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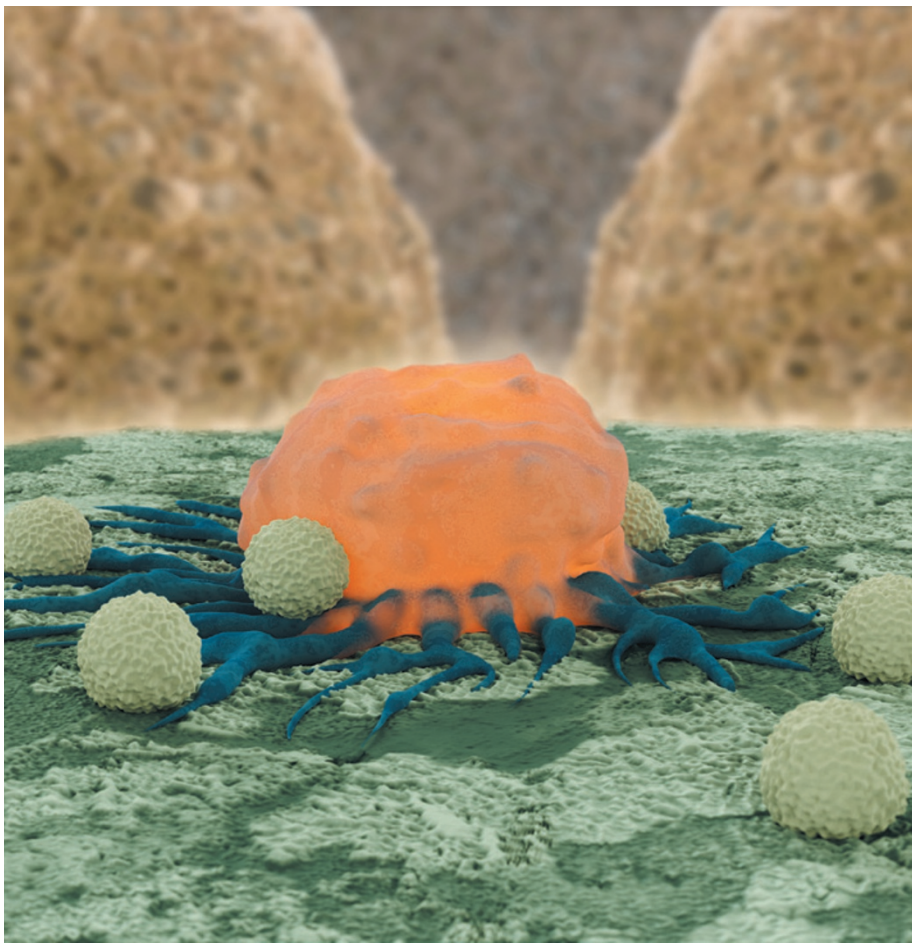

White blood cells (grey) can be engineered to attack specific types of cancer (red).

TRANSLATIONAL RESEARCH

Cancer killers

Promising results in cancer immunotherapy offer growing opportunities – and challenges – in translational research.

BY RACHEL BERNSTEIN

Michel Sadelain recalls his colleagues' response to his postdoctoral research project: a combination of amusement and incredulousness. He wanted to eschew the vaccine-based approaches that were common at the time, and instead kill cancer cells by tinkering with the immune system genetically.

Twenty years later, his insight seems to have been vindicated. Early successes in treating people with cancer using engineered immune cells called T cells have breathed new life into the once-maligned field of cancer immunotherapy (see page 24), and the result has been an influx of funding, as well as growing opportunities in academia and industry. Indeed, Sadelain's gamble has brought him career success: he is now director of the Center for Cell Engineering and Gene Transfer at Memorial Sloan Kettering Cancer Center in New York City.

Until now, the field has "always been a little bit of a stepchild", says cancer immunotherapy pioneer Steven Rosenberg, head of the tumour immunology section at the US National Cancer Institute in Bethesda, Maryland. Researchers have been reluctant to get involved because it is difficult to genetically engineer mammalian cells and because cancer cells are very similar to normal cells, making them particularly difficult to target with immunotherapies.

But during the past few years, promising results from early clinical trials have shown that therapies based on T-cell engineering can force some stubborn cancers into remission. With these successes, "cancer immunology has come to the forefront both in immunology and in cancer treatment", Rosenberg says.

Numbers documenting the rise in prominence are hard to come by. But an auspicious sign is that the amount of money awarded to the field by the American Association for Cancer Research in Philadelphia, Pennsylvania, has risen from just US$400,000 in 2011 to $27.2 million in 2013. For the foreseeable future, the field is rife with opportunity.

RESEARCH RESURGENCE

The results of these early clinical trials — done mostly in blood cancers — are not just promising for patients, they are also opening up research avenues in the laboratory. "What we've done now is established that this is a valid new field of cancer therapy," says Marco Davila, who in January took up a position studying the potentially toxic side effects of T cell-based therapies at Vanderbilt University Medical Center in Nashville, Tennessee. "This is going to lead to an entire new set of questions that need to be evaluated in a very basic manner, as well as in a translational manner."

A key focus is on expanding the success of immunotherapies. The trials that have been successful so far have mainly targeted B cells, which are white blood cells that become mutated in B-cell leukaemia and lymphoma. T cells can be engineered to kill cells that display the CD19 protein, which is found on both healthy and cancerous B cells. This non-specific approach is acceptable because B cells are not crucial to survival, but investigators are working to identify targets for other cancers and to develop approaches that target just cancerous cells. They are also trying to work out why some patients do not respond to B-cell immunotherapy.

The fledgling immunotherapy field is being led by a handful of key players, including ▶

Rosenberg, Carl June of the University of Pennsylvania in Philadelphia and Laurence Cooper of the University of Texas MD Anderson Cancer Center in Houston. But young researchers such as Davila are joining the effort — and with diverse questions still to be answered, scientists from a variety of backgrounds are in demand.

MULTIPLE ENTRY POINTS

"There are so many different ways to get [into the field] — you don't have to limit yourself to doing cancer immunotherapy during graduate school or your postdoc," says Marcela Maus, who works with June and is the director of medical affairs for translational research at Penn's Abramson Cancer Center. She cites entry points such as virology, T-cell biology and cancer signalling. Maus herself did not start in the field until she was a graduate student, having conducted evolutionary-biology research on *Escherichia coli* as an undergraduate. She found that bacterial concepts such as selection pressure apply to cancer as well — and to her current work on interactions between T-cell therapies and other cancer treatments.

One of June's postdocs, Joseph Fraietta, switched from his graduate work on HIV after reading about the exciting progress in cancer immunotherapy. And Rosenberg says that there is a growing demand for geneticists and bioinformaticians who can analyse tumour-genome data to identify potential immune targets. "There's a lot known about immunology, and a lot known about genomics, but the two have not been tied together in a meaningful, applicable fashion until very recently," he says.

"I have this hybrid situation where I get to see the best of both worlds."
Joseph Fraietta

Those interested in developing cancer immunotherapies should carefully consider the clinical facets of the work. "To apply research to patient-related problems, you either need training in medicine or very close collaborations with people who are trained in medicine," Rosenberg says. Ton Schumacher, a group leader at the Netherlands Cancer Institute in Amsterdam, recommends acquiring a good understanding of immune reactions and knowledge of how to translate concepts into clinical trials. Many in the field earn a joint MD–PhD degree, but an MD is not required as long as researchers interact with clinicians to make sure that their work is relevant to patients.

One reason that cancer immunotherapies are so promising is that they are engineered for individual patients, using a person's own T cells to specifically target the cancer. But if cancer immunotherapy is to succeed, practitioners will have to find ways to scale up manufacturing capabilities despite their personalized nature. "This is not a well-known path to making drugs," says Sadelain. "There are many components of manufacturing and distribution for which there is no precedent."

To help to work out such issues, pharmaceutical and biotechnology companies are seeking academic partners, which could pave the way for opportunities for early-career scientists. For example, June teamed up with Novartis a few years ago after successfully testing an immune therapy that used genetically modified T cells called chimaeric antigen receptors (CARs). Since then, Novartis and Penn have jointly established the Center for Advanced Cellular Therapies on the university's campus to further develop CAR technologies, and Novartis is hiring cancer-immunotherapy researchers.

And in March last year, researchers at the Center for Cell and Gene Therapy at Baylor College of Medicine in Houston, Texas, a hub for cancer-immunotherapy work, teamed up with two biotech companies, Celgene in Summit, New Jersey, and bluebirdbio in Cambridge, Massachusetts. And in December, Sadelain worked with scientists at the Memorial Sloan Kettering Cancer Center and two other cancer-research institutions to form Juno Therapeutics in Seattle, Washington, which will work closely with academic researchers to develop T-cell therapies. All this means that postdocs now have opportunities beyond just university-based research, June notes.

Lenka Hurton, a graduate student who is working on improving the persistence of the engineered T cells in Cooper's laboratory, says that she hopes to pursue an industry job after completing a postdoc and is encouraged that companies such as Novartis are recruiting. "I'm anticipating that there will be other companies that do the same, assuming that the clinical trials continue to show promising results," she says.

For those working at a university, collaborations with industry can provide valuable exposure and resources. "I'm really getting a lot of bang for my buck because I'm in a semi-academic, semi-industrial postdoc," says Fraietta, who is involved in the Penn–Novartis work. "I have this hybrid situation where I get to see the best of both worlds."

TRANSLATIONAL CHALLENGES

Many in the field agree that those who stay at academic institutions must learn how to conduct translational research in a culture and environment that may be unaccustomed to supporting such work. There are, for example, practical considerations. Clinical trials generally require a longer time frame than do conventional grant cycles — it can take two to three years just to get a trial off the ground. "If you need to write grants every year, that's going to be tough," Maus says. And although trials that result in a blockbuster drug can be great career boosters, they constitute only a tiny part of the research needed to develop effective therapies. Although essential for safely manufacturing new therapies, projects that focus on the painstaking trouble-shooting, optimization and process-development work do not usually garner high-impact publications, which may discourage ambitious young researchers.

Michel Sadelain is an immunotherapy trail-blazer.

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Davila, a new professor who is establishing his own research group, has a strategy to stay on track. "I'm sticking with very finite goals that are going to be meaningful, that are going to contribute to the field," he says. He chose his project with care: developing an animal model of cytokine release syndrome, a potentially fatal side effect of CAR T-cell treatment. He hopes that this approach will enable him to complete projects within the short time frame required for publishing and obtaining grant funding in an academic setting.

First and foremost, immunotherapy researchers focus on creating and improving effective treatments — not just pursuing intriguing phenomena. Hence, they might not have the luxury of dallying in research just to sate their intellectual interest. The aim is always to push forward towards better treatments.

Cooper therefore encourages graduate students to earn their PhD by investigating the more fundamental research questions in cancer immunotherapy, then waiting until their postdoc or later to pursue the translational angle. Maus followed this track. "As a graduate student, I wasn't really able to do the translational aspects directly," she recalls. "It was frustrating at the time — but now I realize it was really important to focus on basic science." So far, Maus and others who have been able to balance these priorities are reaping the career rewards. "For young people getting into the field," says Cooper, "there's never been as good a time as this." ■

Rachel Bernstein *is a science writer based in San Francisco, California.*