antigen-presenting molecules (major histocompatibility complexes, or MHCs) on the cell surface. There, they are recognized by T cells that then destroy other antigen-presenting cells. The dendritic cells also form MHC-bearing exosomes (dexosomes) that pass to other dendritic cells and thereby amplify the immune response.

According to Anosys CSO Jean-Bernard Le Pecq, Anosys scientists realized dexosomes could be used to prepare potent vaccines and therefore set out to develop methods to both isolate dexosomes and determine how to get them to present other target molecules to the immune system. In particular, the com-

pany is using natural and artificial dexosomes to target cancer.

"In this disease, a state of immune tolerance has been established," Le Pecq explains. "Thus, simple vaccine approaches that are efficacious as preventative treatments of infectious diseases are unable to break through this tolerance."

By incorporating cancer-related antigens to dendritic cells via dexosomes, Anosys scientists can effectively immunize people against a particular cancer or trigger an immune response that will hopefully help the body fight a tumor. According to Le Pecq, Anosys has recently completed Phase I clinical trials in lung cancer and melanoma and will shortly initiate Phase II trials. Likewise, it also hopes to begin trials on treatments of cervical, pancreatic, and prostate cancer.

Size matters

Regardless of the drug delivery vehicle format or formulation, there is every indication that nanotech methods will continue to be an active research avenue in the pharmaceutical community.

"Smaller is better," NanoMed Pharmaceuticals' Benoit opines. "Below 100 nm, materials exhibit different, more desirable physical, chemical, and biological properties. Given the enormity and immediacy of the unmet need for therapeutic areas, such as central nervous system disorders, substantial investment is warranted in technologies, including nanotechnologies, that can lead to the development of new drugs that can extend, and ultimately save, lives."

"Last, but not least," NanoDel Technologies' Balan adds, "In view of the drugs going off patent at Big Pharma and with no new drugs in the pipeline, the strategy is to defend the old drugs from generic attack by creating and patenting new galenic formulations and so extend the life cycle of the old drug." ■

Reading the nano print

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