Therapeutic cancer vaccine survives biotech bust

Pharmaceutical company rescues landmark prostate-cancer treatment, Provenge.

- Heidi Ledford

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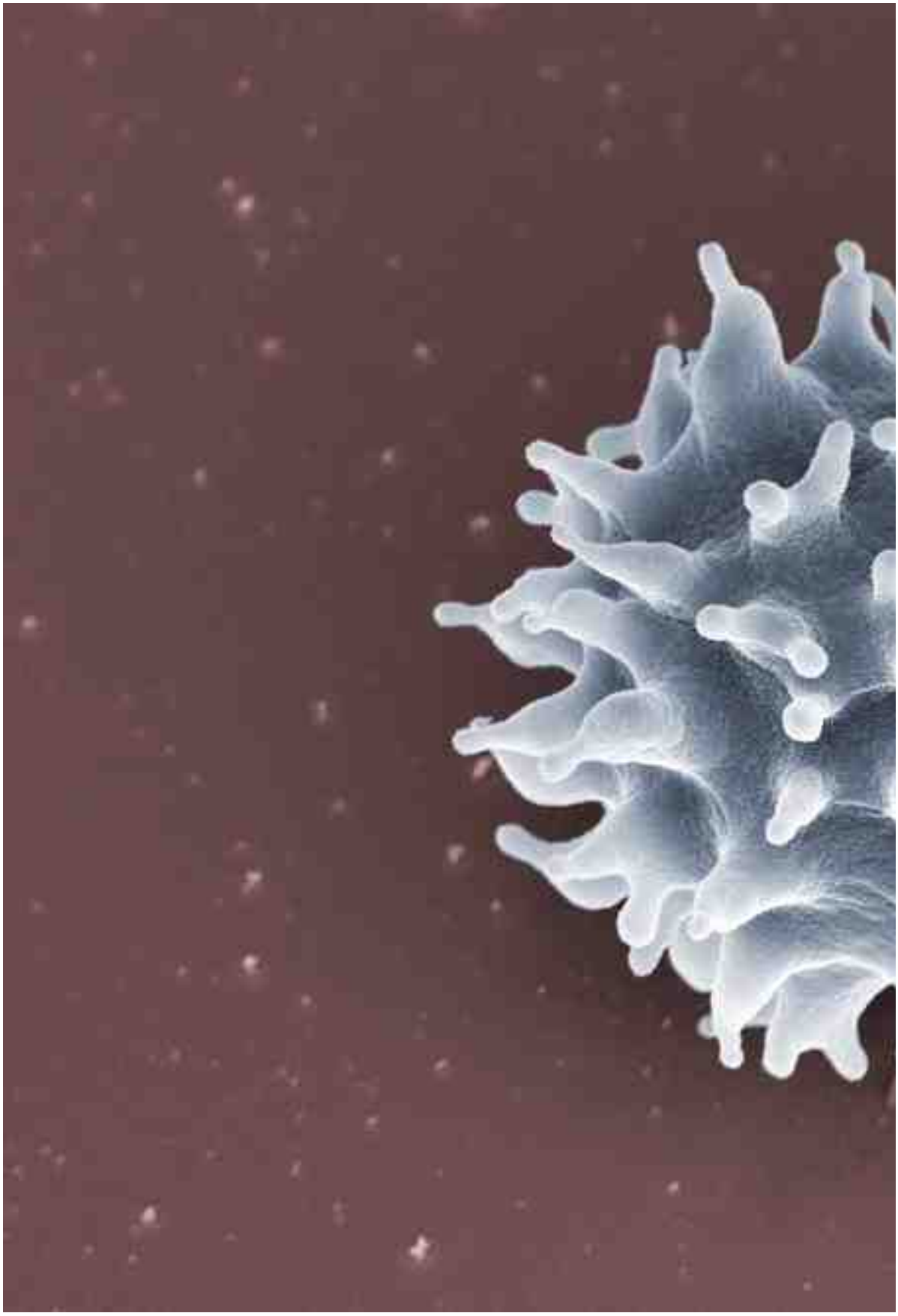

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Therapeutic cancer vaccines harness the patient's own immune system to fight tumours.

The first therapeutic cancer vaccine to be approved in the United States will stay on the market despite the financial collapse of the trailblazing biotechnology company that developed it. The vaccine, Provenge (sipuleucel-T), was purchased on 23 February by Valeant Pharmaceuticals of Laval, Canada, which paid US$415 million for the prostate-cancer treatment and other assets of the bankrupt Dendreon Corporation.

The now-defunct Dendreon, of Seattle, Washington, made history in 2010 by showing that complex treatments made fresh for each patient could win regulatory approval, and could be expanded beyond the realm of specialized academic hospitals. Industry took note: today, experimental cancer therapies that spur patients' immune cells to attack tumours are among the hottest properties in biotechnology.

“Dendreon had vision and foresight,” says Usman Azam, head of cell and gene therapies at Novartis, a Swiss pharmaceutical company that has purchased one of Dendreon’s manufacturing plants to fuel its own cell-therapy efforts. “Don’t view Dendreon as a failure: it paved the way.”

But although Dendreon created the market for cell therapies, it ultimately could not survive in it.

Primed for attack

Provenge is made by harvesting a patient’s dendritic cells and then mixing them with a protein that is particularly abundant in prostate tumours. After being primed by that process to recognize and attack the tumour, the cells are infused back into the patient.

The technique was pioneered in the early 1990s by Edgar Engleman, an immunologist at Stanford University in California, who had seen promising results in animal studies of a different cancer, lymphoma. Engleman teamed up with fellow Stanford immunologist Samuel Strober to work out ways to make the process more efficient.

When the two pitched their idea for a company to investors, they had little clinical data and were too optimistic about how fast the treatment could reach patients, says Strober. The company was an enormous gamble: harnessing the immune system to fight cancer was still a controversial idea, and no other company had marketed a therapy so personalized and labour-intensive. “But at that time it was a little different from now,” says Strober. “Companies were getting funded on the basis of promise, rather than actually looking at their capacity for early commercial success.”

Engleman and Strober founded Dendreon in 1992; the US Food and Drug Administration approved Provenge in 2010.

Short-lived victory

The approval was celebrated as an important proof of concept by researchers working to develop cancer vaccines and other treatments that stimulate immune responses to the disease. But Dendreon, already strained by the long wait for approval, soon ran into financial difficulty.

Confusion over how payment for Provenge would be reimbursed by insurance companies left

many doctors in the United States hesitant to use it, says Corey Davis, an analyst at Canaccord Genuity, an investment bank based in Toronto, Canada. When revenues came in far below the company's initial estimates, Dendreon failed to adjust its operations accordingly, Valeant chief J. Michael Pearson told investors on 23 February.

Provenge is, at first glance, an odd purchase for Valeant, a company known for acquiring relatively simple, established products — for example, it controls 10% of the US contact-lens market. But Valeant saw an opportunity to cut costs and improve how the vaccine is marketed to doctors, and thinks it can make back its investment in less than two years, says Davis.

The vaccine's rescue is a relief to Engleman, who had feared that Provenge might disappear along with Dendreon. As the company struggled financially, the scientists who founded it watched helplessly from the sidelines. "This was our baby," says Engleman. "It was extraordinarily frustrating. There was nothing we could do."

Early choices

In retrospect, Engleman says, some early scientific choices may have exacerbated Dendreon's struggle. The company decided not to develop ways to freeze the stimulated immune cells, he notes, which could have simplified the procedure and lowered its cost.

And both scientists lament the choice of prostate cancer as the inaugural disease target of the technology. Although the early lymphoma data had been very promising, recalls Engleman, the company decided to switch to a more common cancer with a bigger potential market. And prostate cancer had another advantage: people can live without a prostate, which helped to calm fears (since proved unfounded) about what would happen if the primed immune cells attacked healthy tissue.

But the results in prostate cancer were not as dazzling as Engleman had hoped on the basis of his animal results in lymphoma. Dendreon did extend survival in some people with advanced prostate cancer, but by a median of only four months[1]. This week, the UK National Institute for Health and Care Excellence advised that at more than £47,000 (US$73,000) per course of treatment, Provenge is too expensive to justify its use by the National Health Service.

The Dendreon experience has not dampened Engleman's enthusiasm for entrepreneurship. He and Strober, along with other collaborators, have teamed up on a company that aims to develop a technique to reduce the likelihood that recipients of transplanted organs will develop an immune response to the new tissue.

They are again on the hunt for funding, but this time the team is backed by more than a decade of clinical-trial data that backs the method. "We're thinking that this one will progress a lot faster than the Dendreon thing," says Strober.

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References

1. Kantoff, P. W. *et al*. N. Engl. J. Med. 363, 411–422 (2010).

Immune cells boost cancer survival from months to years

Firms embrace costly immunotherapy to fight intractable leukaemias and lymphomas.

- Heidi Ledford

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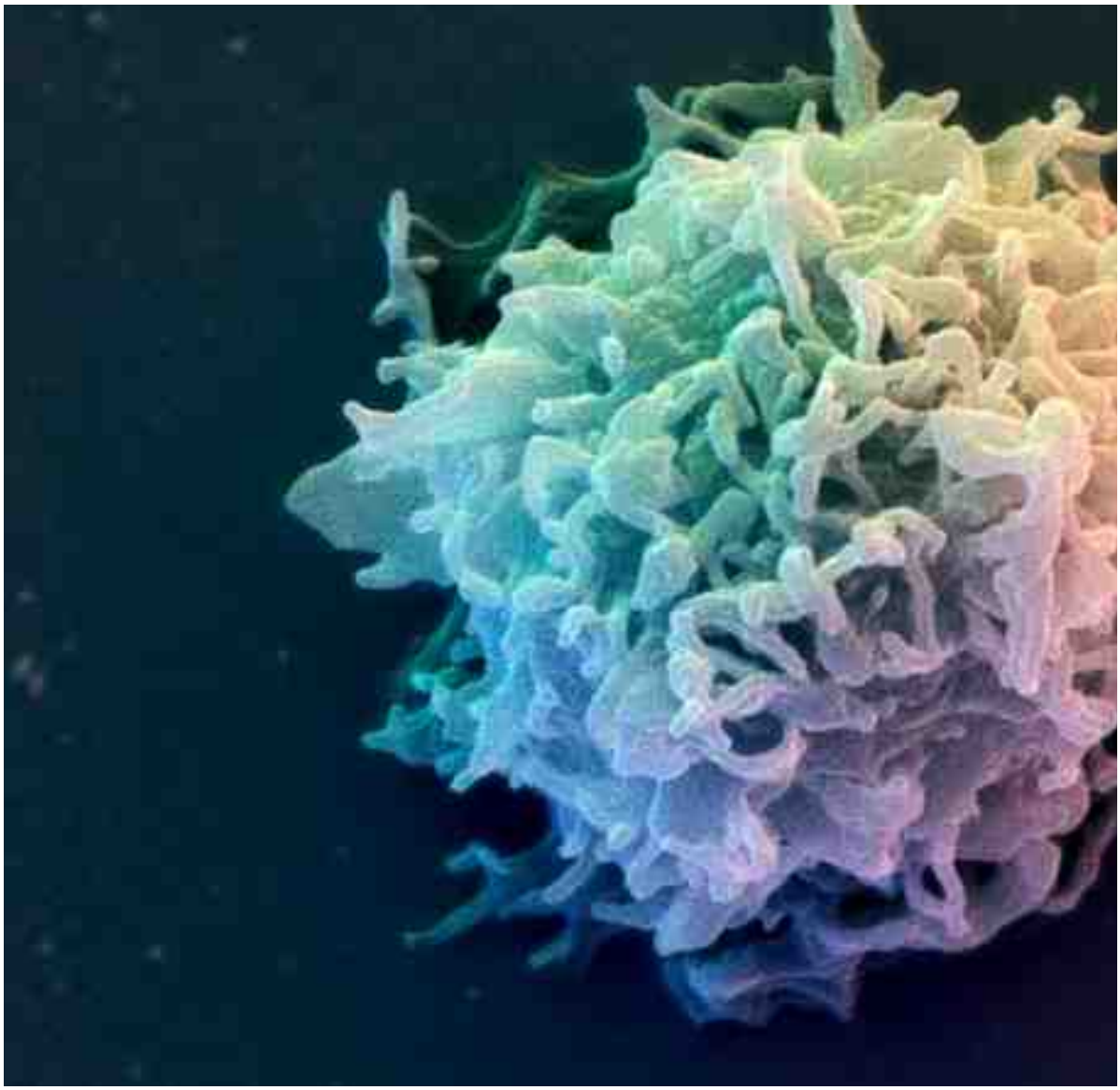

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Therapies that make use of a patient's own T cells, a component of the immune system, are showing promise in the clinic.

When immunologist Michel Sadelain launched his first trial of genetically engineered, cancer-fighting T cells in 2007, he struggled to find patients willing to participate. Studies in mice suggested that the approach — isolating and engineering some of a patient's T cells to

recognize cancer and then injecting them back — could work. But Sadelain did not blame colleagues for refusing to refer patients. “It does sound like science fiction,” he says. “I’ve been thinking about this for 25 years, and I still say to myself, ‘What a crazy idea’.”

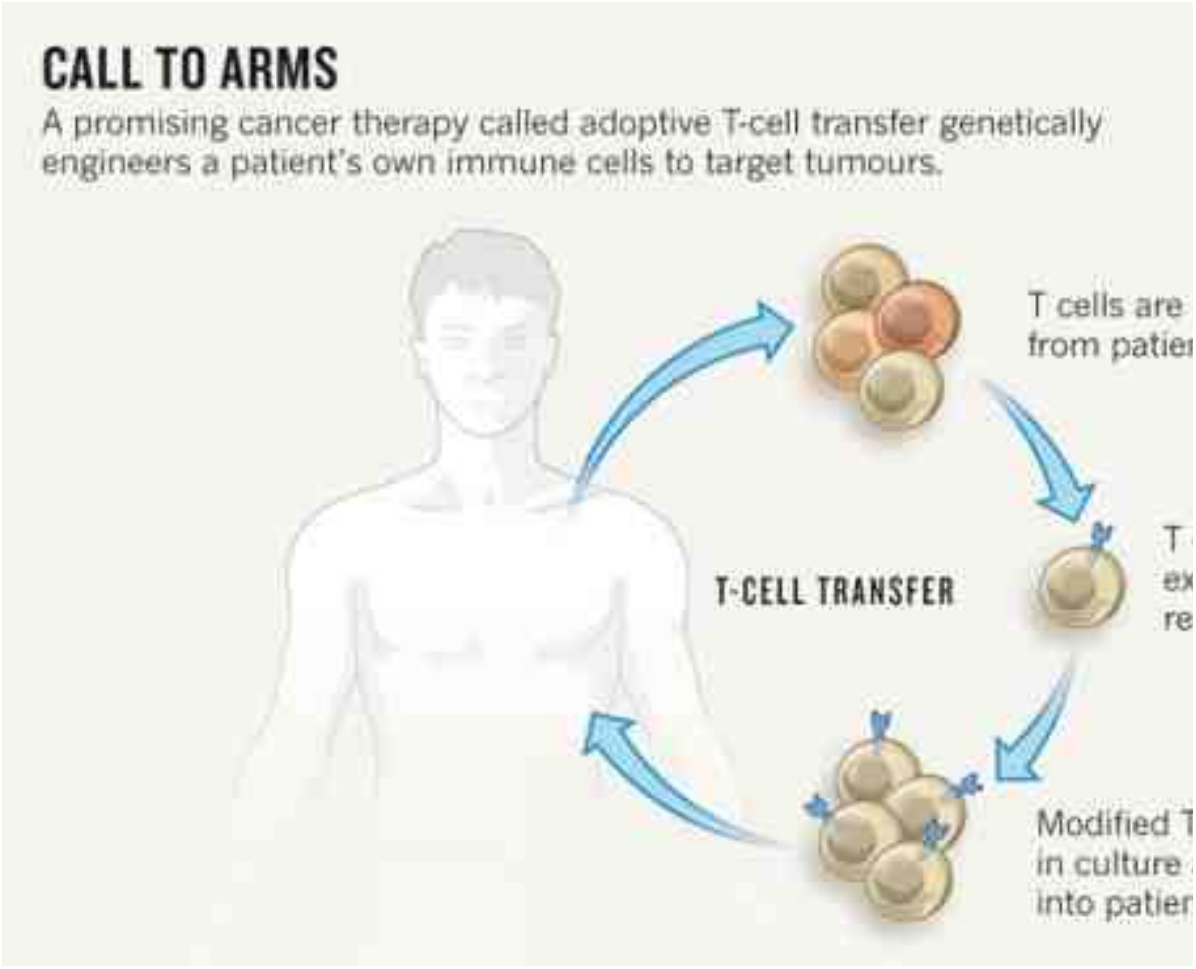
Since then, early results from Sadelain’s and other groups have shown that his ‘crazy idea’ can wipe out all signs of leukaemia in some patients for whom conventional treatment has failed. And today, his group at the Memorial Sloan Kettering Cancer Center in New York City struggles to accommodate the many people who ask to be included in trials of the therapy, known as adoptive T-cell transfer.

At the American Society of Hematology (ASH) meeting held in San Francisco, California, on 6–9 December, attendees heard dozens of talks and poster presentations on the promise of engineered T cells — commonly called CAR (chimaeric antigen receptor) T cells — for treating leukaemias and lymphomas. The field has been marred by concerns over safety, the difficulties of manufacturing personalized T-cell therapies on a large scale, and how regulators will view the unusual and complicated treatment. But those fears have been quelled for some former sceptics by data showing years of survival in patients who once had just months to live.

“The numbers are pretty stunning,” says Joseph Hedden, an analyst for the London-based market-research firm Datamonitor Healthcare. “Companies have clearly decided that it’s worth the pitfalls of how much this therapy is going to cost to develop.”

At least five major pharmaceutical companies have invested in developing CAR-T-cell therapy over the past three years. Such interest from industry is a dramatic turn for a field that once consisted of a handful of academic medical centres. Small biotechnology firms have also sprung up to develop CAR T cells, including Kite Pharmaceuticals of Santa Monica, California, which raised US$127.5 million when it went public in June. And investors pumped $310 million into another CAR-T-cell company, Juno Therapeutics of Seattle, Washington, this year. “There is no doubt there has been a shift,” says Juno chief executive Hans Bishop.

Most of these efforts focus on killing the cancerous, antibody-producing B cells behind some leukaemias and lymphomas. Researchers do this by engineering T cells to recognize a protein on the surface of most B cells — CD19 — and attacking cells that display it (see ‘Call to arms’). Finding proteins that are expressed only on cancer cells can be difficult, and CD19 represents a compromise: the treatment sometimes wipes out all B cells, cancerous and healthy alike, but patients can survive without them.



At the ASH meeting, Sadelain and his colleagues reported that this approach left no signs of cancer in all six patients with lymphoma who were enrolled in one trial. In another presentation, immunologist Carl June of the University of Pennsylvania in Philadelphia showed that targeting CD19 reduced cancer burden in 9 of 23 patients with chronic lymphocytic leukaemia. In a more aggressive disease called acute lymphoblastic leukaemia, 27 of 30 patients had no signs of cancer after therapy and the CAR T cells remained in their blood two years later.

But studies also highlight the risks of revving up immune responses. In April, at least five CAR-T-cell trials were halted after a series of patient deaths linked to unusually high levels of a protein called interleukin-6, which promotes inflammation, as well as other inflammatory molecules. Interleukin-6 is part of the body's normal response to infection. But the intense immune onslaught launched by CAR T cells can send interleukin-6 levels soaring. The trials resumed after investigators adjusted their protocols to better monitor and treat the problem.

These safety risks, as well as the difficulty of manufacturing CAR T cells, are still putting many drug companies off, says Andrew Baum, the London-based head of global health-care research for Citi, an investment bank headquartered in New York City. "The bulk of the multinationals are standing back and watching, rather than getting engaged here," he says.

When CAR T cells do reach the market, they will not be cheap. Baum says that some sponsors are tentatively planning to price their therapies higher than bone-marrow transplants, which can exceed $500,000. The cost may be so high, he says, that companies are forced to set up a reimbursement scheme in which they are paid only when a patient benefits from the treatment. Baum estimates that peak sales of CAR-T-cell therapies will reach $10 billion annually,

although that amount will depend on what competing therapies emerge and whether the treatment can be extended to other cancers.

For now, Sadelain, a scientific founder of Juno Therapeutics, hopes that the attention from industry will spur the field. He remembers his postdoc days, when he struggled to insert genes into T cells and colleagues asked him why he was bothering. “We’ve never had this kind of investment in the field before,” he says. “It’s hard to believe — sometimes I still pinch myself.”

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Immune system offers clues to cancer treatment

Molecular signatures hint at who will benefit from next-generation cancer drugs.

- Heidi Ledford

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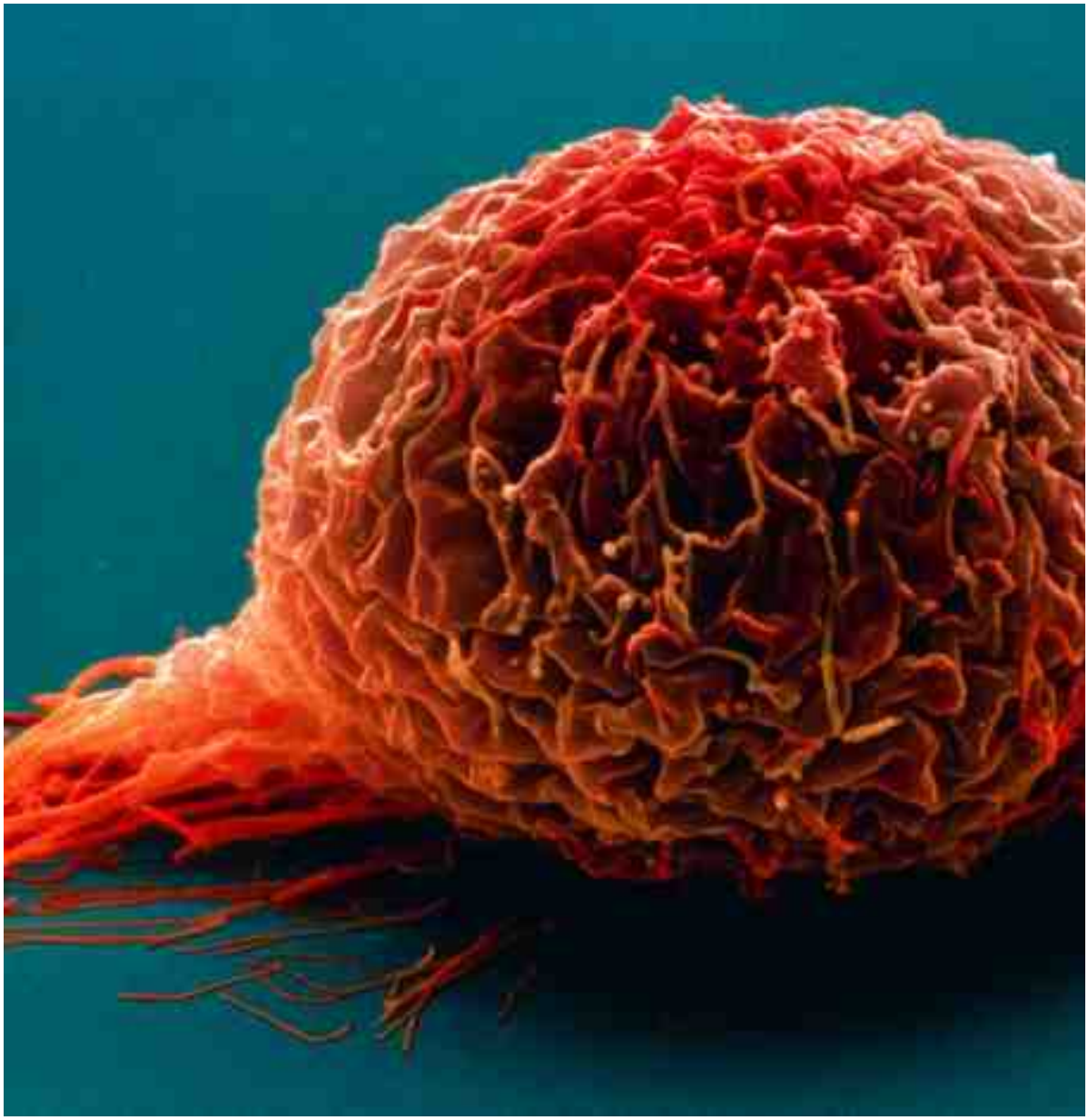

Steve Gschmeissner/Science Photo Library

Some bladder cancers appear susceptible to a treatment that interferes with a tumour's ability to suppress a patient's immune response.

In the quest to develop personalized cancer therapies, researchers are increasingly examining an individual's immune response to cancer to find ways to tailor treatments.

The shift comes with the emergence of therapies designed to unleash the immune system on cancer cells. Five studies in the 27 November issue of *Nature*[1–5] turn to the immune system to investigate which patients are likely to respond to cancer drugs that inhibit the activity of a protein called PD-1, and how tumours trigger immune responses. The approach is in contrast to earlier attempts at personalised therapies that focused on the tumour itself.

“We’re looking at a very different biomarker paradigm,” says Thomas Powles, an oncologist at the Queen Mary University of London, and lead author of one of the papers[1]. “We’re not focusing on the tumour cells, we’re focusing on the immune cells around the tumour.”

The PD-1 receptor on some T cells sends them into hibernation when bound to signaling protein PD-L1. This mechanism, which normally prevents autoimmune reactions, can be co-opted by opportunistic tumour cells to help them evade the immune system. Tumours that express PD-L1 are sometimes surrounded by a phalanx of impotent T cells.

Drugs that block PD-1 or PD-L1 can release those T cells and reactivating the immune system against the tumour. Those drugs have generated tremendous excitement for their ability to spark long-lasting responses in some patients with advanced cancers for which other treatments had fallen short.

But the drugs work for only a fraction of patients, and it is still unclear which cancers are susceptible. For example, Powles's paper provides the first evidence that a drug that blocks PD-L1 may work in bladder cancer[1], but early data from other studies suggest that prostate cancer may not be as vulnerable.

Signs of success

All of this has sent researchers scrambling to find ways to identify the patients and tumour types most likely to benefit from PD-1 therapy. Early efforts focused on measuring PD-L1 expression by tumour cells. But three of the five *Nature* papers instead explore the importance of PD-L1 expression on immune cells that have infiltrated the tumour[1–3].

The findings fit with models of how PD-1 and PD-L1 suppress immune responses to cancer, says Suzanne Topalian, an oncologist at Johns Hopkins University in Baltimore, Maryland, who was not involved with the studies. But because different researchers and companies use different methods to measure PD-L1 expression, it is impossible to compare results across studies, she notes. That means it is too soon to discount earlier results from her lab and others finding a correlation between response to therapy and PD-L1 expression on tumour cells, she says[6].

Antoni Ribas, a cancer researcher at the University of California in Los Angeles, argues that lack of PD-L1 expression on immune cells could be a sign that it is worth the added expense and toxicity to combine PD-1 drugs with another therapy that lures T cells to the tumour. But he and others warn against using the absence of PD-L1 expression to exclude patients from treatment with PD-1 therapies. "There is a certain percentage of patients whose tests are negative and they still respond to this drug," says Topalian.

Beneficial mutations

Two other reports pinpoint how mutant proteins on mouse tumours alert T cells in the first place[4,5]. Both teams catalogued the mutated protein sequences that are recognized by T cells and used them to design personalized vaccines to boost immune responses to the tumours. The approach worked: most of the mice rejected their tumours.

Clinical trials are underway to test similar personalized vaccines in humans, says Robert Schreiber, a tumour immunologist at Washington University in St Louis, Missouri.

But even if the approach works, it leaves behind those who lack the mutations needed to recruit T cells, says Jedd Wolchok, a cancer immunologist at the Memorial Sloan Kettering Cancer Center in New York, who was not involved with the work. "The question then becomes: what

do we do for the patients who don't have these favourable mutations?"

Wolchok notes that some conventional therapies, such as radiation and classical chemotherapies, may help to alert the immune system to the tumour by introducing new mutations to the tumour genome. "Only by bringing all of this together are we going to make progress," he says.

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References

1. Powles, T. *et al*. Nature 515, 558–562 (2014).
    - Article
    - PubMed
    - ChemPort
2. Herbst, R. S. *et al*. Nature 515, 563–567 (2014).
    - Article
    - PubMed
    - ChemPort
3. Tumeh, P. C. *et al*. Nature 515, 568–571 (2014).
    - Article
    - PubMed
    - ChemPort
4. Yadav, M. *et al*. Nature 515, 572–576 (2014).
    - Article
    - PubMed
5. Gubin, M. M. *et al*. Nature 515, 577–581 (2014).
    - Article
    - PubMed
    - ChemPort
6. Topalian, S. L. *et al*. N. Engl. J. Med. 366, 2443–2454 (2012).
    - Article
    - PubMed
    - ISI
    - ChemPort