

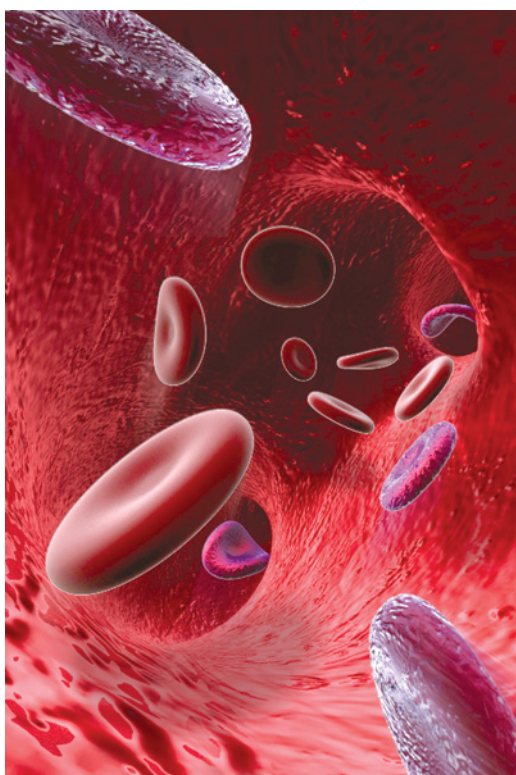
Beyond Fantastic Voyage: Drug delivery research at UCSB

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Delivering therapeutic and diagnostic agents where they're needed (and not where they're not) in the body.



Beyond *Fantastic Voyage*...
Drug delivery research at UCSB

In the 1966 science fiction film *Fantastic Voyage*, the principals were put in a submarine which was then shrunk to one micron in length and injected into a comatose scientist's body so that they could navigate through the body to the site of a life-threatening cerebral blood clot and destroy it. That was a fantasy approach to getting the right therapy to the place in the body it's needed, but at UC Santa Barbara, cross-disciplinary teams of researchers from materials science, chemical and mechanical engineering, biology, and chemistry are creating drug delivery technologies that do just that and more—drug delivery technologies that are more targeted, effective, and efficient, and at the same time safer and cheaper, than those in use today.

“The goal is to save lives and save money,” says Samir Mitragotri, professor of chemical engineering. “We’re looking at how to treat the patient in the most effective way, getting the drugs to the right place in the body and making sure they remain active

when they reach that site.?

Mitragotri sees benefits in trying to bring the parallel paths of drug discovery and drug delivery much closer together. ?They are typically considered two distinct elements,? he says. ?But the sooner we can integrate them, the better.?

UCSB researchers are creating nanoparticles that can detect and home in on nascent cancerous tumors, exit blood vessels and penetrate the diseased tissue, send back imaging signals to assess the extent of malignancy, and deliver a controlled payload of drugs.

Erkki Ruoslahti, distinguished professor at Sanford|Burnham Medical Research Institute at UCSB, is among those pushing these multi-functional boundaries. ?We can engineer nanoparticles to do many different things, and that has all sorts of advantages in developing both diagnostics and therapeutics,? he says.

UCSB researchers are also knocking on the door of gene therapy, investigating altering DNA to combat major medical conditions such as cancer, cardiovascular disease, and Alzheimer?s.

Delivering the enhanced DNA across the cell membrane and into the cell nucleus has proved a stumbling block, but Mitragotri says such therapy is getting close to becoming a clinical reality.

Mitragotri and his team are researching a wide range of drug delivery options: transdermal, ultrasound, jet injectors, gene therapy, nanoparticles, and engineering particle shapes.

While acknowledging the convenience of pills and injections, he also identifies their weaknesses and limitations in trying to outsmart such natural biological defenses as degradation by enzymes in the stomach and cleansing by the liver?weaknesses and limitations that can be effectively addressed by engineering the delivery package.

Transdermal (through the skin) drug delivery is not a new idea, but researchers in Mitragotri?s lab are refining the process by making the stratum corneum, or outermost skin layer, more porous.

The objective is to temporarily make pores large enough for specific drug molecules to pass through, but not so big that bacteria or viruses can also slip past. Mitragotri says ways to achieve this include ultrasound and chemical mixtures.

One result of this research may be to replace chemotherapeutics which work well but have ?terrible side-effects??through better targeting, it should be possible to deliver more of those healing drugs where they?re needed but eliminate the adverse reactions.

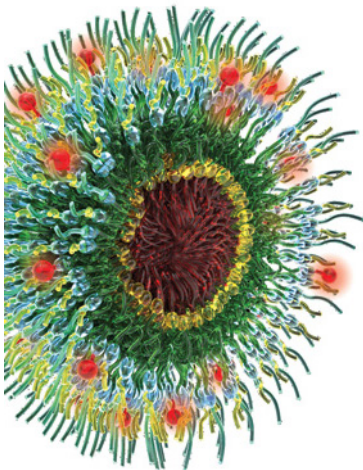
Finding the right formulations for a wide range of patients, however, requires screening

millions of possible permutations. That prompted the development of INSIGHT, a rapid screening system using electrical conductivity to determine the best formulations to deliver therapeutics previously administered only as injectables.

His research team is also looking to improve high velocity jet injectors, another needle-free, virtually painless way of delivering liquid vaccine through the skin.

For drug delivery at the cellular level, Mitragotri's team turns to nanoscale engineering. Drugs in the bloodstream risk becoming diluted and degraded, but encapsulating them in polymeric particles enables sustained concentrations and sustained release.

Mitragotri says most such particles are spherical, while cells in the body come in all sorts of shapes. "We're making them non-spherical and studying what they can do," he says. "We're finding that shape has a huge impact on how they behave." For example, the immune system cleanses some shapes more readily than others, so changing shapes may increase a drug's circulation time and improve the prospects of reaching its target.



Erkki Ruoslahti, distinguished professor at Sanford|Burnham Medical Research Institute at UCSB, and former College of Engineering Dean Matthew Tirrell have developed lipid-based nanoparticles that form micelles with peptides on the surface that can attack the surface of plaque, a major cause of cardiovascular disease. The micelle preferentially targets the places in the plaques that are prone to rupture.

Mitragotri's research group recently made a major advance in this area by developing synthetic particles that closely mimic the characteristics and key functions of natural red blood cells, including softness, flexibility, and the ability to carry oxygen. The synthetic red blood cells (sRBCs) also have been shown to deliver therapeutic drugs effectively and with controlled release, and to carry well-distributed contrast agents for enhanced resolution in diagnostic imaging.

Similar finely-tuned engineering lies at the heart of research being conducted in other labs at UCSB by Ruoslahti, Joe Zasadzinski, Patrick Daugherty and Craig Hawker.

Ruoslahti is working on early detection and treatment of cancer tumors, and on

prevention and treatment of atherosclerotic cardiovascular disease, which is characterized by plaque building up inside arteries, obstructing blood flow, and sometimes rupturing and causing heart attacks or strokes.

His latest work on targeting nanoparticles to attack plaque was recently described in the Proceedings of the National Academy of Sciences. The paper's co-author was Matthew Tirrell, then dean of the College of Engineering, now chair of UC Berkeley's Department of Bioengineering.

The plaque-targeting nanoparticles are collections of molecules that self-assemble to form a sphere called a micelle. Each micelle has a peptide, a piece of protein, on its surface which binds to the plaque, usually at the points most likely to rupture.

The research paper concludes that self-assembled micelles are the best vehicles for this type of drug delivery, largely because of "the ease with which small particles, with sufficiently long circulation times" can be constructed.

Other contributors to the paper included David Peters, Venkata Ramana Kotamraju and Kunal Gujrati of Sanford|Burnham (La Jolla), and Mark Kastantin of UCSB's Department of Chemical Engineering.

Ruoslahti sees similarities between plaque and tumors, since tumors also display subtle clotting on the inner lining of their blood vessels. Through his pioneering work using mice, he's able to screen libraries containing billions of peptides, identifying and replicating those with specific affinity for tumor vessels.

These "homing" peptides can even distinguish between the vessels of pre-malignant lesions and those of malignant tumors. This enables earlier targeted treatment, increasing drug efficacy, reducing side-effects and improving patient prognosis.

Recently, his research team discovered how nanoparticles can penetrate more deeply into tissue and resist being swept up before reaching their target as the liver scavenges for foreign bodies in the bloodstream.

Patrick Daugherty, associate professor in the Department of Chemical Engineering, works closely with Ruoslahti, Mitragotri and others in researching ways to refine drug delivery to very specific sites.

"We want a drug to accumulate in a specific tumor and not go everywhere else in the body," he says. "We're trying to improve the therapeutic index of drugs, getting more into diseased tissue and less into healthy tissue."



Professor Craig Hawker and his research team, including Matt Kade (left), are exploring the use of nanoparticles to detect, diagnose, and treat diseases.

Daugherty's team has developed several new technologies for isolating and engineering protein-binding ligands with this improved affinity and specificity.

They use in vitro bacterial cell surface peptide display libraries to scan billions of molecules and identify their binding affinity for various cells, tissues and organs. It's a process Daugherty likens to looking for a "molecular needle in a huge haystack."

One result of this research may be to replace chemo-therapeutics which work well but have "terrible side-effects" through better targeting, it should be possible to deliver more of those healing drugs where they're needed but eliminate the adverse reactions.

While Daugherty characterizes certain cancers and vulnerable plaques as the "low-hanging fruit" for researchers, he believes the same biotechnology may help patients battling more complex autoimmune and neurological conditions such as rheumatoid arthritis and perhaps multiple sclerosis (MS).

His group's present focus is on breast and ovarian cancer, but Daugherty says this method of drug delivery could be equally applicable to pancreatic cancer and to brain and bone tumors.

Professor of Chemical Engineering Joe Zasadzinski, and Craig Hawker, director of the Materials Research Laboratory and professor of chemistry and materials, are doing work that dovetails with that of colleagues like Ruoslahti and Daugherty.

"We provide the packaging, someone else provides the labeling," says Zasadzinski. "And then I make it go 'Pop!' at the end." Naturally, it's a little more complicated than it sounds.

Researching lipid-based drug carriers, Zasadzinski and his team—including post-doc Guohui Wu and graduate students Ben Wong and Tallie Forbes—needed to extend the life of the lipid membrane which is attacked by enzymes in the bloodstream, causing it to leak and lose cargo in as little as 15 minutes.

Their solution is the equivalent of double-bagging groceries at the store: wrapping the drugs inside a tiny balloon and placing that inside a second slightly larger balloon.

Zasadzinski says enzymes can chew a hole in the outer balloon large enough for small molecules of drugs to escape. For the enzyme to make a hole big enough for it to pass through and then start attacking the interior balloon, however, can take up to 24 hours.

After evading the body's defense mechanisms and reaching the optimum delivery location, Zasadzinski's researchers have come up with a unique method of releasing the drug payload.

They use bio-compatible gold particles which absorb specific wavelengths of laser light, heating up sufficiently to boil minute quantities of water and expand a vapor bubble, rupturing the lipid membrane "the 'pop'" Zasadzinski talks about.

Hawker and his research team are developing a three-stage nanoparticle package: detecting and diagnosing disease, and delivering the appropriate therapy.

“We work in an extremely collaborative environment,” says Hawker. “You have to have very diverse teams, and one of the great things about UCSB is that, although it’s not a medical university, a lot of the components for medical research are already here.”

Hawker, focusing on cardiovascular disease, says his team constructs a nano-vehicle with the homing peptides on the outside. Inside they tuck away a diagnostic unit for later scanning, usually by magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging, plus the therapeutic payload.

Both imaging techniques deliver enhanced 3-D pictures of the body showing where the targeted nanoparticles have bound to the diseased tissue, what stage the disease has reached, and thus where and how much treatment the patient requires.

Attaching the targeting peptides to a specifically-designed nanoparticle, effectively changing its shape, size and surface chemistry, makes it more difficult for the liver and kidneys to recognize and expel. This added stealth crucially prolongs circulation in the bloodstream, giving the nanoparticle more time to find and latch onto its target.

Hawker says it’s possible to fine-tune this process for between one and 48 hours, allowing enough time to screen suspect patients. The bottom line, he says, is to catch the disease as early as possible and treat it before it spreads or becomes more life-threatening.

Frank Doyle, professor of chemical engineering, focuses on controlled drug delivery for one very specific medical issue: improved insulin dosing for Type 1 diabetes.

Doyle and his research group are developing an artificial pancreas system (APS) which will automatically maintain desired blood sugar levels without patient involvement, monitoring and adjusting those levels by administering insulin.

Type 1 diabetes most often initially affects children and young adults, who then have to manage the condition for the rest of their lives. Among juveniles especially, says Doyle, compliance is not always 100 percent, and mistakes can be made, sometimes with serious consequences.

The artificial pancreas software Doyle’s group has developed, combined with a continuous blood glucose monitor and an insulin delivery pump, provides an extra level of care and eases the burden on patients.

The artificial pancreas system will use wireless signals to take readings and make adjustments almost continuously, thereby smoothing out the peaks (hyperglycemia) and troughs (hypoglycemia) in blood sugar which typically plague diabetics.

Doyle says the device will eventually be tailored for individual patients, taking into account changeable elements like exercise and stress, and creating a fully automated system working without any outside intervention.

Clinical trials started in Israel last year; Doyle and his team are now waiting for the FDA

to green light U. S. testing. The team, including senior investigator Eyal Dassau, Matt Percival, Benyamin Grosman, Rebecca Harvey and Youqing Wang, have been working with doctors Lois Jovanovic and Howard Zisser at the Sansum Diabetes Research Institute in Santa Barbara.

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