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MIT Lincoln Laboratory, Lexington, MA USA

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The Rockefeller University, New York, NY, USA

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Micro QRcode (250μm×250μm)

Specifications

<table>
<thead>
<tr>
<th>Type</th>
<th>SIJ-S030 (desktop system) ※includes PC, monitor and software</th>
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<td>Droplet volume (fL)</td>
<td>0.1 (femtoliter) - 10 pL (picoliter)</td>
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<tr>
<td>Line width (μm)</td>
<td>0.6 - several tens of μm</td>
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<tr>
<td>Applicable Viscosity Range (cps)</td>
<td>0.5 - 10,000 (non-heated)</td>
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<tr>
<td>Patterning design</td>
<td>Arbitrary shape (dot, line, circle, polygonal shape)</td>
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<td>Patterning area</td>
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<td>Repeatability of work stage</td>
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<tr>
<td>Power</td>
<td>AC100-120V ※A transformer is required for some areas.</td>
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<tr>
<td>Body size</td>
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※) These specifications depend on ink.

Remarks

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Prognosis for Nanotechnology Treatments

In This Issue
Nanotechnology-based tools and treatments promise sensitive disease diagnosis and accurate drug delivery. Most important, the physical features of nanometer-size materials provide capabilities that larger objects cannot match. Nonetheless, some of the challenges, such as biocompatibility and toxicity, require ongoing research and improved solutions. Despite these obstacles, some nanoscale approaches to medicine can already be used.

See full story on page 112.

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Prognosis for Nanotechnology Treatments

Nanotechnology-based tools and treatments promise sensitive disease diagnosis and accurate drug delivery. Most important, the physical features of nanometer-size materials provide capabilities that larger objects cannot match. Nonetheless, some of the challenges, such as biocompatibility and toxicity, require ongoing research and improved solutions. Despite these obstacles, some nanoscale approaches to medicine can already be used. By Mike May

Around the world, biomedical researchers are exploring the possible ways that nanotechnology could enhance human health. At the University of Melbourne in Australia, for example, Frank Caruso, professor of chemical and biomolecular engineering, explores a variety of self-assembly strategies to create particles for potential use as therapeutics. “We develop systems with defined physical and chemical properties to nanoengineer these systems to enhance payload delivery and achieve site specificity,” says Caruso. For drug delivery, the particles can be in the range of roughly 20 nm to 1 μm. “The size depends on the application,” Caruso says, “but targeting specific delivery sites usually requires a small particle to get it there.” He adds, though, that the actual size constraints also depend on a particle’s shape, plus mechanical properties like elasticity and even the particle’s surface chemistry.

The ideal drug delivery system should possess several features. Of course, it needs to get the drug to the intended target, but there’s more. The particle must also be biocompatible and biodegradable, so that the cellular machinery can break down the particle to release the therapeutic. Then, the remaining particle components need to be nontoxic. It seems like a lot to ask, but Caruso says, “There’s an enormous range of polymers that can be used for assembling particles.”

For example, Caruso and his team developed a polymer-based carrier with a roughly 10 nm–thick wall that could transport drugs. “It provides highly elastic mechanical properties that can be tuned,” Caruso says. “We’re working on understanding how size, shape, and elasticity influence biological interactions, and this helps us nanoengineer the control of drug release and the particle’s circulation lifetime.” He makes sure to add that such work depends on a multidisciplinary team, including biologists, chemists, immunologists, materials scientists, medical researchers, and more.

EASIER NANO-VIEWS
Some medical applications could benefit from a nanoscale view, like the one provided by field emission scanning electron microscopy (FESEM). Compared with conventional SEM, says Craig Schwandt, senior research scientist at McCrone Associates in Westmont, Illinois, “The biggest difference is the size of the beam, which is 100 to 1,000 times narrower in FESEM.” As a result, FESEM can distinguish structures that lie closer together than SEM can. “The best resolution for SEM is usually about 500 nm apart,” says Schwandt, “but FESEM can resolve artifacts that are only 1 nm apart.”

Robert Karlinsey, founder of Indiana Nanotech in Indianapolis, approached McCrone Associates about applying FESEM to a nano-size dental challenge. Karlinsey’s company developed a toothpaste called Clinpro 5000 (sold through a partnership with 3M in St. Paul, Minnesota) that reduces tooth sensitivity to pressure and temperature. Karlinsey wanted to understand the underlying cause of this improvement. Typically, tooth sensitivity arises from nerves inside the dentin. Karlinsey wondered if the toothpaste could be blocking the tubules that provide a pathway to the nerves, so that’s where he wanted to look.

“The dentin tubules are just over a micrometer in cross-section,” says Schwandt. “Conventional SEM can’t see down into the tubules.” However, FESEM images were able to reveal spheres—ranging in size from 100–500 nm in diameter—within the tubules after the toothpaste was applied.

UPCOMING FEATURES
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This is just one example of a FESEM application in the realm of nano-imaging and medicine. As Schwandt says, “FESEM can almost get to the resolution of transmission electron microscopy.” He adds, though, that transmission electron microscopy requires extremely thin samples and other modifications that raise concerns over introducing artifacts. With FESEM, a sample requires virtually no preparation, which increases one’s confidence in generating accurate images.

Nano-size particles can also be used to monitor physiological processes. As an example, Philips Research in Hamburg, Germany, uses nanotechnology with magnetic particle imaging (MPI). In this technology, roughly 20 nm in diameter particles of iron-oxide get injected into the bloodstream and a specially designed magnetic field causes the particles to orient, like millions of compass needles all aligned along field lines, except for in a small area called the field-free point, where the field is zero. Then, applying an alternating electromagnetic field point causes the nanoparticles in the field-free point to oscillate. An antenna measures this oscillation, which correlates to the nanoparticle-concentration in the field-free point. The Philips platform will scan the field-free point over any desired area.

Jörn Borgert, a Philips senior scientist and project manager, says, “You could use MPI to measure the volume of blood ejected by the heart or measure the amount of blood in any location.”

In the future, the technique may be used in cardiovascular diagnostics. “MPI has the potential to be several hundred times more sensitive than MRI in detecting the nanoparticles,” says Borgert. “This may, in one examination, provide a physician with a comprehensive overview of the cardiac system by tracking nanoparticles through the body.”

So far, this product is not for use with human patients and is still in the research phase. “We’ve demonstrated feasibility in a technical sense, and we’re building a big enough system to find out if it works in a whole-body scenario,” says Borgert.

VIRAL SURVEILLANCE

In the United States, sepsis—a life-threatening condition that can arise from an infection caused by bacteria, fungi, or viruses—impacts almost two million people each year. A nanotechnology-based tool from Nanosphere in Northbrook, Illinois, however, helps medical professionals detect this infection from a blood sample and determine which drugs will be most effective.

The nanotechnology lies inside this system. “Verigene uses 13 nm in diameter gold particles with oligonucleotides stuck to their surface,” says William Moffitt, Nanosphere’s chief executive officer and president. For the blood stream–infection panel, oligonucleotides add function to the surface of the Verigene particles, which then bind to nucleic acids from the infection-causing pathogens. “Gold nanoparticles with oligonucleotides make highly selective probes,” says Moffitt. “They are very specific to the targets they will bind to, which makes the assays extremely accurate.”

Current methods for diagnosing sepsis can take up to 72 hours or even longer, but the Verigene platform provides results in about two hours. The Verigene assay starts with a blood sample that goes into the Verigene Reader, which includes a cartridge for the sepsis assays. Roger Moody, Nanosphere’s chief financial officer, calls the reader an “electromechanical device that manipulates a self-contained cartridge, which contains the reagents needed to perform a test.” Nanosphere’s sepsis assay remains under review by the U.S. Food and Drug Administration.

The company has a number of other assays in development. For example, Nanosphere has a test in clinical trials for Clostridium difficile, a bacterial infection that is growing in prevalence and can be life threatening. It also makes an influenza assay cartridge that is already approved for clinical use in the United States. Some other tests currently under way include ones for various forms of bacterial infections, intestinal infections, and genetic diseases.

CHIP TECHNOLOGY FOR TREATMENTS

As an expert in polymer chemistry at IBM for a quarter century, Jim Hedrick understands how to develop computer-chip applications, as he says, “make computers perform at outrageous speeds.” That requires plenty of nanotech-knowhow. When he met Yi Yan Yang, an expert in nanomedicine at the Institute of Bioengineering and Nanotechnology in Singapore, they discussed how microelectronics might impact medicine.

As a start, Hedrick and Yang worked on developing nanotechnology-based antimicrobials to make the most of their capabilities. “With Jim’s chemical expertise,” Yang says, “we can make polymers with predictable molecular weights, narrow molecular weight distributions, and controlled end-groups, which is an important feature for therapeutic polymers because different molecular weights provide a different pharmacological activity in the body.” Furthermore, the nano-size antimicrobial polymer assemblies possess a slight positive charge that attracts these polymers to the slightly negative bacterial cells. “So you can target these microbes,” Hedrick says. Upon contacting a bacterial cell, these antimicrobial polymers insert in the membrane and rip it open. Hedrick adds that these antimicrobial polymers are biocompatible and biodegradable.

Hedrick and Yang hope to aim these nano-darts at methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant tuberculosis. “A bloodstream infection, continued>
MRSA, requires an injection,” says Yang, “but for TB, we are looking for alternative delivery strategies.” Since their approach provides so much control over the size and properties of the antimicrobial polymers, they can experiment to see what parameters provide the best therapies for different applications. For example, Hedrick mentions that they recently created a nano-size antimicrobial polymer that knocks out gram positive and negative bacteria—such as MRSA and E. coli, respectively—as well as yeast and fungi.

COMBINING PARTICLES AGAINST CANCER Part of the challenge of using nanoparticles for drug delivery starts with combining the pieces. That turns out to be easy for James Tour, T.T. and W.F. Chao Chair in Chemistry at Rice University in Houston, Texas. He uses carbon clusters that are only a couple nanometers wide and 40–60 nm long. To make them soluble, he covers the surface with polyethylene glycol. Then, he puts the so-called functionalized carbon clusters in a solution that contains a tumor-targeting monoclonal antibody called cetuximab and a chemotherapeutic called paclitaxel.

“Just shake it up, and they find their place,” Tour says. That is, the three pieces bind together during the shaking, but they don’t make hard-to-break covalent bonds. “That way, you don’t have to hope that an enzyme comes along later to cleave off the drug,” Tour says.

Originally, Tour developed this therapy for head and neck cancers. Using this trio of carbon clusters, antibodies, and drug with radiation proves very effective. In fact, the two therapies combine to give more than the sum of the parts. “The radiation causes the cancer cells to express more [epidermal growth factor] receptors on their surface and the antibody binds to those sites,” Tour explains. “More targets leads to more drug delivered to the tumor.”

However, Tour doubts that this approach will move forward on the regulatory pathway for head and neck cancers because effective treatments already exist. Instead, he might aim at diseases that still need better therapies, such as pancreatic cancer and glioblastoma multiforme in the brain.

Other investigators also study nanoparticle-based drug delivery. For example, nanotechnology could help researchers target the limited number of surface receptors on tumor cells. Only some receptors make good targets, but they do not cover the entire surface of every tumor cell. Moreover, receptors continually turn over, with old ones being broken down and new ones being constructed, which further limits the availability of such receptors as sites for drug attacks. That made Erkki Ruoslahti, distinguished professor at Sanford-Burnham Medical Research Institute in La Jolla, California, interested in combining tumor-targeting peptides with drug-bearing nanoparticles.

“It seems like a perfect marriage,” Ruoslahti says. “Peptides have a relatively low affinity for their targets, but you could put many peptides on the surface of a particle, which makes up for their low affinity. Plus, you can add a payload.”

Other approaches for treating cancer rely on drugs migrating to the desired site via leaky blood vessels in tumors. “This is very inefficient,” Ruoslahti says. “Plus, nanoparticles are not very good at getting out of blood vessels.” So Ruoslahti’s team is working with tumor-penetrating peptides. These peptides target blood vessels around tumors and bind to the surface protein neuropilin-1, which activates a transport pathway that carries the proteins from the blood vessel into the tumor. So, if Ruoslahti turns a nanoparticle into a drug carrier and coats it with these proteins, it will find a tumor, work its way into it, and bring the drug right where it needs to be. “It could get the nanoparticles deep into the tumor tissue,” Ruoslahti says.

So far, some of the tumor-penetrating peptides seem specific to certain kinds of tumors and some seem to be more general-purpose. Ruoslahti adds that the tumor needs to express neuropilin-1. “Most do, and even overexpress it,” he says, “but some probably don’t.” His academic group is already moving one protein, called iRGD, to the clinic. “This protein includes an integrin-binding sequence that I discovered almost 30 years ago,” Ruoslahti says, “and we can make it a tumor-penetrating peptide.”

This approach could go far beyond cancer. Ruoslahti points out that the target could be atherosclerotic plaque, inflammatory arthritis, and so on. “Pretty much any disease is targetable,” Ruoslahti says. “It will be a very general approach.”

Still, Ruoslahti points out one fundamental issue that must be handled to make nanoparticles effective at delivering drugs. “Nonspecific uptake by the liver and spleen have not really been solved,” he says. “That reduces the ability of specific targeting and causes the potential for liver toxicity.” He adds, “It would be better if the nanoparticles fall apart and don’t concentrate except at the target.” Making that happen, though, will take more research.

Mike May is a publishing consultant for science and technology.

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