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Panacea

A new generation of drugs promises stealth, precision, monitoring and cure all in one package, says James Mitchell Crow

MODERN medicines are weapons blunted by compromise. All they need to do is home in on a target and hit hard. But that is nigh on impossible even for the most advanced of their kind. Delivering a drug into the bloodstream, where the body's immune defences and waste-disposal agents are ready to spring into action, is hard enough. Then, more like cluster bombs than guided missiles, most drugs will cause some collateral damage as they spread willy-nilly through your body. The force of the hit inevitably comes down to a trade-off between a medicine's effect on the disease and its effect on you.

So painkillers ease pain, but can interfere with other parts of the nervous system and make you drowsy; drugs for autoimmune conditions such as arthritis and multiple sclerosis can suppress the whole immune system and increase the risk of serious infection; and anti-cancer drugs kill tumours and healthy tissues alike. Such side effects severely restrict the dosage of some drugs and rule out the use of others entirely.

Perhaps not for much longer. Futurists make much of the prospect of nanobots, tiny, electrically-steered drones that might one day enter our bodies and cure all from inside. But a new class of minuscule, multifunctional stealth drugs might do much of what nanobots promise with only a fraction of their complexity. Equipped with stealth cloaks to pass through the bloodstream, they know how to protect both themselves from our bodies and our bodies from them. They can be programmed to deliver their toxic cargo on cue exactly where it is needed and nowhere else. Tweak them a little more, and they might even diagnose and monitor a disease's progression. And with these medical multi-tools, the smarts are all in the design.

Talk of smart drugs for cancer and other diseases has been around for decades, with little really to show for it. One exception was an anti-tumour treatment called Doxil, approved by the US Food and Drug Administration (FDA) in 1995. For patients with an AIDS-related cancer called Kaposi's sarcoma, it seemed a sure step into the future. Doxil was based on an existing drug, doxorubicin, which could only be given in very low doses due to a troublesome side effect – it was cardiotoxic, potentially triggering heart failure.

Protective packaging

Doxil's innovation was to pack the drug's active ingredient into a fatty envelope just a few tens of nanometres across, known as a liposome. The potential of liposomes to slow a drug's release and reduce toxic side effects had been recognised in the 1960s, but the first attempts to harness it proved pretty hopeless. Rather than unloading their cargo only when they reached their targets, they leaked slowly as they went. More damningly, from the outside liposomes looked rather like viruses. They were quickly disposed of by the immune system before they could even set to work.

The solution to this second problem took two decades to find. It was to decorate the surface of liposomes with water-loving materials called polyethylene glycol, or PEG, polymers. The sheath of water molecules that clung to the PEG-coated particles proved enough to mask the liposomes' true identity from the immune system's sentries and allow them free passage. With the drug's active molecule encased in this nanoscale capsule, a slow trickle of anti-tumour agent could be let out without troubling the heart.

"Doxil was a landmark in the field," says Kostas Kostarelos, a chemical engineer who heads the Centre for Drug Delivery Research at University College London. The drug has since been approved to treat other cancers, such as ovarian cancer. But it and a couple of other drugs using subtly different forms of nanocapsule have been rare successes. When Kostarelos started work in the early 1990s, up to 40 labs were working on liposome technology. "All of this effort collectively led to the approval of one compound," he says.

And Doxil only partially delivered on the promise of encapsulated drugs. While it has cut the side effects, it is no more selective in targeting cancer cells than naked doxorubicin. "Current cancer therapy is a sledgehammer approach," says chemical biologist Ali Tavassoli of the University of Southampton, UK. "We are indiscriminately hitting all cells with very toxic molecules."

In theory, changing that should have been simple. Since Doxil's release, researchers ›

have been developing techniques for decorating the capsules with antibodies that latch specifically onto tumours. But it has proved difficult to design a liposome envelope that is robust enough to prevent the active ingredient leaking out in transit, while also unloading its cargo quickly once the antibodies have docked. Too much of it is left inside by the time the body's defences discover the capsule and remove it, generally within a few days.

As so often on the tortuous routes of drug discovery, an alternative approach stretches back a long way. In the 1970s, researchers such as Robert Langer of the Massachusetts Institute of Technology began to develop controlled-release polymers for medical use. Unlike liposomes, which essentially contain a single ingredient, these polymers can be made from complex mixtures of molecules. By varying the recipe slightly, different drug-release properties can be induced.

Perhaps the most promising material is PLGA, a polymer that combines glycolic acid and lactic acid. Once inside the body, it slowly starts to break down. The more glycolic acid the mixture contains, the faster this happens, allowing drug makers to determine, to an extent, how soon the drug nestled within it is released. Implants using PLGA have been approved for human use since the mid-1990s, inserted under the skin to release a steady trickle of the drug into the blood. Examples include the brain tumour treatment Gliadel and a prostate cancer implant called Zoladex.

"Results so far seem to show the capsules' improved seek-and-destroy abilities: those treated are responding at half the dose of the naked version"

In 2002, Langer teamed up with Omid Farokhzad of Harvard Medical School in Boston. The pair began to experiment with bringing together in one nanoscale package all the components needed for targeted, effective drug delivery: the controlled release core with the active ingredient inside, the surrounding PEG stealth cloak, and an outer layer of targeting antibodies. Such a package would be small enough to bring its cargo directly into cells. But this promise came with a problem. The large number of components and variables such as size, surface properties and rate of drug release and degradation made engineering the most effective drug a huge challenge.

To tackle it, Langer and Farokhzad have pioneered a way to generate an array of self-assembling candidates, using high-speed screening to pick out the best one. "To re-optimise the drug after encapsulation, you need to create libraries of nanoparticles with slightly different properties," says Farokhzad. By making small changes to the ratio of ingredients, or the temperature or processing time, they could progressively alter – and so optimise – their particles.

The result is two medicines, developed by spin-off companies, that have passed rapidly through preclinical testing and into small-scale phase I clinical trials. BIND Therapeutics is trialling a tumour-hunter called BIND-014, a polymer-wrapped version of the cancer drug docetaxel. Results so far seem to show the capsules' improved seek-and-destroy abilities: those treated are responding at half the dose of the naked version (*Science Translational Medicine*, vol 4, p 128ra39). Kostarelos, who is not involved with the research, is encouraged. "The trial illustrates that actively targeted nanoparticles can offer patient benefits," he says.

Meanwhile, Selecta Biosciences is developing a multi-component vaccine to help people quit smoking. Its controlled-release polymer sets loose an "adjuvant" that primes the immune system for action, alongside an antigen that trains immune cells to seek and destroy nicotine. The principle should work for other potential vaccines, says Farokhzad. One possibility might be to selectively shut down the overactive immune responses seen in diseases such as multiple sclerosis without compromising the ability of the immune system to fight off infections, as existing immunosuppressant drugs do.

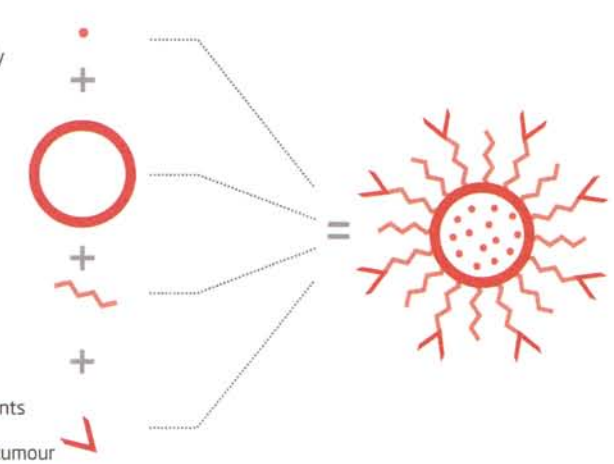
It is too early to say how well the vaccine does in humans, as Selecta has yet to release any data, but the company recently announced a deal with pharmaceutical giant Sanofi Aventis to develop nanoparticle-based vaccines against food allergies.

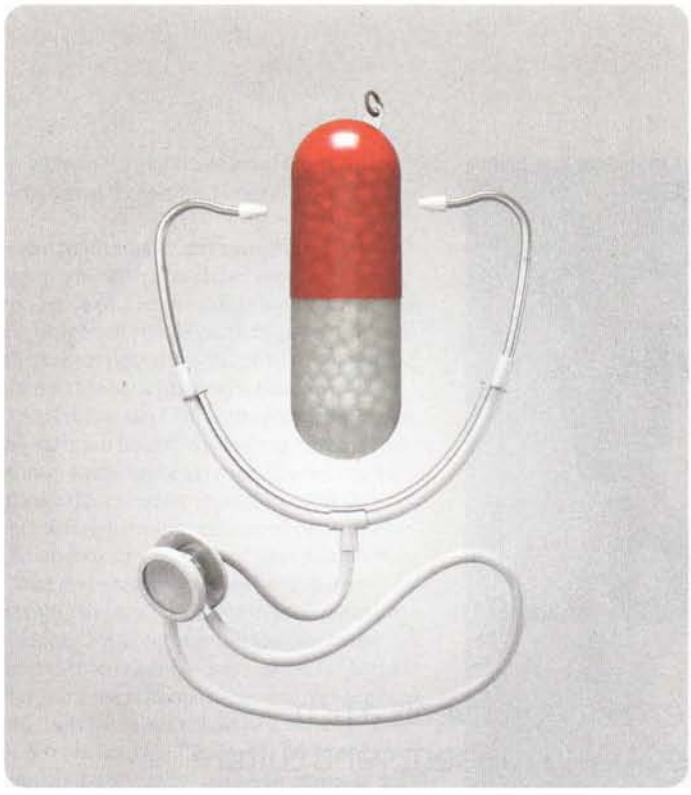
Meanwhile, in the lab, Farokhzad and Langer are extending the multi-cargo principle to cancer drugs. In one proof-of-concept study, they showed that nanocapsules loaded with two drugs – one to soften up the tumour, and one to deliver a precisely timed knock-out blow – were at least five times as potent as either encapsulated drug alone (*PNAS*, vol 107, p 17939).

Joseph DeSimone of the University of North Carolina, Chapel Hill, is trying a different approach. Rather than self-assembly, he is making nanoparticles in the equivalent of an ice-cube tray, giving him full control over their size and shape and a freer hand over their constituents. His spin-out company, Liquidia Technologies, has a seasonal flu vaccine in phase I trials, and another pharmaceutical giant, GlaxoSmithKline, is testing the

All in the design

With cunning chemical engineering, drugs can be cloaked with components that protect them from the body's defences and steer them to the right place, making treatment more effective





technology with its own vaccines.

The moulded particles can be engineered into many sizes and shapes for different purposes. Pollen-shaped particles, for example, make a dry powder that can be inhaled rather than injected, and can also be sculpted to attract the attention of specific target cells in the body. That could provide a route to more effective vaccines against tuberculosis, a disease caused when airborne bacteria attack immune cells known as macrophages in the lungs. Inhaled vaccine particles with an affinity for macrophages could prime the cells to spew out antibody-generating antigens, allowing the immune system to recognise and deal with them in the event of a real infection.

DeSimone thinks that the uniformity of his particles compared with those formed by self-assembly could be a help when it comes to approval by regulatory agencies. "The FDA hates heterogeneity in size and shape because it means that the particles can go in different places," he says. Farokhzad points to the counter-example of Doxil, which is not made up of particles of a single size, but a uniform range. Variation could even be a boon, he says. Cancer is such a heterogeneous disease, for example in the shape and size of the blood vessel network that tumours develop, that a treatment based on particles with a range of sizes potentially offers a better treatment.

Kostarelos says the existence of rival approaches to make encapsulated drugs can only be beneficial. "Thanks to all the different nanoparticle technologies people are exploring, acceleration of the drug approval rate is bound to happen." Tavassoli is working on alternative ways to target drugs, such as by homing them in on the extensive new blood supplies that tumours have to create. That might remove the immediate need for a protective capsule, but even so he thinks the approach could help. Before a molecule will even be considered as a potential drug, it must conform to tough criteria. For example, it must be water-soluble enough to dissolve within a cell, but hydrophobic enough to cross the lipid membranes that surround them. If you can give a capsule those properties, the active molecule doesn't have to have them, possibly making many more structures available for use.

Innovation ahead

There are more radical options out there, too. One is to design particles to catch a ride on a cancer cell's machinery for ferrying deliveries to its innards. Only once sucked inside the cell does the capsule release its payload, for instance in response to the relatively acidic environment found in tumour cells. That's what Nobuhiro Nishiyama and Kazunori Kataoka at the University of Tokyo and their colleagues did recently, using capsules loaded with a DNA-targeting anticancer drug called DACHPt and tagged with a further fluorescing molecule. By tracking the fluoresence they showed how the drug was delivered right to the doorstep of the cancer cell's nucleus, where its DNA is stored, evading the defensive proteins that drug-resistant tumour cells deploy on their periphery (*Science Translational Medicine*, vol 3, p 64ra2).

This inbuilt imaging capability is one step towards what the researchers regard as the big prize: theranostics. These are capsules that, alongside their therapeutic cargo, also carry a medical imaging payload to give doctors patient-specific diagnostic data. "Imagine being able to treat cancer, and every time you dose the patient you follow it with a test scan to show disease regression as a function of your drug delivery," says Farokhzad.

It is something he and others are already experimenting with in their labs. Adding fluorescent dyes to the capsules, or brightly fluorescing nanocrystals called quantum dots, is one possibility. These might be engineered to fluoresce only once the drug cargo is released, tracking delivery. Another avenue is to add specks of a magnetic material, such as iron oxide, so that the theranostic can be tracked using MRI scans. For a drug selectively targeting tumour cells, monitoring where they stick could reveal whether a cancer is shrinking or spreading.

Based on progress so far, Farokhzad predicts that theranostics will enter clinical trials within the decade. Kostarelos is also working on the idea, mainly as a tool to enable researchers to assess whether a nanocapsule is behaving as intended.

In a clinical setting, though, Kostarelos is less convinced of the need to combine so many functions in one drug. "The more complicated they get, the less attractive they are to pharmaceutical companies and the regulatory authorities," he says. It becomes more difficult, and more expensive, to make a commercial product that is reliably safe in all situations.

Although Farokhzad does not disagree, he points out that commercialisation always lags behind innovation. "If we can be equally innovative as to the way that these particles are manufactured, there is no reason why they shouldn't ultimately appear in the clinic," he says. In the meantime, nanocapsule weapons will be judged not by how cleverly they are designed, but whether they help win the war against disease. "If you're a patient with cancer, that's all you really care about – to get better," says Farokhzad. ■

James Mitchell Crow is a freelance writer based in Melbourne, Australia