

NANOBIOTECHNOLOGY

CANCER'S NEWEST DEADLY FOE

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An array of nanoscale developments are poised to revolutionize cancer-diagnosis and drug-discovery efforts, and create new ways to target the delivery of potent, often toxic drug therapies, while reducing their dose-limiting side effects.

Cancer. There was a time when that dreadful diagnosis signaled a sure-fire death sentence for its recipient. Today, such a dire outcome is no longer a foregone conclusion, thanks to the tireless efforts of cancer researchers worldwide.

In recent years, medical, life sciences and oncology pioneers have partnered with the engineering and material science communities in search of more-effective diagnostic tools that will allow them to pinpoint particular cancers earlier, clever mechanisms to destroy tumors non-invasively and without drugs, and more-targeted ways to make higher doses of potent cancer drugs work more effectively on cancerous cells, while sparing healthy cells and minimizing chemotherapy's many side effects.

Over the past several decades, nanotechnology has become a widely celebrated scientific discipline in industrial and academic circles. So, it is no surprise that the medical community seeks to exploit the intrinsic properties and performance advantages associated with nanoscale materials, devices and systems — namely the extraordinary surface-area-to-volume ratio and novel properties that they demonstrate at these unimaginably small dimensions — in the war against cancer.

CANCER DETECTION AND DIAGNOSIS

The prevailing wisdom in cancer care is that when detected early, many cancers are treatable, and that early intervention leads to better outcomes. Thus, devising more-effective strategies to detect cancer on a molecular level, before advanced-stage tumors have formed, is a priority for nano-related medical researchers.

Quantum dots

Over the last two decades, the evolution of fluorescent semiconductor nanocrystals known as quantum dots has ushered in a new era in medical and laboratory diagnostics. These nanocrystals are typically made of cadmium selenide, cadmium sulfide or cadmium telluride, and have an inert polymer coating that both safeguards human cells from potential cadmium toxicity, and facilitates the attachment of a variety of molecules to foster the preferential uptake by targeted cells.

Quantum dots can be tailored to absorb and emit light of different wavelengths by changing their diameters. In turn, the dots can be used to color-code and track different cell processes, cancers or stages of the same cancer, explains UCLA researcher Xavier Michalet.

Working with Stanford Univ. researcher Shimon Weiss, Michalet is pursuing quantum dots for high-resolution cellular imaging and the long-term observation of individual molecules and their intracellular movements. For instance, this team has labeled quantum dots with a positron-emitting isotope and injected them into mice. Then, using positron emission tomography (PET) scanning, the researchers observed the movement of the quantum dots over time through the vascular system and to the liver. With their narrow, symmetric emission spectra, these highly luminescent quantum dots are said to outperform some of the chemical and organic dyes that are used for conventional radiological imaging.

New research suggests that quantum dots that are imaged using a fiber optic scope could provide an improved method for earlier detection of cervical cancer. The theory is being investigated by Rebecca Richards-Kortum of the Univ. of Texas at Austin and Michelle Follen of the MD Anderson Cancer Center in Houston, TX. They have developed a water-soluble formulation of fluorescent quantum dots labeled with a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Because cervical cells that increase their production of EGFR are likely to become malignant, the presence of EGFR is being investigated as an early predictive marker for cervical cancer.

Using the labeled quantum dots, which fluoresce strongly when irradiated with white light, the Texas investigators were able to distinguish between cultured cells that overproduce EGFR and those that do not. Animal testing is being planned.

Meanwhile, to improve the sensitivity of quantum dot-based assays, researchers at Vanderbilt Univ. have found a way to modify quantum dots by attaching short pieces of the biocompatible polymer polyethylene glycol (PEG). According to lead investigator Sandra Rosenthal, this modification helped the dots to substantially reduce

nonspecific binding to various cell types, and had no negative impact on their fluorescence.

To address concerns about the potential toxicity associated with the heavy metals found in traditional quantum dots (most often cadmium, but in some cases, lead), Evident Technologies has commercialized its T2-MP EviTags. Containing no heavy metals, these dots are based on a new type of indium gallium phosphide (InGaP), and can be used for fluorescent labeling in a variety of life sciences applications, especially *in vivo* imaging.

Last October, to bolster its Molecular Probes advanced biomolecular labeling and detection product offerings, Invitrogen Corp. acquired both Quantum Dot Corp., — which is said to hold the broadest intellectual property portfolio in the life sciences industry for semiconductor nanocrystals, with more than 160 patents and applications — and the BioPixels unit of BioCrystal, Ltd., which provides novel coatings and metal alloys for quantum dots.

Functionalized magnetic nanoparticles

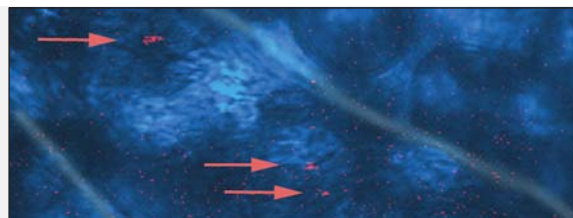
Recently, a team of investigators led by Jeon-Soo Shin and Jinwoo Cheon of Yonsei Univ. in Seoul, South Korea, has shown that using antibody-labeled magnetic nanocrystals in conjunction with magnetic resonance imaging (MRI) can improve the detection of breast cancer cells in a living animal. The researchers have modified their nanocrystals by attaching an antibody that binds tightly to the so-called HER2/neu receptor. This receptor is overexpressed in certain types of breast cancers and is targeted by the anticancer therapy Herceptin (trastuzumab). When injected into mice bearing human breast tumors, this formulation traveled quickly to the site of the tumors and rendered them visible in an MRI scan within an hour of nanocrystal injection.

Alnis BioSciences has also developed a magnetic nanoparticle formulation called MagNaGel, to improve tumor detection using MRI. Meanwhile Advanced Magnetics' Combidex platform was approved last March by the FDA as an MRI imaging agent for cancer detection in lymph nodes. Combidex consists of ferumoxtran-10 nanoparticles, which accumulate in non-cancerous lymph node tissue, thereby enabling doctors using MRI to have improved diagnostic confidence.

Gold 'nanorods,' carbon nanotubes

Researchers at Purdue Univ. are relying on tiny "nanorods" of gold, which are roughly 200 times smaller than a red blood cell, to create an ultra-sensitive medical imaging technique for cells. By injecting the rods into the bloodstream of mice and shining a laser through the skin, these researchers produced images nearly 60 times brighter than those made using conventional fluorescent dyes, including rhodamine (Figure 1).

Meanwhile, because their optical and electrical conductivity properties can be readily manipulated, carbon nanotubes are also being pursued to improve diagnostic



■ Figure 1. Gold nanorods, which fluoresce red, were photographed inside the blood vessels of a live mouse by researchers at Purdue Univ. Photo courtesy of Purdue's Weldon School of Biomedical Engineering and Dept. of Chemistry.

imaging applications. Nanotubes are seamless, single-walled or multi-walled cylinders composed of carbon atoms in a regular, hexagonal arrangement.


For use in diagnostic imaging applications, carbon nanotubes have several advantages over fluorescent proteins and quantum dots — namely, the cadmium found in quantum dots is toxic to living cells, and nanotubes produce a narrower, more precise beam of light, which may make them easier to detect.

However, nanotubes have been found to be relatively inefficient at converting absorbed light into emitted light. For instance, because of tiny structural defects, many nanotubes can absorb up to a thousand photons for every photon they emit (a ratio called quantum efficiency), according to researchers at Vanderbilt Univ., Siegen Univ., and the Max Planck Institute, led by Vanderbilt's Tobial Hertel. In fact, their work reveals that some individual carbon nanotubes can be 1,000% more efficient than others. The scientists hope that as their nanotube-synthesis processes are improved to reduce structural defects, their overall efficiency in diagnostic imaging will improve.

By inserting gadolinium (Gd) into carbon nanotubes, researcher Lon Wilson of Rice Univ. has been able to produce improved contrasting agents for high-resolution MRI. The Gd-bearing nanotubes created and tested at Rice are said to be more powerful than conventional contrasting agents. And, according to Wilson, Gd-C nanostructures can be cycled in magnetic fields to kill targeted cells via thermal ablation.

TARGETED DRUG DELIVERY

Today's nanotech pioneers are working to identify, synthesize and deploy a diverse array of nanoscale structures and devices that improve the way in which highly effective therapeutic agents are administered — especially those that are underutilized because they are either hydrophobic and are thus poorly soluble in blood and other human cells, or those that have severe, dose-limiting side effects. Their arsenal includes biodegradable and biocompatible polymeric nanoparticles and dendrimers, nanocages and silica-gold nanoshells, which smuggle tiny payloads of anticancer drugs or imaging agents into cancer cells (Note that dendrimers are discussed in article appearing on pp. 35–37). Efforts are also underway to engineer effective triggering mechanisms to get these pint-sized Trojan horses, once accumulated within cancer



cells, to release their payload on demand, either suddenly or in a sustained, time-release fashion.

Consider the example of hydrophobic paclitaxel — better known as Taxol. To make paclitaxel more soluble, this powerful anticancer drug is often mixed with various toxic solvents, a step that limits the amount of drug that patients can receive and often calls for the use of corticosteroids to counteract solvent toxicity.

In January 2005, American Bioscience received final approval from the U.S. Food and Drug Administration (FDA) for its drug Abraxane, for patients with metastatic breast cancer who have failed combination chemotherapy. Abraxane consists of nanoparticles made of albumin that contain paclitaxel. American Pharmaceutical Partners markets this drug.

Compared to patients getting paclitaxel alone, Abraxane allows patients to safely receive 50% more paclitaxel per dose, according to its maker. And, in clinical trials involving 454 patients with metastatic breast cancer showed, those receiving Abraxane achieved almost a doubling of tumor-response rate, compared to those receiving paclitaxel alone.

Polymer-based nanoparticles

While Abraxane uses albumin-based nanoparticles, many researchers are focusing their efforts on developing novel polymer-based nanoparticles to improve drug delivery. For instance, scientists at Rutgers Univ., led by Joachim Kohn, have developed a biocompatible polymer, comprising both water-soluble segments and water-insoluble segments that self-assemble when added to water, forming compact nanoparticles (40–70 nm in dia.) that entrap poorly soluble drugs. Kohn's team has confirmed that paclitaxel-loaded nanoparticles were readily taken up by cultured tumor cells, that the loaded nanoparticles were as toxic to the cells as was a comparable amount of paclitaxel alone, and that drug-free nanoparticles were not toxic to the cells.

Meanwhile, in preclinical results, the anti-cancer drug IT-101, which combines the potent anti-cancer compound camptothecin with Cycloset nanoscale drug-delivery polymers from Insert Therapeutics, a subsidiary of Arrowhead Research Corp., has demonstrated its efficacy against non-small-cell lung cancer, Ewing's sarcoma, and other tumor types. While the use of camptothecin alone has never been FDA-approved for use in humans due to its toxicity, instability and insolubility in human blood, two approved analogues of the drug, irinotecan and topotecan, currently enjoy annual sales of more than \$1 billion/yr. Insert is currently preparing to begin human clinical trials using IT-101.

For most nanoscale drug-delivery applications, encapsulating the cancer drug or imaging agent represents only half the battle. Getting the particles to accumulate preferentially within target cells is equally important. To do this, researchers are working to attach a variety of targeting ligands, such as peptides, proteins or antibodies, to nanoparticle surfaces (p. 37).

Meanwhile, at the National Univ. of Singapore, a team led by Kee-Yong Lim, has attached a protein called wheat germ agglutinin (which binds to specific sugar molecules on cell surfaces) to paclitaxel-loaded nanoparticles made from a biocompatible polymer poly(lactic-co-glycoside) (PLGA). When injected directly into tumors growing in mice, a single injection stopped tumor growth for at least 25 days, while tumors injected with paclitaxel alone doubled in size in 11 days.

Researchers at the Univ. of Nebraska Medical Center, led by Vinod Labhsetwar and Sanjeeb Sahoo have focused on transferrin — a naturally occurring protein that transports iron through the bloodstream — to help breast cancer cells preferentially absorb paclitaxel-loaded nanoparticles made from PLGA. They showed that the cells with higher loadings of their loaded, targeted nanoparticles experienced higher morbidity rates compared to those receiving untargeted, drug-containing nanoparticles, or paclitaxel alone. According to the researchers, this form of the drug was even able to kill breast cancer cells that had developed resistance to paclitaxel therapy.

Nucleoside analog triphosphates, which can sabotage cell growth by blocking DNA replication, have been touted as promising anticancer agents. However, their utility has been limited, because they are quickly degraded by naturally occurring enzymes in the body before they can reach tumors. To solve this problem, Alexander Kabanov and his colleagues at the Univ. of Nebraska Medical Center have encapsulated this therapeutic agent using hydrophilic nanoparticles that are made from polyethyleneimine (PEI), coated with polyethylene glycol (PEG), and targeted using folate (folate targets a high-affinity folic acid receptor that is overexpressed in many cancer cells). Their work has shown that cultured breast cancer cells readily took up the targeted nanogel particles and that this drug-nanogel formulation was far more toxic to the cancer cells than was either of the two controls.

Another anticancer strategy, photodynamic therapy (PDT), relies on a light-sensitive photosensitizer chemical which, when exposed to light, produce “reactive oxygen” that destroys cancer cells. A multi-institutional research team led by Ralph Weissleder of the Massachusetts Inst. of Technology (MIT) Harvard Center of Cancer Nanotechnology Excellence developed a polymer-based nanoparticle to ferry photosensitizers more effectively into cancer cells. When the therapy was injected into tumor-bearing mice, and light therapy was administered 24 hours later, the nanoparticle-borne photosensitizer accumulated preferentially in tumor cells, and was shown to kill those cells when exposed to light, while inflicting less collateral damage to healthy cells nearby.

While many nanotechnology researchers are working with hydrophobic (poorly soluble) anticancer drugs, researchers at Cardiff Univ. in Wales, led by Ruth Duncan, are developing nanoscale polymer-drug combinations that can improve the delivery of certain water-soluble anticancer drugs to tumors. Duncan's group

employs doxorubicin and platinum compounds, whose efficacy in cancer therapy is proven, but whose severe dose-limiting toxic effects limit their widespread use. Early results from human clinical trials involving her polymer-doxorubicin formulation has shown a five-fold reduction in toxicity vs. free doxorubicin. Once inside the cell, targeted enzymes cleave the drug molecules from the nanoparticle carrier.

The proprietary NanoGels from Alnis BioSciences can also incorporate bioactive components and include tumor-targeting ligands to effectively ferry potent drugs into cancer cells. Meanwhile, its MagNaGels line of nanoparticles includes a magnetic core to allow the nanoparticles to be manipulated using an external magnet. For instance, by using an alternating magnetic field, these magnetic particles can be heated locally to destroy tumors and to improve tumor detection using MRI. The NanoGel formulations also being used to encapsulate antibiotics to combat microbial infections.

Other companies that are working to commercialize novel, nanotechnology-based drug-delivery platforms for third-party product developers include Access Pharmaceuticals, whose Nanoparticle Aggregate Technology is being developed to deliver therapeutic, water-soluble proteins, pSivida Limited, whose BioSilicon product line includes a family of nanotechnology-based, drug-delivery products, and MIV Therapeutics, developer of the Smart III nanoparticles to ferry drug and imaging agents into patients via drug injection, inhalation, spraying, pill or capsule ingestion.

Similarly, Elan Corp. and EntreMed recently entered into a licensing agreement in which EntreMed was given the right to use Elan's proprietary NanoCrystal Technology (a nanoscale drug-delivery platform for poor-

ly-water-soluble compounds) to develop its oncology product candidate Pannzem NCD (2-methoxyestradiol). That product is already in Phase 1 trials, and Phase 2 trials are expected to begin in 2006.

Meanwhile, to precisely engineer the release of drugs within a tumor microenvironment, MIT's Robert Langer, along with colleague Michael Cima, has invented an implantable microfluidic device with programmable circuitry to facilitate the sustained local release of specific quantities of the potent anticancer drug carmustine (also known as BCNU). The drug is stored in nanoscale reservoirs that are capped with thin gold membranes, which are dissolved using electric current to release the drug. Langer notes that animal testing was successful and that further work will evaluate the microfluidic device against a particular polymer-based, local-delivery device that is now being tested in humans.

THERMAL ABLATION

While novel drug-delivery platforms show great promise, another nanotechnology-based way to treat cancer that is gaining a foothold among researchers is to target cancer cells non-invasively, using not drugs but heat to destroy malignant cells from the inside out. While the specific approaches vary, they all rely on a unifying concept — first, some type of magnetic nanoparticle is introduced to cancer cells or tumors, and then, an exogenous energy source (via laser or magnetic activation) is applied to generate heat that destroys the diseased cells. Researchers are evaluating the use of carbon nanotubes, iron oxide nano-particles, gold nanoshells and gold nanocages to function as such "thermal scalpels."

Gold nanoshells are hollow spheres of non-conducting silica with an ultra-thin gold coating. When exposed to

Companies applying nanotechnology to cancer diagnosis and treatment.

CANCER DETECTION AND DIAGNOSTICS

BioCrystal (biocrystal.com)
Evident Technologies (evidenttech.com)
Invitrogen (invitrogen.com)
MagnaMedics GmbH (magnamedics.com)
Max Planck Institute (mpg.de)
Nanobiotix SA (nanobiotix.com)
Purdue Univ. (purdue.edu)
Quantum Dot (qdots.com)
Siegen Univ. (uni-siegen.de)
Stanford Univ. (stanford.edu)
Univ. of California, Los Angeles (ucla.edu)
Univ. of Texas at Austin (utexas.edu)
Vanderbilt Univ. (vanderbilt.edu)

TARGETED DRUG DELIVERY

Access Pharmaceuticals (accesspharma.com)
Acusphere (acusphere.com)
Alnis BioScience (alnis.com)
Amer. Bioscience, formerly Vivox Pharmaceuticals
Amer. Pharmaceutical Partners (appdrugs.com)
Arrowhead Research (arrowres.com)
Avidimer Therapeutics (avidimer.com)
Cardiff Univ. (cardiff.ac.uk)
Dendritic NanoTechnologies (dnanotech.com)
Dow Chemical (dow.com)
Elan (elan.com)

EntreMed (entremed.com)
Georgetown Univ. (georgetown.edu)
Immunicon (immunicon.com)
Insert Therapeutics (inserttherapeutics.com)
Jefferson Univ., Kimmel Cancer Ctr. (kcc.tju.edu)
Midatech Group (midatechgroup.com)
MIV Therapeutics (mivtherapeutics.com)
Nanogen (nanogen.com)
Nanospectra Biosciences (nanospectra.com)
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Univ. of Tokyo (tokyo.edu.jp)

THERMAL ABLATION

Georgia Institute of Technology (gatech.edu)
MagForce Nanotechnologies (magforce.de)
MD Anderson Cancer Center (mdanderson.org)
NanoBioMagnetics (nanobmi.com)

Oak Ridge National Laboratory (ornl.gov)
Rice Univ. (rice.edu)
Triton BioSystems (tritonbiosystems.com)
Univ. of California, San Francisco (ucsf.edu)
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Univ. of Paris (paris.edu)
Yonsei Univ. (yonsei.ac.kr)

DRUG DISCOVERY

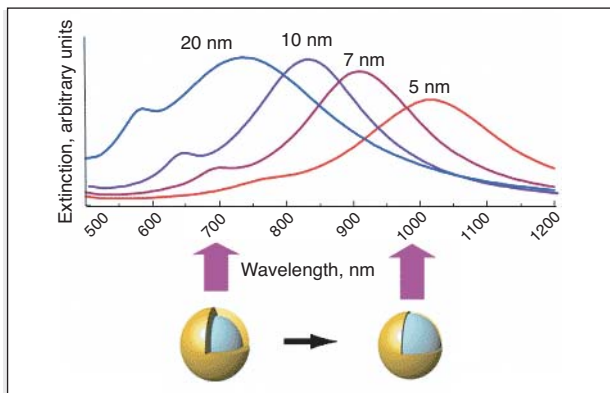
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Massachusetts Institute of Technology (mit.edu)
Penn State (penn.edu)

R&D / TECHNOLOGY ADVANCEMENT

The National Cancer Institute (cancer.gov)
Scripps Research Institute (scripps.edu)

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clinicaltrials.gov	voyle.net



■ Figure 2. Nanoshell plasma resonances are calculated for a 120-nm core with the shell sizes shown. The ability to “tune” nanoshells to absorb light of a desired wavelength enables the use of an external laser to deliver light to Nanoshells in a tumor for thermal destruction or imaging. Courtesy of NanoSpectra BioSciences.

light of varying wavelengths, gold nanoshells will either absorb light (thereby generating heat that can be used to kill cancer cells), or scatter light (making them useful as highly effective contrasting agents for imaging applications). In research carried out by Rice Univ.’s Jennifer West, biocompatible silica-gold nanoshells coated with tumor-specific antibodies were shown to accumulate preferentially in tumors. “All of the tumors had completely regressed within 120 days, and even now, a year later, the mice are still alive with no regrowth of the tumors whatsoever,” says West.

Rice Univ. has licensed its gold nanoshell technology to Nanospectra Biosciences, which is now working with cancer researchers at Houston’s MD Anderson Cancer Center to commercialize their use. Nanospectra is planning to initiate human clinical trials for the treatment of mesothelioma soon, and is also investigating nanoshell use to reduce angiogenesis — the rapid blood vessel network formation that is associated with tumor growth and other diseases.

Magnetic nanoparticles

Triton Biosystems is working to commercialize its Targeted Nano-Therapeutics (TNT) System, an anticancer therapeutic that uses localized heat to destroy cancer cells with negligible damage to healthy tissues. The product is expected to begin human clinical trials in 2006.

The TNT System consists of an injectable serum that contains trillions of “T-probes”— polymer-coated iron oxide nanoparticles tagged with a particular antibody. When circulated in the blood, the T-probes are taken up by cancer cells. Then, an external, alternating magnetic field generator (which creates a magnetic field thousands of times per second) is used to activate them, killing the diseased cells with negligible damage to surrounding healthy tissue. In pre-clinical animal models, no obvious side effects comparable to current chemotherapies or radiotherapies have been observed, according to Triton CEO Samuel Straface, who notes that the firm’s R&D efforts are focused on prostate and breast cancer tumors.

Similarly, MagForce Nanotechnologies’ product is based on the use of magnetic nanoparticles with an iron oxide core, about 15 nm in size, with an uptake-enhancing coating. While Triton’s T-probes are injected into the bloodstream, MagForce’s nanoparticles, dispersed in an aqueous solution, are injected directly into the tumor. The patient is then exposed to an alternating magnetic field, which heats the particles, destroying the cells. The treatment is in Phase II trials involving 65 patients with recurrent glioblastoma multiform or anaplastic astrocytoma.

Carbon nanotubes

When irradiated with near-infrared light, carbon nanotubes — seamless, single-walled or multi-walled cylinders that are composed of carbon atoms in a regular, hexagonal arrangement — naturally absorb light in the near-infrared region of the spectrum. Because neither biological molecules nor water absorb light in this frequency range, near-infrared light is able to pass harmlessly through human tissue to reach carbon nanotubes that have accumulated in tumors, says Hongjie Dai, a researcher at Stanford Univ. “When you shine a beam of near-infrared light on a carbon nanotube, the electrons in the nanotube become excited and begin releasing excess energy in the form of heat.”

Dai’s team found that once nanotubes tagged with folic acid have accumulated inside the cancer cells and are radiated by a near-infrared laser beam, they quickly destroy the cells. Meanwhile, cells without nanotube invaders showed no effect when placed under near-infrared light.

Capitalizing on the rapid heat buildup that can be induced in carbon nanotubes using laser light activation, researchers Balaji Panchapakesan of the Univ. of Delaware, and Eric Wiskstrom of the Kimmel Cancer Center at Thomas Jefferson Univ. have created what they call a “nanobomb,” which literally blows cancer cells apart from the inside out.

In their work with breast cancer cells, the researchers found that the nanotubes “work almost like cluster bombs— once they are exposed to light and the resulting heat, they start exploding, one after another. The resulting shockwave may also kill the small blood vessels that nourish the diseased cells,” says Panchapakesan. However, cells not targeted by the nanobombs are unaffected by the localized explosions. Macrophages — cells that circulate in the blood system and remove foreign materials — can effectively clear the cell debris, as well as the exploded nanotubes.

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