FUTURE OF MEDICINE 2015

SMALL WONDERS

Nanomedicine is inventing new ways to fight cancer, heal wounds and pilot drugs into cells

By Josh Fischman

A molecule of DNA, holding its blueprint for life, is about 2.5 billionths of a meter in diameter. Scientists now have the ability to push and pull and build molecules of that size, as well as to create devices that sense them with unprecedented precision. These skills, gained through painstaking work during the past decade, are leading to new medicines and ways of diagnosing disease. In this special report, SCIENTIFIC AMERICAN examines what nanomedicine is bringing us now, what is coming soon and what the future will likely hold.

Right now chemotherapy is a major focus, and drugs that can slip into tumors because of their fine-grained construction are showing success where other medications fail patients [see "Cancer Drugs Hit Their Mark," on page 44]. Diagnostic tests are also taking advantage of the small sizes, using probes of unusually shaped DNA that can detect cancer with remarkable accuracy. Next, in the near future, patients should be able to use smart bandages made with nanosized molecules that enhance the healing of severe wounds—or that signal doctors when healing is not happening [see "A Smarter Bandage," on page 47]. Further out in time, researchers hope to attach tiny molecular motors to drugs, driving them through the bloodstream to their targets [see "Launch the Nanobots!" on page 50]. These are feats of nanoengineering, invisible to the eye, yet they could have an outsize effect on health.

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NANOMEDICINE NOW

CANCER DRUGS HIT THEIR MARK

Tiny vehicles deliver more medication to tumors and reduce side effects

By Dina Fine Maron

IN BRIEF

Chemotherapy drugs have trouble hitting their targets. The body attacks them, they do not penetrate tumors well, and they often mistake healthy cells for cancer cells.

By crafting drug shells on the nanoscale, scientists have created medicines that avoid these problems. Fine-grained control over the shell components lets researchers create drugs that slip past immune system alarms and home in on malignancies.

These medications are already in the final stages of clinical trials. Nanoparticles are also being developed that are more than shuttles but can shut down cancer-causing genes by themselves.

Cancer plays a deadly game of hide-and-seek in the body, and the drugs sent to treat it are often the losers—as is the cancer patient. The drugs have trouble distinguishing between tumor cells and healthy ones and may drop their payload on the normal cells, causing miserable side effects and leaving nearby cancer cells untouched. Malignancies may also get a helping hand from the body's own leading defense weapon, the immune system. It often mistakes anticancer drugs for harmful bacteria or other foreign invaders and breaks them down. The shattered pieces are conveyed to the body's trash receptacles in the liver, kidneys and spleen, again, before they reach their intended target. Even when the drugs do manage to arrive at a tumor, many of them become entangled in the dense undergrowth of the malignant mass—unable to penetrate it completely.

Recent advances in nanomedicine are now allowing drugs

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With its design and protective coating, the nanoscale drug is better poised to get to tumors without being destroyed by the body.

to better traverse this fraught landscape and hit tumors where they live. The key is a uniquely crafted drug vehicle, wrapped in a protective outer shell, that shuttles the chemotherapy drugs through the body. Fine-grained control over the components from which the vehicles are built, which can be just a few billionths of a meter across, has let scientists create a specialized architecture that, among other things, does not trip immune system alarms. Researchers such as Kazunori Kataoka of the University of Tokyo and his colleagues have tucked potent chemotherapy drugs inside sheaths the size of a hepatitis C virus—some 200 times as small as a red blood cell. On a molecular level, those drugs look a lot more like something the body makes. These compounds also have the advantage of being able to slip into tumors and steer clear of healthy cells.

Several versions of nanodrug vehicles from Kataoka's team, each holding different medications and aimed at different types of tumors, are now wending their way through the final stages of clinical trials in Asia. Drugs in these new carriers have slowed or reversed disease progression in people with breast or pancreatic cancer. Still another nanoparticle is in the second stage of clinical trials in the U.S. "With science like this, the initial stages take time, but I believe the field is starting to show promise," Kataoka says. "The development speed will be much faster in the coming five years."

DRUGS IN DISGUISE

EMPLOYING NANOTECHNOLOGY for chemotherapy drugs is not a brand-new idea. Medications such as Abraxane for metastatic breast cancer and Eligard for advanced prostate cancer, which are already on the market, are nanodrugs. But these pharmaceuticals attack only certain tumors, so more therapies are needed. Subsequent advances in engineering have allowed scientists to tweak the structure of nanocarriers so they work against a wider array of cancers with even greater precision. The nanotherapies now being tested—administered via an intravenous injection—seem to be more effective at eliminating tumors.

Most of these newer nanomedicines encase a drug-containing core in a soft sheath dotted with polyethylene glycol, a synthetic material that acts as a cloaking agent. That cloak is a covering of water molecules, which are attracted by the sheath material and thus surround it with a common body liquid. Water helps to block electrical charges from the particle that

TRACKING ILLNESS

A Flare for Cancer

Diagnostic spheres of DNA seek out and tag malignant cells

Cancer travels. Large tumors shed cells that move through the body and seed new malignancies. Now scientists are tinkering on the nanoscale to build unusual spheres made of DNA—a molecule that became famous as another shape, the double helix—that can find, tag and potentially kill off these tumor cells.

The spheres look a bit like toothpicks stuck in a small Styrofoam ball. The toothpicks are really a dense crowd of single DNA strands jutting out from a central core. The strands are chosen for their ability to bind to complementary DNA in cancer cells. When a bond happens, it displaces tiny light-emitting molecules stuck to the tips of the DNA in the sphere, essentially sending up a flare that indicates the presence of cancer. The brighter the flare, the more cancer DNA that is present, says Chad A. Mirkin, a chemist and director of the International Institute for Nanotechnology at Northwestern University, who has spearheaded the research.

These encounters occur in a sample of a patient's blood. When the spheres run into a cell, they move through pores in the cell membrane into the interior. Because spheres have more surface area than other shapes, the DNA that forms that outer rim has a much higher chance of encountering and latching on to cancer DNA than isolated strands would. Spherical nucleic acids "bind to other nucleic acids 100 times more strongly," Mirkin says.

Mirkin's spheres, also called Nanoflares, are already being used by hospitals for rapid cancer diagnosis. Other systems fish out dead tumor cells based on proteins on their outer surfaces, but because these spheres identify live cells, Mirkin says, scientists could test how the cells respond to different drugs and eventually develop personalized treatments based on the results. —*Joshua A. Krisch*

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would otherwise alert the immune system to the presence of a foreign substance.

The liquid buffer also covers the nanoparticle's edges, making it too smooth to provide purchase for any passing sentries from the immune system, such as antibodies. The size of the nanoparticle—somewhat larger than a traditional chemotherapy drug—also helps to ensure that it is not broken down too quickly by the body's enzymes. That resistance to degradation gives the drug more time to reach a tumor and do its job. For example, the first approved nanotherapy for cancer, called Doxil, has a half-life in the bloodstream that allows it to survive much longer than its conventional chemotherapy cousin, doxorubicin. (Both drugs are used to treat ovarian cancer.) With its design and protective coating, the nanoscale version is better poised to get to tumors without being destroyed by the body. The soft, flexible texture of the newest nanoshell-type drugs also allows them to skip through one of their final obstacles: the dense, irregular ecosystem of the malignant tissue that could snag something more rigid.

The final weapon of the new nanoparticles lies within their inner depths. The drug-containing core can be broken down by acid, so it will readily disintegrate and shed its drug cargo only after it leaves the neutral environment of the blood and arrives at its tumor destination, which has much higher acid levels.

To better steer the nanocarriers toward cancers and away from healthy cells, other scientists are trying to dot their exteriors with selected antibody molecules that are attracted to proteins that are particularly abundant on cancer cells. Proteins such as EGFR are one such example, and University of California, Los Angeles, bioengineer Dean Ho has done preliminary experiments, published in *Advanced Materials* in 2013, showing that nanoparticles can be layered with antibodies that link to those proteins.

Nanoparticles can also be built to serve as actual medicines, not just the delivery vehicles. Scientists at Northwestern University created nanoparticles made from bits of gold and laced with genetic material—RNA—selected for its ability to silence cancer-causing genes. Because of the particles' small size and other yet to be determined factors, gold nanoparticles studded with RNA can penetrate one of the hardest places to reach with a drug: the brain. In October 2013 researchers reported that, in animals, the nanoparticles can cross the blood-brain barrier—a tight mesh of small blood vessels—to help combat brain tumors. The approach caused overall tumor size to shrink in rodents, but ultimately the creatures still died from the cancer, says researcher Alexander Stegh of Northwestern. Exactly how this technique managed to clear the blood-brain barrier is still being explored, he notes. It is possible that the particles' structure binds to receptor molecules on the surfaces of blood vessel cells, and the receptors help to pull them in.

Still other types of nanoparticles made from nucleic acids are being studied as probes to detect cancer cells that circulate through human blood [*see box on this page*]. Chad A. Mirkin, a Northwestern chemist leading the project, says the research may lead to nanoparticles that carry both diagnostic chemicals and medicine—a formidable package that could eliminate hard-to-find cancerous cells before they spread to new places in the body. Devising that kind of tiny powerhouse would be no small feat.

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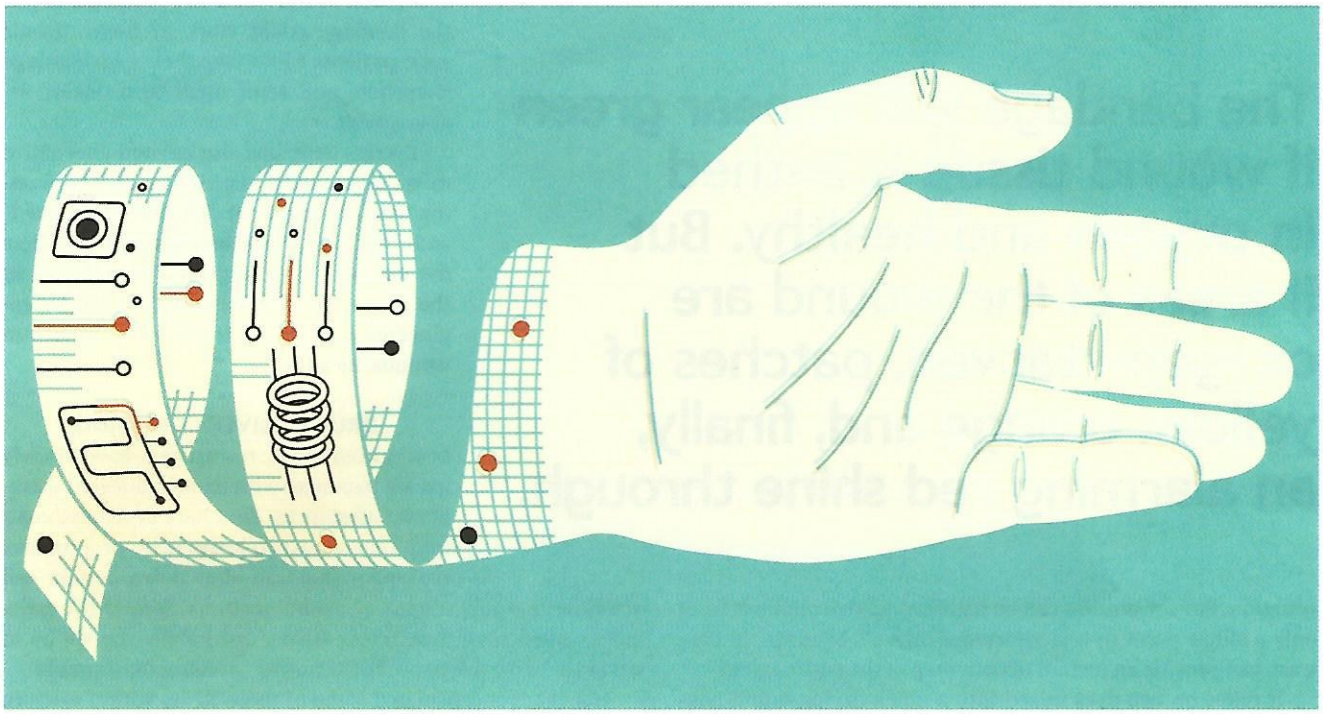
NANOMEDICINE SOON

A SMARTER BANDAGE

New materials will not simply cover wounds—they will alert doctors to problems and deliver drugs

By Mark Peplow



The injured soldiers had been treated well since their return from fighting in Afghanistan. At the San Antonio Military Medical Center in Texas, surgeons had carefully grafted healthy tissue over their burns and wounds, using microsurgery to connect their blood vessels to the new skin. But the patients still faced an uncertain recovery. The vessels might not supply enough oxygen for the transplants to thrive.

When Conor Evans visited San Antonio in 2010 and saw these soldiers, he realized that conventional techniques for monitoring oxygen levels did not work very well, and they often failed to give enough warning if the graft was failing. "What these physicians do is nothing short of amazing," says Evans, a chemist at Harvard Medical School and the Wellman Center for Photomedicine at Massachusetts General Hospital. "But the sensors they had just weren't cutting it."

So Evans built a better bandage. He and his colleagues started with dyes that react to different oxygen levels, added nanosized molecules that control the dye activity, and used them to

create a liquid bandage that indicates the health of the wound it covers. "The bandage changes color, just like a traffic light, from green through yellow and orange to red," depending on the amount of oxygen present, Evans says. After success in laboratory animals in 2014, human trials are set to begin this year.

By taking advantage of newfound abilities to manipulate materials as small as a few billionths of a meter, scientists such as Evans can not only improve rapid health assessments, they can also turn wound dressings into precise drug-delivery systems "Nanotechnology plays a large role in being able to control the amounts released and how well formulations get to the area of a wound that we need them to reach," says Paula Hammond, a chemist at the Massachusetts Institute of Technology. That precision has a major advantage over flooding body parts with drugs, only some of which find their targets.

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COMING UP FOR AIR

POOR WOUND HEALING caused by a lack of oxygen affects more than six million people in the U.S. every year, and the medical costs are estimated to reach $25 billion. Typically physicians stick needle electrodes into injured tissue to measure tissue oxygenation, but the needles can be painful and give readings from only a single point in a large wound. Evans's bandage, in contrast, can provide an instant oxygen map of the entire injury.

It relies on two dyes mixed into a quick-drying liquid bandage that can be painted onto wounds. A brief burst of blue light energizes and illuminates both dyes: one glows bright red, the other green. Then oxygen molecules switch off the red dye's phosphorescence, so the bandage will appear green if the adjacent tissue is bathed in oxygen and is healthy. But if areas of the wound are oxygen-starved, patches of yellow, orange and, finally, an alarming red shine through.

The bandage will appear green if wound tissue is bathed in oxygen and healthy. But if areas of the wound are oxygen-starved, patches of yellow, orange and, finally, an alarming red shine through.

The key to the alert is a nanoscale addition to the red dye molecules. Evans coupled each of these molecules to a dendrimer, a treelike molecule with a branching structure up to two nanometers across. This molecular thicket prevents neighboring molecules from overlapping and quenching one another's phosphorescence. They also physically block some—but not all—of the oxygen molecules from reaching the dye; starting with lower levels makes any changes more obvious.

In a hospital, the warning red would prompt a nurse to photograph the bandage, and doctors would to try to improve the blood and oxygen circulation in the trouble spots. In principle, the bandage could work at home, Evans says: patients could take their own bandage snapshots and send them to a doctor for assessment.

Evans's team has also created alternative dyes that are much more efficient at converting blue light into red. "Our new bandage is so bright that it can be seen with very low dye loading, in a sunlit room," Evans says. In the future, the bandage might even be engineered to dispense therapeutic drugs into wounds, he adds.

DRUG-DELIVERY DRESSING

IN HAMMOND'S LAB, researchers have already loaded bandages with nanoengineered therapeutic substances. They have developed coatings that slowly release RNA or proteins, molecules that can shut down certain cell activities that might hamper wound recovery. Some RNA molecules, called small interfering RNAs, can hobble the ability of genes that give rise to problem-causing proteins, for example.

Her team encapsulated some of these RNAs within calcium phosphate shells, each about 200 nanometers wide, sandwiched the shells between two layers of a positively charged polymer made of biological molecules and then "buttered" one side of this sandwich with a negatively charged clay. (The opposite charges stick the layers to each other.) Stacking up 25 of these sandwiches formed a coating roughly half a micron thick, which Hammond placed on a conventional nylon bandage.

IN BRIEF

Wound dressings can be transformed into precise drug-delivery systems by manipulating materials sized at a few billionths of a meter (nanometers).

Nanotechnology enables researchers to sandwich drugs between the layers of a bandage and to control how much gets released.

Sensitive bandages can detect the conditions of serious wounds. They can also release molecules that hobble problem-causing proteins.

Small, layered devices can be placed in heart arteries, and dissolving layers release DNA for a protein that helps to reconstruct damaged blood vessels.

COMPUTER IMPLANTS

Gentle on the Heart

Soft electronic circuits that do not tear flesh enfold and monitor vital organs

The hardware in electronics has been a poor fit for the software of human flesh. Rigid circuits do not flex with pliable organs, and hard edges tear soft tissue. This problem has severely limited efforts to improve devices such as artery-clearing catheters by adding computerized control and finesse. Silicon may support the entire computer industry, but it is notoriously brittle.

Yet even the most stubborn materials become flexible if you make them thin enough, says John Rogers, a materials scientist at the University of Illinois at Urbana-Champaign. He is building stretchable electronic sheets, just 10 nanometers thick, for devices that could be placed within or around organs such as the heart and do their jobs without causing harm. Rogers calls them "soft electronics."

The circuits that Rogers builds must use high-fidelity conductors, such as silicon and gallium nitride, because they have to relay computer signals without a glitch. To get around silicon's tendency to break when bent, he has used nanoscale engineering to thin the material while maintaining its conductive ability. Shaved down to around 10 nanometers, silicon acts more like a rubber band and less like glass.

In animals, Rogers has already successfully tested a flexible membrane, with embedded electronics, that can be wrapped around a beating heart to watch for abnormal rhythms. If tests continue to show success, he imagines adding electronic monitors to artery-opening devices such as balloon catheters so they can sense narrow sections of blood vessels. "Dumb mechanical devices could become sophisticated surgical tools," Rogers says. —*J.A.K.*

As natural enzymes in the body break down the layers, the dressing discharges the RNA molecules into the wound over the course of a week. The slow, steady release could reduce side effects caused by a single, large dose of a conventional drug; this release method could also ensure that the wound is constantly treated.

Hammond has also used this so-called layer-by-layer coating to supply a therapeutic protein that aids wound healing in diabetic mice. The protein is already available as an ointment, but she says that the formulation is not very effective—after initially delivering a huge burst of protein, its activity fades away within 24 hours. Hammond's bandage, in contrast, sustains a steady flow over five to seven days to maintain the optimum dose of protein.

The layer-by-layer strategy could improve treatments for another ailment: coronary artery disease, which is caused by a buildup of plaque in vessels that carry blood through heart muscle. Treatment usually involves widening the artery with an inflatable balloon and keeping it open by inserting a small tube of stainless-steel mesh known as a stent. Some stents come loaded with therapeutic molecules to prevent the artery from narrowing again, but patients must then take more drugs to reduce the associated risks of blood clots that could break free from the area.

Treating the artery with doses of DNA, carefully delivered by devices with nanoscale coatings, could offer a better solution, according to David Lynn, a chemist at the University of Wisconsin–Madison. Inside the body, the DNA could make cells produce a protein that helps to stabilize and reconstruct blood vessel walls. To deliver such genetic therapies exactly when and where they are needed, Lynn has coated stents with successive layers of DNA and a biodegradable polymer, each several nanometers thick. By varying the number of layers, researchers can control the amount of DNA released into blood vessel walls. Experiments on pigs showed that the DNA gradually penetrated the surrounding tissue during the days after the stent was implanted. Fine-tuning the design of the coating, other tests show, can change the rate of release. "We now have reasonable control that allows us to time the release from seconds to months by modifying the structure of the polymer or how we put the film together," Lynn says.

The basic nanoengineering behind these inventions could be adapted for a wide range of other applications. Lynn is using polymer coatings to deliver biological molecules called peptides that interrupt the chemical conversations among bacteria. Cut off from one another, the bacteria cannot team up to form tough biofilms that resist breakup by antibiotics. Evans, for his part, is using his phosphorescent dyes in tissue samples to identify oxygen-poor tumor cells, which can be particularly resistant to chemotherapy, and he plans to test the technique in animals later this year. The same dye approach could also be used to detect the presence of infectious bacteria in wound tissue or reveal other kinds of molecules. "Really, the sky's the limit," Evans says.

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Larry Greenemeier is an associate editor at *Scientific American*.

NANOMEDICINE IN COMING DECADES

LAUNCH THE NANOBOTS!

Overcoming all the technical challenges may take 20 years or more, but the first steps toward remote-controlled medicine have already been taken

By Larry Greenemeier

The long-term future envisioned by nanomedicine researchers includes incredibly tiny therapeutic agents that smartly navigate under their own power to a specific target—and only that target—anywhere in the body. On arrival, these self-guided machines may act in any number of ways—from delivering a medicinal payload to providing real-time updates on the status of their disease-fighting progress. Then, having achieved their mission, they will safely biodegrade, leaving little or no trace behind. These so-called nanobots will be made of biocompatible materials, magnetic metals or even filaments of DNA: all materials carefully chosen for their useful properties at the atomic scale, as well as their ability to slip past the body's defenses undisturbed and without triggering any cellular damage.

Although this vision will likely take a decade or two to fulfill, medical researchers have already begun addressing some of the technical problems. One of the biggest challenges is making sure the nanodevices get to their target in the body.

WAVE POWER

MOST DRUGS on the market today readily float through the body in the bloodstream, either after being injected directly into the blood or, in the case of pills, getting absorbed into the bloodstream from the gastrointestinal tract. But they wind up traveling both to where they are needed and to where they can cause unwanted complications. Sophisticated nanomedicines, in contrast, are being designed to be guided to a tumor or other problem site, where their medicinal payload is released, reducing the chance of side effects.

Magnetic fields and ultrasound waves are the leading candidates for guiding nanomedicines in the near term, says Joseph Wang, chair of nanoengineering and a distinguished professor at the University of California, San Diego. In the magnetic approach, researchers embed nanoparticles of iron oxide or nickel, for example, within a particular medication. They then use an array of permanent magnets positioned outside a mouse or other subject and push or pull the metallic medicine through the

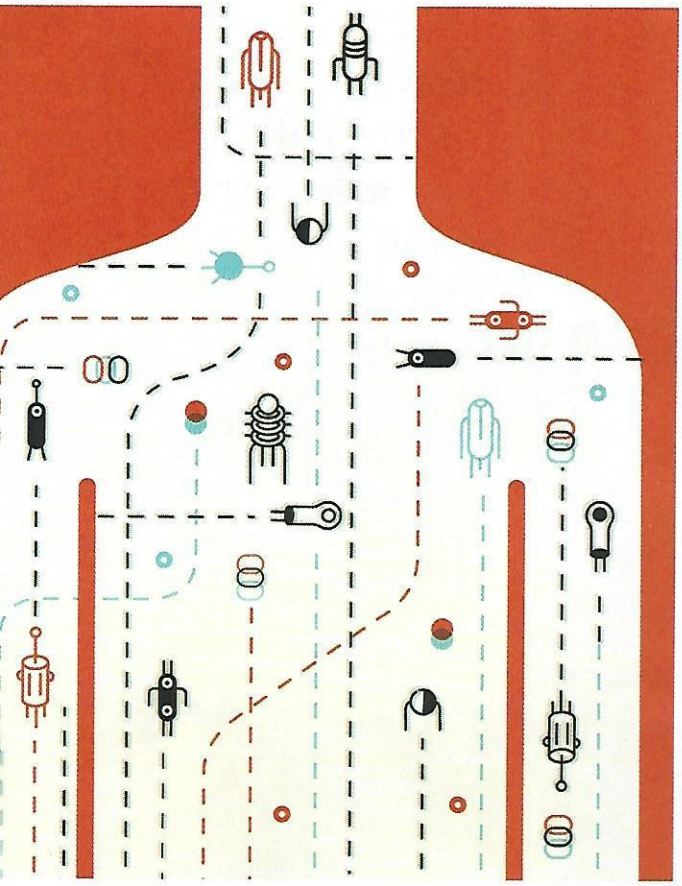
IN BRIEF

Some day a fleet of nanomedicines and devices will travel anywhere it needs to go in the body, under its own power, using biocompatible motors and fuels to get there.

Before that day arrives, however, researchers must learn how to design these compounds so that they can move without damaging or interfering with any normal biological functions.

In the near term, scientists are generating magnetic fields and ultrasound waves to propel nanoparticles to their target areas. But such approaches cannot penetrate deep into the body.

Nanobots made of DNA are another alternative. Some of these compounds are designed to work like boxes that open and release their cargo only under specific circumstances.



body to a selected site by manipulating various magnetic fields. In the ultrasound approach, researchers have directed sound waves at medicine-containing nanobubbles—causing them to burst with enough force that the bubble's cargo can penetrate deep within a targeted tissue or tumor.

Last year medical researchers at Keele University and the University of Nottingham, both in England, added a helpful twist to their magnetic approach in work aimed at healing broken bones. They attached iron oxide nanoparticles to individual stem cells and then injected the preparation into two different experimental environments: fetal chicken femurs and a synthetic bone scaffold made from tissue-engineered collagen hydrogels. Once the stem cells arrived at the break, the researchers used an oscillating external magnetic field to rapidly shift the mechanical stress on the nanoparticles, which in turn transferred the force to the stem cells. This kind of biomechanical stress helped the stem cells to differentiate more effectively into bone. New bone growth occurred in both cases—although overall healing was uneven. Eventually the researchers hope that adding various growth factors to the iron oxide–studded stem cells will make the repair process smoother, says James Henstock, a postdoctoral research associate at Keele's Institute for Science and Technology in Medicine.

AUTONOMOUS NANOMEDS

THE PRIMARY DRAWBACKS to the magnetic and acoustic approaches are the need for external guidance—which is cumbersome—and the fact that magnetic fields and ultrasound waves can penetrate only so far into the body. Developing autonomous "micro motors" for the delivery of therapeutic cargo could surmount those problems.

Such micro motors would rely on chemical reactions for propulsion, but toxicity is an issue. For example, oxidizing glucose, a sugar molecule found in the blood, would generate hydrogen peroxide, which could be used as a fuel. But researchers already know that this particular approach would not work in the long run. Hydrogen peroxide corrodes living tissue, and glucose in the body would not produce enough hydrogen peroxide to adequately power micro motors. More promising are efforts to use other naturally occurring substances, such as stomach acid (for applications in the stomach) or water (which is abundant in blood and tissues), as power sources.

Accurate navigation by these self-propelling devices may be an even greater hurdle, however. Just because nanoparticles can move anywhere does not mean that they will necessarily travel exactly where researchers want them to go. Autonomous steering is not yet an option, but a work-around would be to make sure that nanomedicines become active only when they find themselves in the right environment.

To accomplish this trick, researchers have begun creating nanomachines out of synthetic forms of DNA. By ordering the subunits of the molecule so that their electrostatic charges force it to fold in a particular configuration, scientists can engineer the constructs to perform various tasks. For example, some DNA segments may fold themselves into containers that will open and release their contents only when the package comes across a protein important to a disease process or encounters the acidic conditions inside a tumor, says University of Chicago chemistry professor Yamuna Krishnan.

Krishnan and her colleagues envision more advanced, modular entities made of DNA that could be programmed for different tasks, such as imaging or even assembling other nanobots. Yet synthetic DNA is expensive—costing about 100 times more than more traditional materials used to deliver drugs. For now, then, the price discourages drug companies from investing in it as a candidate for treatments, Krishnan says.

All of this may be a far cry from building a fleet of smart submarines reminiscent of *Proteus* in the 1966 film *Fantastic Voyage*. Still, nanobots are finally moving in that direction. SA

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