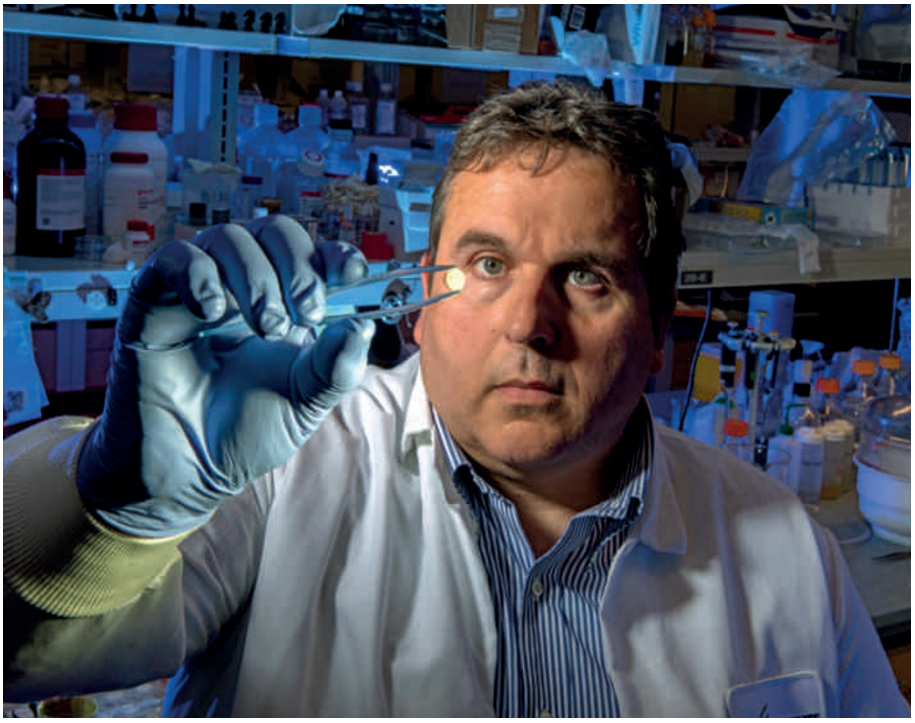

RICK FRIEDMAN

Biomaterials specialist Ed Doherty inspects a freshly made vaccine implant.

CANCER VACCINES

Material breach

An experimental vaccine implanted beneath the skin could usher in biomaterial-based immunotherapies for cancer.

BY ELIE DOLGIN

Ed Doherty ejects a tiny white disc from the hydraulic lab press in front of him and drops it into the palm of his hand. This device, about the size of an aspirin tablet, is a surgical implant that could have a huge clinical impact: it recruits and stimulates immune cells to attack tumour cells specific to an individual patient. And it is so easy to make that it could herald the future of personalized cancer-vaccine therapy. "You could have one of these set-ups at every hospital across the country," says Doherty, a biomaterials researcher at Harvard University's Wyss Institute for Biologically Inspired Engineering in Boston, Massachusetts.

Each implant contains cellular growth factors, DNA and bits of freeze-dried cells excised from a patient's own tumour, all contained within a scaffold that dissolves safely in the body over the course of about six months. This experimental vaccine does not contain living cells, which means that researchers can make multiple implants at once with just one round of manufacturing per patient. By comparison, other patient-specific cancer vaccines — such as sipuleucel-T, a cell–based vaccine marketed as Provenge by biotech company Dendreon of Seattle, Washington — take days of labour-intensive cell preparation for each round of treatment. And Provenge, the only FDA-approved therapeutic cancer vaccine, requires a processing plant to grow the required number of cells needed to stimulate an anticancer response from the immune system, whereas the implantable vaccine from Doherty and his colleagues uses a patient's own body as its immune-stimulating factory.

The disc resting in Doherty's hand has been designed to test cancer treatments in mice. But a few blocks away at the Dana-Farber/Brigham and Women's Cancer Center, Doherty's colleagues are fabricating similar devices for an experimental vaccine to treat people with advanced melanoma, the only clinical trial of its kind. "It's extremely exciting to couple materials science with the new insights into cancer immunology," says Glenn Dranoff, a cancer immunologist at the Dana-Farber who helped develop the vaccine, dubbed WDVAX. "This is one of the most exciting projects of my career."

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See how one patient is faring on a cancer vaccine:
go.nature.com/yfvwwi

Beyond WDVAX, researchers are combining biology and materials science to engineer a host of delivery devices for potential cancer immunotherapies, from nanoparticles to injectable gels. Each new approach is an attempt to solve substantial problems with existing immunotherapies, such as a lack of cell specificity, dangerous side effects, and a short half-life once inside the body. The new materials-based strategies can deliver immunotherapies to specific organ systems and, at least in pre-clinical models, elicit more controlled and prolonged antitumour responses. "There's a trend now to rationalize the design of these systems so they can deliver different types of immune-modulating drugs in a reliable way," says Tarek Fahmy, a biomedical engineer at Yale University in New Haven, Connecticut.

So far, the most promising results of bioengineered immunotherapies come from studies on mice. In fact, data from the WDVAX vaccine in mice were so compelling[1,2] that all eyes have turned now to the human trial. "The biology and preclinical work completely make sense to go forward," says Dana-Farber oncologist Stephen Hodi, who is leading the trial. "Now, we just have to determine safety and efficacy."

As part of Hodi's phase I trial, patients with metastatic melanoma, in which the cancer has spread from its original site, began receiving the cancer-killing implants in late August 2013. The two-year trial aims to enrol 25 participants, each of whom will receive a total of four vaccine implants over the course of several months.

SCAFFOLD SPECIFICATIONS

WDVAX is the brainchild of Dranoff and Harvard bioengineer David Mooney and its strategy is predicated on recruiting and programming immune cells within the biomaterial implant. To facilitate this, the implant includes a backbone of biodegradable plastic loaded with a mix of the same three ingredients used by Doherty in his mouse prototype — a combination of dried-up tumour proteins, a growth factor and DNA molecules — all of which are brought together using a high-pressure gas foaming procedure to yield a porous scaffold into which immune cells can penetrate. The end product, says Doherty, feels like a "punched out kitchen sponge".

Now that WDVAX has proven effective in mice, it must be proven safe in humans — something the researchers believe should be straightforward. All four elements, individually, "are known to be safe", Mooney says, "and are known to be safe at much greater quantities than what we're using."

The plastic backbone is made from a polymer called polylactide-co-glycolide, which is commonly found in dissolvable stitches. The growth-factor protein, granulocyte-

macrophage colony-stimulating factor, is already sold as sargramostim (Leukine) to help cancer patients make more white blood cells; it acts by recruiting immune-system messengers called dendritic cells (see 'Evidence presenter', page S9) into the plastic structure. And the synthetic DNA molecules known as CpG oligonucleotides, which stimulate dendritic cells by mimicking a bacterial infection, have been tested extensively in clinical trials as a vaccine adjuvant.

The only novel ingredient is the patient-derived melanoma extract. This ground-up tumour biopsy serves as the antigenic material that the dendritic cells relay to other parts of the immune system, teaching it that these are foreign substances that must be eliminated. Since the melanoma extract is taken from the patients' own tumours, it should not pose a health risk, according to Mooney.

In 2009, Mooney, Dranoff and their colleagues, led by Harvard graduate student Omar Ali, showed that dendritic cells activated by the mouse version of the WDVAX implant headed directly to lymph nodes near the tumour, where they primed the immune system's T cells to kill cancerous cells, leading to tumour regression. Such a targeted approach avoided the side effects caused by systemic therapies, and it proved extremely effective in mice with an aggressive form of melanoma that normally kills the animals within three weeks. Ninety per cent of the mice that were vaccinated before tumour onset survived for at least three months[1], and about half of the animals that received two vaccine implants after the cancer had already taken hold displayed similar rates of survival[2].

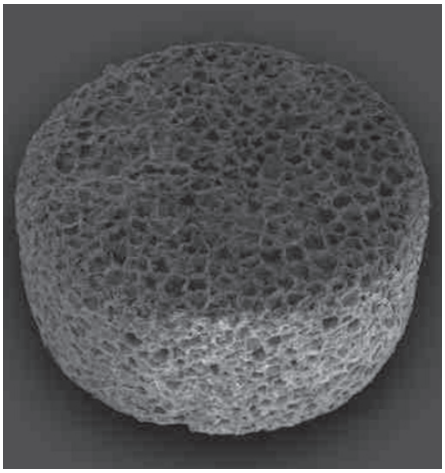
Willem Overwijk, a tumour immunologist who studies melanoma vaccines at MD Anderson Cancer Center in Houston, Texas, finds the data impressive. "The immunology is sound and the antitumour effects are pretty significant," he says. "I think there's some real possibility for this approach."

In unpublished work, the researchers have also combined their vaccine with antibodies that block either the protein cytotoxic T-lymphocyte antigen 4 (CTLA-4) or a protein called programmed death 1 (PD-1), two immune checkpoint receptors that are a major focus of the pharmaceutical industry. A single dose of the vaccine alone slowed cancer growth (but did not eliminate disease) in mice with established melanoma, and the anti-CTLA-4 or anti-PD-1 antibodies provided little benefit on their own. However, the combined approach led to tumour eradication in more than half the animals tested. "There may be some synergy between these approaches to promote tumour regression," says Mooney.

TARGET PRACTICE

Although WDVAX may be the first bioengineered immunotherapy used to treat patients, it is not the only one in development. Rather than using a device that must be surgically implanted, other researchers are engineering materials that — once injected into the body — can track down immune cells either around the tumour itself or in nearby lymph nodes.

For example, Darrell Irvine, a bioengineer at the Massachusetts Institute of Technology in Cambridge, is targeting tumours and the corresponding lymph nodes at the same time. As with WDVAX, Irvine is aiming for a treatment that is more specific than current therapies so as to kill only the malignant cells and leave healthy ones intact. He and his team tethered two molecules — both of which promote T-cell responses against many types of tumours but which can lead to inflammation — onto plastic-coated fat globules, each about 200 nanometres in diameter[3].



JAMES WEAVER/WYSS INSTITUTE

A vaccine implant up close and personal.

When injected directly into melanoma tissue in mice, these drug-coated nanoparticles became trapped inside the tumours and the nearby lymph nodes. Around two-thirds of the animals treated in this way experienced complete tumour regression, with no signs of the inflammatory side effects that can be lethal in this mouse model. "You're getting very potent immunotherapy stimulation, but you're avoiding toxicity because you keep the therapeutics out of the systemic circulation," Irvine says.

Similarly, Fahmy and his colleagues at Yale have engineered even smaller drug-laced nanoparticles that get trapped in the blood vessels surrounding tumours, where they release their payload to activate both the adaptive and non-adaptive arms of the immune system[4]. Meanwhile, bioengineers Melody Swartz and Jeffrey Hubbell at the Swiss Federal Institute of Technology in Lausanne made nanoparticles just 30 nanometres across, with CpG molecules anchored to their surfaces. When injected into the skin, these tiny particles migrate into the lymph nodes where the CpG adjuvant helps augment the body's natural anticancer responses[5].

"You just load that lymph node up with adjuvant," says Swartz, "and then you can activate T cells against the tumour antigens that have drained there naturally."

BEYOND MELANOMA

Now that WDVAX has moved into clinical trials for melanoma, Mooney has stepped back into the lab to see how else his implantable-vaccine design might be used.

Together with InCytu, a Lincoln, Rhode Island–based company that had licensed the technology (the licence has since been returned to Harvard, which is co-sponsoring the ongoing clinical trial), Mooney's team has shown that a vaccine containing antigens from a type of brain cancer known as glioma successfully induced tumour regression when implanted into the heads of afflicted rats[6]. Now, Mooney and Dranoff have funding to test the strategy in breast cancer, perhaps with a defined antigen like human epidermal growth factor receptor2 (HER2) instead of the extract from a patient's tumour. Although not patient-specific, such a vaccine could have the advantage of mass production. "We're beginning to explore much more broadly," Mooney says.

Because all of Mooney's vaccine implants require minor surgery, he is also exploring ways to make the strategy less invasive. For example, he's investigating a method that would swap out the polymer scaffold for a gel of porous microparticles; following injection under the skin, these particles clump together to form a sort of immune-priming depot. "This could be more easily administered than something that needs to be implanted," says Krishnendu Roy, a biomedical engineer at the Georgia Institute of Technology in Atlanta.

In his own lab, Roy has shown that this kind of gel-based vaccine, when loaded with immune-activating components, can boost antitumour T-cell activity in a mouse model of the blood cancer B-cell lymphoma[7]. "It's just an injection like anyone would take for any other kind of vaccine," he says.

Therein lies the beauty of most materials-based immunotherapies, says Mooney. The engineering may seem complex to cancer biologists, who might not be as familiar with certain technologies, but the implementation is very easy for any physician to understand. "It's stunning," he says, "just how simple this is." ■

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