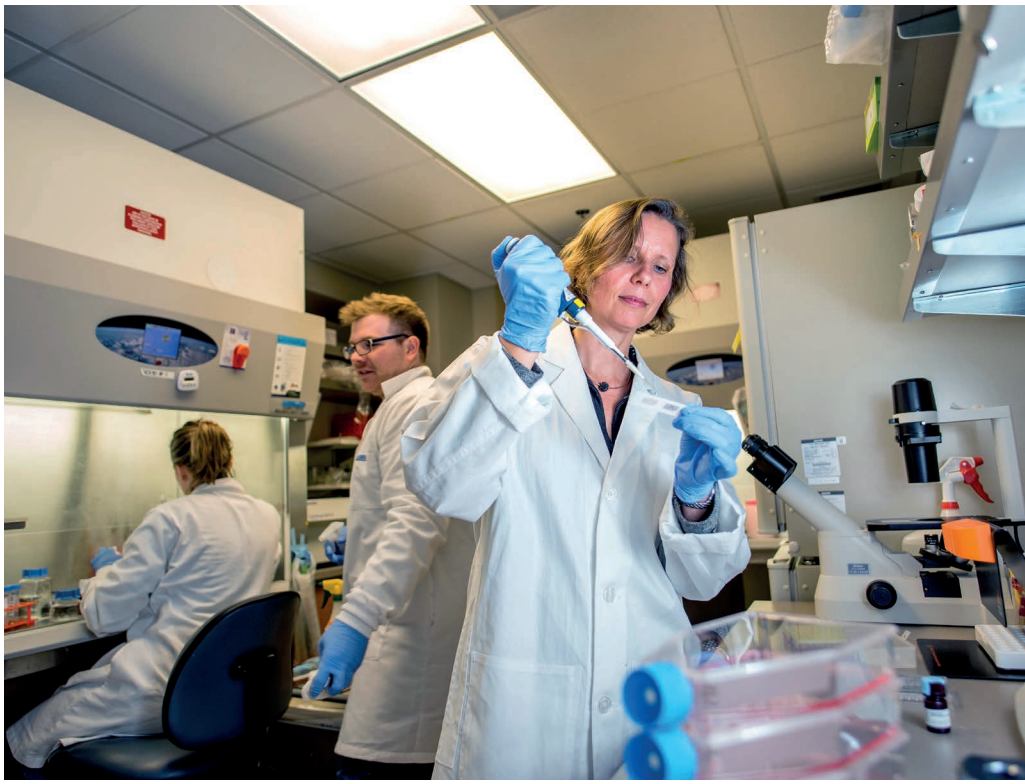
IMMUNOLOGY

Teaching tolerance

Researchers are seeking to tame the immune system with the aim of alleviating, or even preventing, autoimmune disease.

BY KATHERINE BOURZAC



Megan Levings and her team are engineering regulatory T cells to help keep autoimmune diseases in check.

PAUL JOSEPH

There is no cure for type 1 diabetes. Instead, the condition, in which a person's immune system destroys their ability to produce the glucose-regulating hormone insulin, must be carefully managed. But even the most vigilant of those affected will experience organ-damaging bouts of high blood-sugar levels, and will be at an increased risk of cardiovascular disease, nerve damage and blindness.

Immunologists suggest that it doesn't have to be that way. In August 2017, Mark Peakman, a clinical immunologist at King's College London, and his colleagues published the results of an early clinical trial of a treatment that aims to teach the immune systems of people with type 1 diabetes to spare the insulin-producing cells of the pancreas[1]. The study was designed to assess the safety of the treatment in those who have been newly diagnosed with the disease, but it also showed hints of efficacy, says Peakman. Six months after their initial diagnosis, most of the treated participants were still producing enough insulin to avoid the need to increase their use of synthetic insulin, unlike those who received a placebo. The researchers are now planning a phase II clinical trial.

"In principle, you would treat this as early as possible, in people who have high-risk genes," says Peakman. He calls the approach "extreme prevention".

Many researchers are setting up clinical trials of treatments for type 1 diabetes and other incurable autoimmune diseases, such as multiple sclerosis and Graves' disease, to test ways of bringing hyperactive immune systems into line. Immunologists think that by treating people with molecules that can induce an immune response (antigens), bacteria or engineered immune cells, it could be possible to train the immune system to tolerate the tissue it is on track to damage — an intervention that has the potential to cure a range of autoimmune disorders.

There is much to prove. So far, this new generation of treatments has proved to be safe, but its efficacy is uncertain — the field is one in which the findings of clinical trials often fail to reflect encouraging results from the laboratory. But armed with a deepening understanding of the molecular basis of autoimmunity, as well as advances in genetic engineering and cell-based therapy, immunologists are hopeful that, this time, the results will be different.

GROWING PROBLEM

Autoimmune diseases can affect almost any part of the body. In each case, the body loses tolerance towards its own tissues — certain proteins are seen as antigens, and the immune system attacks. Lack of tolerance also jeopardizes recipients of organ or bone-marrow transplants, leading to rejection of the transplanted organ or causing immune cells in the bone-marrow graft to attack the recipient's body.

Autoimmune conditions are on the rise, particularly in the developed world and in women[2]. "There are numerous environmental influences," says David Wraith, an immunologist at the University of Birmingham in the United Kingdom. Precisely what such influences are is unclear, but suggestions include diet, exposure to sunlight and pollution, and stress, he says.

Researchers also anticipate that the growing number of people with cancer who are treated with immunotherapy will further increase the prevalence of autoimmunity. Such treatments deliberately unleash the immune system to fight tumours, but they can also trigger autoimmune diseases, including rheumatoid arthritis and colitis. In May 2017, researchers at the University of California, San Francisco, and the nearby Parker Institute for Cancer Immunotherapy, proposed that these unintended consequences have become "the Achilles' heel of immunotherapy"[3].

Conventional treatments for autoimmune diseases are limited either to managing symptoms or to aggressively targeting the whole immune system, which can cause side effects and make recipients vulnerable to infection. Immunologists see a third way: downregulation of only the specific immune reactions that are harmful.

"We know what we want the immune system to do, but it's been really hard to do it," says Megan Levings, an immunologist at the British Columbia Children's Hospital Research Institute in Vancouver, Canada. "The key is to have an antigen to target."

Tapping into the immune response's existing

control system, and doing it with specificity, is seen as the way forward. The main immune players are the regulatory T (T_{reg}) cells, which Levings calls "the brakes of the immune system". Even when it is responding to genuine infections, the immune system can go too far, causing harmful inflammation. T_{reg} cells help to prevent this. Similarly to other T cells, they are activated by specific antigens. But instead of mounting an attack, T_{reg} cells rein in the immune cells that are doing damage.

Wraith and other immunologists think that the body can be made to produce the T_{reg} cells required to dampen a certain autoimmune response, by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. The approach is counter-intuitive: antigens such as those given in a vaccine typically put the immune system on alert. But if administered without the immune-system stimulants called adjuvants that are usually included in vaccine formulations, antigens can induce a calming effect through T_{reg} cells.

Wraith's group completed a phase II trial in people with relapsing multiple sclerosis in 2016. Those with the disease develop lesions in the brain and spinal cord when the immune system attacks the protective sheath that surrounds nerves. Wraith's experimental treatment, which has been licensed by Apitope, a biotechnology company based in Chepstow, United Kingdom, comprises a cocktail of peptides from especially antigenic regions of myelin basic protein — the main target of the immune system in multiple sclerosis. Wraith says that the people they treated had less inflammation in their brains, as measured by magnetic resonance imaging.

Peakman's trial for a type 1 diabetes treatment used a single peptide based on proinsulin, a precursor to insulin and the antigen that the immune system targets in the pancreas. But similar to Wraith, he and his colleagues intend to use a cocktail of peptides from the targeted protein in later phases of the study. Although loss of tolerance to a particular protein such as proinsulin lies at the core of many autoimmune diseases, immunologists think that other antigens could also contribute to the manifestation of such diseases in some individuals — making a cocktail of peptides more likely to succeed than one alone. In Peakman's preclinical studies, this approach has been more effective than using a single peptide. "More peptides are better," says Peakman.

CELL-BASED THERAPY

There may be other ways to tame a rogue immune system. Researchers propose that bacteria dwelling in the body thrive by inducing immune tolerance, and would like to turn this to the advantage of medicine. In February 2017, researchers led by endocrinologist Chantal Mathieu at the Catholic University of Leuven in Belgium reported that genetically modified *Lactococcus lactis* bacteria can reverse diabetes in two-thirds of mice with the condition by inducing T_{reg} cells[4]. The bacteria were engineered to produce proinsulin and an anti-inflammatory cell-signalling molecule called interleukin-10. This work has been licensed by Intrexon Actobiotics of Gent, Belgium, and will enter clinical trials this year, says Mathieu.

Levings sees promise in manipulating the T_{reg} cells of patients more directly, by removing them from the body, training them and then returning them. She is working on ways to engineer large numbers of T_{reg} cells to respond to specific antigens that have been wrongly recognized by an individual's immune system as being foreign. Levings' lab modifies T cells using a protein called a chimaeric antigen receptor (CAR) — a method that has already been approved for use in cancer treatment. Whereas cancer researchers use CAR proteins to make T cells attack tumour cells, Levings uses them to make T_{reg} cells that will dampen harmful inflammation.

She is able to engineer the cells to respond to an antigen of choice. At the moment, her lab is focusing on type 1 diabetes. Levings sees the potential to prevent a lifetime of complications in young people who have just been diagnosed with the disease. Such a treatment would be expensive, but could transform the quality of life of its recipients. "When I started, people looked at me like I was crazy," says Levings. Because a low-risk treatment for type 1 diabetes already exists — the administration of synthetic insulin — there has been little acceptance so far of the potential risks of genetically engineering a person's immune cells. That's changing, thanks to a growing safety record for the method in treating cancer. "Cancer immunology has changed the world's perception of cell therapies," says Levings.

T_{reg}-cell therapy might also offer a way to induce tolerance following an organ or bone-marrow transplant. When a solid organ such as a kidney is transplanted, the recipient can have an immune reaction to the donor tissue. T_{reg}-cell therapy could stop the reaction without systemically weakening the immune system and leaving the recipient vulnerable to infection. The transplanted tissue can also be the source of autoimmunity — in graft-versus-host disease (GVHD), immune cells from the grafted tissue attack the recipient's body. The standard therapy for GVHD is corticosteroids, but about half of the people treated do not respond, says Bruce Blazar, a clinician and researcher at the Pediatric Bone and Marrow Transplant Center of the University of Minnesota in Minneapolis. Reining in GVHD is particularly challenging. Whereas autoimmune diseases are typically confined to a single tissue, transplanted immune cells can go anywhere. "After a bone-marrow transplant, the entire body can be subject to GVHD," Blazar says.

In mice, infusions of T_{reg} cells seem to help. Robert Zeiser, a clinical oncologist and haematologist at the University of Freiburg in Germany, says that the effects of treating GVHD with engineered T_{reg} cells in preclinical studies are dramatic. "The GVHD mice were terribly sick, but the group treated with T_{reg} cells looked completely healthy," he says. "I have not seen any other approach that can block GVHD so effectively."

In people, however, it is unclear whether the antigen-specific approach to tackling autoimmune disease can prevent GVHD. For instance, researchers often struggle to narrow down the molecules that the grafted cells will perceive as antigens. Studies in mice suggest that 50 to 100 antigens are typically involved in GVHD, but "we don't know how many antigens are important in people", Blazar says.

"We know what we want the immune system to do, but it's been really hard to do it."

The possible antigens behind the immune reaction involved in transplant rejection are less numerous and therefore easier to identify. Flavio Vincenti, a specialist in kidney and pancreas transplants at the University of California, San Francisco, hopes that T_{reg} cells can help to prevent organ rejection in people showing signs of inflammation after a kidney transplant. His group is recruiting participants for a phase II trial that will compare the efficacy of infusing transplant recipients with a population of their own T_{reg} cells that has been trained to recognize antigens in the blood of the kidney donor, or with an expanded general population of their own T_{reg} cells.

Levings is excited about the rejection trials. "This is the perfect clinical context to test the cell therapy," she says. "You know what the antigens are, you know what the mismatch is between donor and recipient, and you have control over the day it's going to be done."

Vincenti's expectations, however, are more measured. Getting to this point has been difficult because the immunosuppressive drugs used to prevent transplant rejection work so well, he says. "We are a victim of our own success." Innovative treatments such as infusions of T_{reg} cells have the potential to prevent side effects in the long term, but the upfront risks are greater.

However, he is excited to learn from the trial. "If we don't make the first step now, how are we going to make the giant step to new therapies?" he says. "We may fail, but we will learn a lot." ■

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1. Alhadj Ali, M. *et al. Sci. Transl. Med.* **9,** eaaf7779 (2017).
2. Wraith, D. C. *Front. Immunol.* **8,** 1668 (2017).
3. June, C. H., Warshauer, J. T. & Bluestone, J. A. *Nature Med.* **23,** 540–547 (2017).
4. Takiishi, T. *et al. Diabetes* **66,** 448–459 (2017).