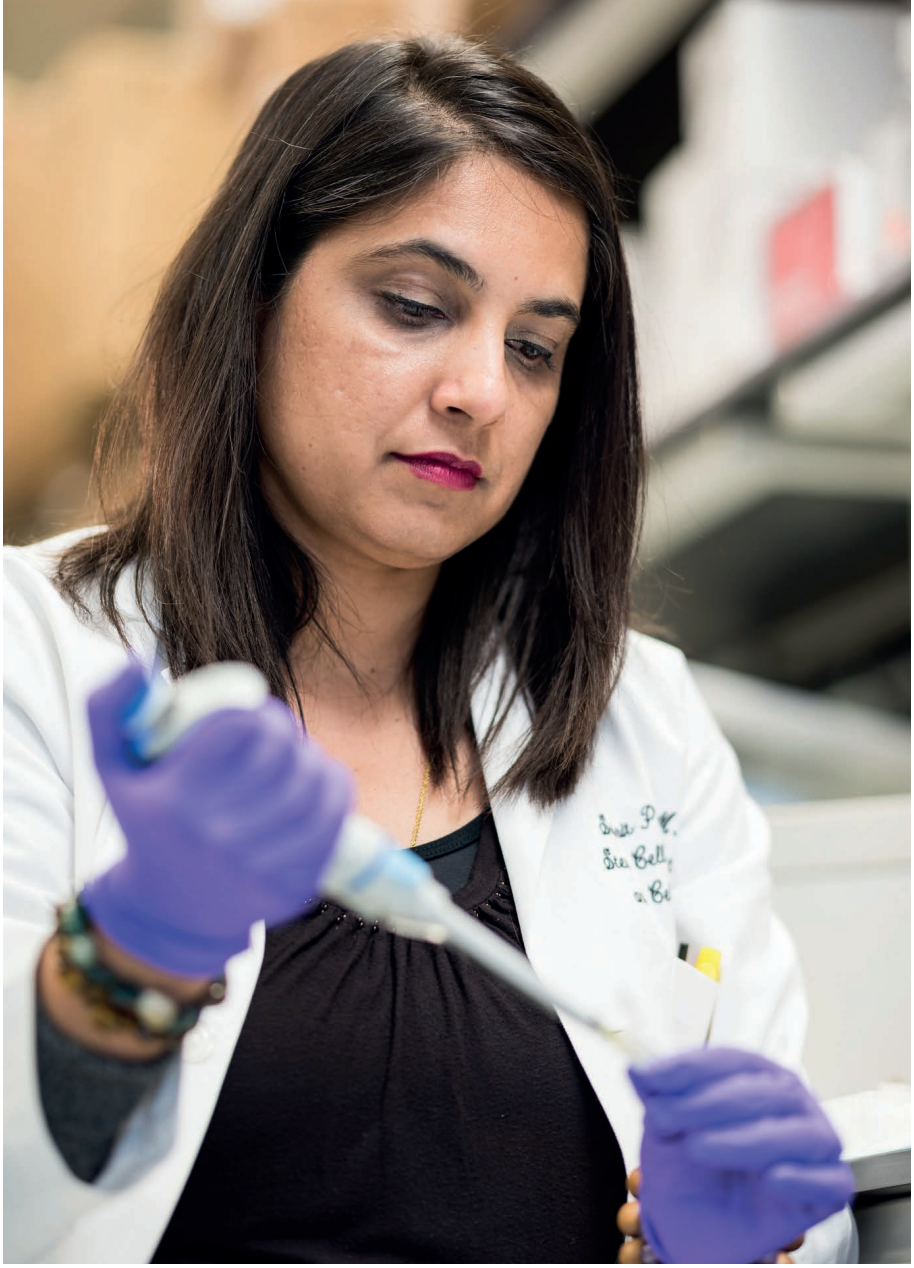

MD ANDERSON CANCER CENTER

Simrit Parmar at the MD Anderson Cancer Center in Houston, Texas, studies ways to stop inflammation.

STEM CELLS

Painful rejection

Solving the problem of graft-versus-host disease could make stem-cell transplants an option for more people.

BY KAT ARNEY

Improved chemo- and radiotherapy regimens and new targeted therapies have dramatically increased lymphoma survival rates over the past 40 years. For example, 8 out of 10 adults in the United Kingdom now survive Hodgkin's lymphoma, compared with less than half in the 1970s. Promising approaches such as chimeric antigen receptor T-cell therapy could raise this rate even further (see page S42). But as many as 1 in 3 lymphomas will either fail to respond to therapy or become resistant and return within 2 years. The next option is a stem-cell transplant: destroying the patient's immune system with high-dose chemotherapy and radiation, then replenishing it with stem cells from their body or from the blood, bone marrow or umbilical cord of a donor.

More than half of all patients with recurrent Hodgkin's lymphoma who receive a transplant of their own cells — known as an autologous transplant — are cured. But the treatment is suitable only for people whose lymphoma has not spread into their blood or bone marrow. In those cases, donated (allogeneic) stem cells are the last hope for a long-term response.

Allogeneic transplant can have a powerful cancer-killing effect by destroying the remaining lymphoma cells in the body, which now appear 'foreign' to the newly installed immune system. And improvements in DNA sequencing of the genes that determine transplant compatibility have increased the chances of a good match between the patient and an unrelated donor. But there is still a chance that donor immune cells will recognize the patient's healthy tissues as foreign and start attacking them, causing a condition known as graft-versus-host disease (GvHD), which affects up to 80% of recipients to some extent. "We're all afraid of harming the patients when we're trying to cure them, and that's what GvHD is — we're treating them with all good intention but have given them a new problem," says Stephanie Lee, a haematologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

Up to half of allogeneic transplant recipients experience acute GvHD. This is a severe immune reaction that occurs in the first 100 days after the procedure and can rapidly become life-threatening. Then there is the long-term immune assault of chronic GvHD. Chronic GvHD affects up to around 40% of transplant recipients, and the incidence has been slowly rising in recent years. This is partly due to the increased use of peripheral-blood stem-cell donations, which bring increased survival but at the expense of a higher chance of long-term GvHD. There is also a greater willingness to attempt potentially curative but less damaging 'mini-transplants' for older patients, even though they are more likely to develop GvHD.

GvHD symptoms include thickening of the skin, including around the mouth and tear ducts, which can cause eating difficulties and sight loss. Inside the body, GvHD can cause kidney and liver damage, lung scarring, diarrhoea and more. Overall, chronic GvHD is a significant cause of ill health in lymphoma survivors, and the leading cause of death in people who have survived two years after their transplant without their cancer relapsing.

FIGHTING BACK

People who develop chronic GvHD are usually treated with immunosuppressive therapies such as steroids. But these drugs come with side effects of their own, particularly with long-term use. And there is the ever-present risk that the cancer will return, leaving little hope other than last-ditch 'salvage' chemo- and radiotherapy or experimental treatments.

The main culprits thought to be responsible for GvHD are effector T cells — the attack soldiers of the immune system. Most research has therefore focused on developing therapies that suppress these cells. One approach is photopheresis, in which a patient's blood is drawn into a machine to separate out the immune cells. The cells are then treated with a photosensitizing drug and ultraviolet light to destroy unwanted T cells, before being infused back into the body. The technique was originally developed as a treatment for T-cell lymphoma

and has been the main option for steroid-resistant chronic GvHD for the past 30 years.

"I use photopheresis a lot, particularly for GvHD affecting the skin, but it tends to be expensive," says Lee. "It's also a huge time commitment for people who have to come in to the hospital to be treated — it can take around three months for us to be able to tell whether it's having an effect, and there are plenty of patients who don't respond."

Haematologists have had to make do with these two flawed options — long-term steroid use and photopheresis — for decades. But the appearance over the past decade of highly selective drugs that target specific components of the immune response is opening up another avenue for treating chronic GvHD.

"There is a lot of work going on to understand how we can manipulate specific components of the immune system and not just go in with the steroid 'atomic bomb' and wipe everything out," says Mary Flowers, a doctor specializing in GvHD at the Fred Hutchinson Cancer Research Center.

The first drug for treating steroid-refractory chronic GvHD, ibrutinib, was approved by the US Food and Drug Administration (FDA) in August 2017. Ibrutinib is an inhibitor of Bruton's tyrosine kinase — a signalling molecule that plays a vital part in the development of B cells — and was originally developed as a treatment for B-cell cancers such as mantle-cell lymphoma (see page S46).

This might seem like an unorthodox approach, given that chronic GvHD was thought to be the result of over-enthusiastic T cells, not B cells. Flowers, who was the lead investigator on the ibrutinib trial, says the drug's success is the result of insights into the underlying biology of chronic GvHD.

"Our understanding of the pathogenesis of GvHD has taken a great advance in the last five years or so, and we now know that not only are T cells involved, but B cells also play a role too," she says. "Ibrutinib targets pathways that are active in both B cells and T cells — it stops the production of antibodies that cause fibrosis and related symptoms — and it also stops T cells attacking the host."

The unusually speedy FDA approval for ibrutinib after just one trial was partly the result of careful forward planning by Flowers and her colleagues. The robustly designed study used end points based on previously agreed US National Institutes of Health consensus criteria and also used a reliable blood-borne biomarker that correlated with response. All of this tipped the balance in favour of approval.

Flowers' unpublished preliminary observations from long-term follow-up of patients from that first GvHD ibrutinib trial suggest that the response rate continues to increase over time. To confirm this, she's running a trial of ibrutinib as the first-line therapy for chronic GvHD after allogeneic stem-cell transplant. Other drugs are starting to come through the pipeline too, such as ruxolitinib and baricitinib, which target the Janus kinase signalling pathway that regulates many aspects of immune-cell function. Another approach is to use therapies designed to block the over-proliferation of macrophages, which contribute to the fibrosis and inflammation seen in chronic GvHD.

"I've been working on GvHD for almost 40 years, and this is revolutionary," Flowers says. "Understanding how the condition works and finding small molecules that affect specific pathways is really amazing. We will be able to look at a patient and say exactly what disease they have and what drug will work for them."

MORSA IMAGES/GETTY

Stem cells can be taken from a donor's bone marrow and transplanted into a person with lymphoma.

REGULATORY T CELLS TO THE RESCUE

Another approach to treating chronic GvHD lies in special immune cells known as regulatory T (T_{reg}) cells. These cells normally make up around 5–10% of the T cells in the bloodstream and damp down the responses of over-excited effector T cells. But a rich source of T_{reg} cells is thrown away by maternity units around the world every day: umbilical cord blood.

"A fetus is 50% mum and 50% dad — it's effectively the biggest allogeneic transplant in biology," says Simrit Parmar from the MD Anderson Cancer Center in Houston, Texas, whose research focuses on turning T_{reg} cells into a viable therapy for GvHD. "Nature itself has created a mechanism to stop the baby being rejected by using these cells to protect against the inflammatory onslaught from the mother's side," Parmar adds. "There's a well-known correlation between low levels of these cells and spontaneous abortion, and patients who respond better to treatment for GvHD have higher levels of T_{reg}s in their blood."

The first trial of T_{reg} cells in allogeneic stem-cell transplantation was published online in 2010 by researchers at the University of Minnesota in Minneapolis (C. G. Brunstein *et al. Blood* **117**, 1061–1070; 2011). They found that giving patients purified cord-blood T_{reg} cells alongside an umbilical-cord-blood transplant reduced the chances of developing acute GvHD.

In 2018, Parmar's team presented results from a phase I trial showing that cord-blood T_{reg} cells can also prevent the appearance of chronic GvHD in people receiving allogeneic transplants. Parmar suspects, however, that concurrent steroid treatment might interfere with the cells' regulatory activity and reduce their protective effects. She and her team are developing genetic-engineering techniques to remove the glucocorticoid steroid receptor from cord-blood T_{reg} cells, rendering the cells impervious to the effects of the drugs.

Parmar is also focusing on developing frozen cord-blood T_{reg} cells that can be given to any patient for the treatment of GvHD. She has launched a company in Houston called Cellenkos to commercialize the idea.

"I think T_{reg}-cell therapy has multiple applications for treating the inflammatory side effects of chronic GvHD, in combination with all sorts of other agents," she says. "We're just scratching the surface and still don't have clear understanding of how these cells work, but I think the yin-and-yang of T_{reg}s and effector T cells will be solved in my lifetime."

Ultimately, the growing interest in chronic GvHD among researchers and support from regulatory agencies and industry partners means that more people with cancer will one day be able to access potentially curative transplants.

"There's a lot of evidence that allogeneic transplants for lymphoma are effective, so mitigating these side effects could bring curative treatment to many more patients," Lee says. "I just wish I could see ten years into the future when these studies have been done and many more people can have transplants because the threat of GvHD has decreased." ■

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