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Empowering the enforcers

High-profile breakthroughs are finally helping immunology to move from the lab into the clinic.

BY NIC FLEMING

Some have a noticeable bounce in their step. Others are persistently cheerful. Immunologists have, in recent years, exhibited a quiet air of satisfaction akin to that of the sports fan whose team makes it to the major league after years languishing in the lower divisions.

It's their time to shine. Students want to join them. Researchers from across the medical sciences want to collaborate with them. Investors want to invest in them. Biotechnology firms want to employ them. And pharmaceutical companies want to buy those biotechs.

The immune system fights off microbial infections, reduces the risk of cancerous cell growth and kicks off tissue-repair processes. Immunology is the study of how this complex system works. Until the end of the twentieth century, clinical interest in the field was mostly restricted to a relatively narrow subset of diseases, and researchers were often stuck working with animal studies, rather than human patients.

That has changed: a series of fundamental research breakthroughs have highlighted the broader part played by the immune system. One high-profile example is the 1980s discovery of the role of cell-to-cell signalling molecules — cytokines — in causing the immune system to attack healthy cells and tissue in a process called autoimmunity. Regulatory T cells, which act as a brake on this process, were discovered in the 1990s (see 'Changing times').

These major advances have led to hopes of improved therapies for a wider spectrum of conditions. Immunologists are working out how to manipulate the body's defence system for medical benefit, and have earned themselves a seat at the clinical table.

"Over the last 30 years, our understanding of immunology at the molecular and cellular levels has advanced dramatically," says Mark Coles, an immunologist at the University of York, UK. "We now have the skills and tools to translate many things we have learnt about mouse immunology into humans. The potential to make a real difference to patients with a wide range of conditions means we've entered probably the most exciting time in the field's history."

BREAKTHROUGHS

It is not so long ago that immunologists' clinical roles focused mainly on autoimmune, respiratory and infectious diseases. One of the field's first major clinical successes came from this narrow scope: infliximab, which works by countering the actions of an inflammatory cytokine called ▶

tumour-necrosis factor-α (TNF-α), was approved to treat the autoimmune disease rheumatoid arthritis in the United States in 1999. More recently, research has highlighted the key roles of immune responses in a much longer list of conditions.

A number of significant clinical breakthroughs have been made against cancer. One turning point came with the development of monoclonal antibodies (mAbs), copies of antibodies that target specific pathogens. A single parent immune cell is cloned in the lab to create a sort of antibody farm. The harvested mAbs are injected back into the immune system, where they bind to the pathogens, drawing the attention of the immune system's reapers.

Another major advance, and one that is still generating excitement, is the use of antibodies to tackle aspects of the immune system itself. T cells patrol the body looking for signs of disease. They identify normal cells through a molecular handshake that involves the binding of 'checkpoint' proteins on the cells' surfaces. But some cancer cells can evade the immune system's defences by disguising themselves with the same proteins. Drugs called checkpoint inhibitors deploy antibodies to bind to the spoof proteins, enabling T cells to unmask the malignant cells for attack. This approach has been shown to be effective against non-small cell lung cancers and cancers of the skin, kidney, bladder, head and neck.

Also promising is a method in which T cells extracted from the patient's blood are genetically engineered so that they can recognize molecules on the surface of cancer cells, and so know their enemy. The cells are then injected back into the patient to mount a defence. This chimaeric antigen receptor (CAR) T-cell technique has shown early promise against several forms of blood cancer.

UNSUSPECTED CONNECTIONS

The old view that the blood–brain barrier mostly protects the brain from immune-system activity has been reversed in the past 20 years. Conditions previously seen as purely neurological, such as Parkinson's disease, Alzheimer's disease, schizophrenia and depression, have been increasingly linked to immune system dysfunction. A growing body of research is also highlighting the roles of immune responses in cardiovascular disease and type 2 diabetes.

"Immunologically driven processes play roles in many disorders that we traditionally didn't think had anything to do with the immune system," says Helen Collins, an immunobiologist at King's College London. "The number of clinical trials of cellular therapies is growing exponentially, and the scope of what immunologists can become involved in has widened greatly."

This growing focus on immunology naturally opens doors for scientists in the field, although the nature of the opportunities on offer is changing. For one thing, experts say, secure lectureships and other university positions have become fewer and further between in many places.

"There are still great opportunities for smart, dedicated people, but even those with PhDs may have to accept their career may not lie within an academic environment," says Neil Williams, founder of the immunology contract-research organization KWS BioTest, in Portishead, UK. "It's always been a problem and it has become more difficult than it was 20 years ago."

Collins, who is also education secretary of the British Society for Immunology in London, agrees. "The pipeline through academia has become narrower because funding is tight. These days, to make the move from postdoc to permanent academic position, you have to be more outstanding and sometimes luckier than before."

Things have changed on the industry side of the job market, too. Some pharmaceutical companies have cut back their internal research programmes, and early-stage research and the discovery of drug targets are increasingly happening externally. Overall, however, those in the field say that opportunities in industry are increasing, as biotech firms emerge and grow.

"Pharmaceutical companies are looking to partner with universities for early-stage research capabilities, and to acquire biotech companies and their projects to build their drug pipelines," says Williams. "Biotech is very buoyant at the moment, and because of the success of immune oncology, biotech with an interest in immunology is doing particularly well."

Although barriers between industry and academia have been crumbling for some time, the drive towards translational work in immunology has further reinforced collaboration between the two sectors. Universities look to industry partners for funds, and are increasingly recognizing them as wells of knowledge on topics such as drug discovery and regulatory processes. Companies are also opening up their collections of potential drug compounds to academics. Meanwhile, industry — in the scientific sector and elsewhere — is looking to universities for innovative thinking, expertise and talented future employees (see 'Capitalizing on a scientific education').

"There is a recognition on the part of both industry and academia that if the end goal is trying to find therapies for patients in need, often they can both bring something to the table," says Arpita Maiti, a senior director of immunological research who focuses on external science and innovation at pharmaceutical company Pfizer in Cambridge, Massachusetts. "Both parties have become more aware of what the other needs and are now able to work together more fruitfully."

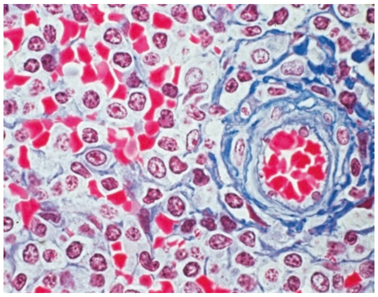
MUTUAL BENEFITS

Industry–academia partnerships take many different forms, from internships for school pupils and summer jobs for PhD students to postdoc positions and joint research facilities, such as the Manchester Collaborative Centre for Inflammation Research, set up by the University of Manchester, UK, and pharmaceutical companies GlaxoSmithKline (GSK) and AstraZeneca. At sites such as the Stevenage Bioscience Catalyst campus, UK, GSK invites academics and their groups to work alongside its employees, using equipment and databases that they may not otherwise have access to.

What is not yet clear is whether these links are translating into extra employment prospects in academia. "Companies are looking to work with universities, and a lot of universities are trying to position themselves to be the

CHANGING TIMES

Immunology's road to clinical impact has been marked by basic research advances.



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1975 Discovery of 'natural killer' immune cells

1983 Discovery of T-cell receptors

1988 The term 'microbiome' is coined

1995 Discovery of regulatory T cells

1997 US Food and Drug Administration approves the use of rituximab, the first monoclonal antibody (mAb) made available to battle cancer

1999 The mAb infliximab approved to treat rheumatoid arthritis in the United States

2011 Chimaeric antigen receptor T-cell therapy clears advanced chronic lymphocytic leukaemia from two patients

2015 Link discovered between brain and immune system, through lymphatic vessels (lymphocytes pictured).

BEYOND THE LAB

Capitalizing on a scientific education

Breaking new ground in the laboratory might motivate some, but it is not for everyone. Thankfully, those with immunology degrees on their CVs have career options that extend well beyond academia and industry.

Aliyah Weinstein hopes to work in science communication when she completes her immunology PhD at the University of Pittsburgh in Pennsylvania next year. Currently on a fellowship at the Cordeliers Research Centre in Paris, she plans to find a job in a university or research institute's press office, or do other work in scientific outreach.

"Scientists are doing some really great work, but there is a lack of trust and understanding among the public which is a real hindrance," she says. "Coming from a field that is often sensationalized by the media, I like the idea of helping to convey the work of scientists more accurately."

Others who like the idea of helping people could consider clinical immunology, which involves diagnosing and treating people with immune disorders such as allergies or rheumatoid arthritis.

Those seeking to use their knowledge of the immune system to earn big bucks could do worse than intellectual-property law. There are also think tanks, learned societies, non-governmental organizations and branches of government looking for people with scientific backgrounds to work on policy.

"The wide variety of fulfilling career options open to those who have studied immunology is not always fully appreciated," says Helen Collins, education secretary at the British Society for Immunology in London, which is running a careers-mapping project to get a better picture of the jobs that people with immunology PhDs end up in. **N.F.**

partner of choice for industry," says Williams. "There have been some good steps to close the gap, but whether careers in academia are being enabled as a result — the jury is still out on that."

Many breakthroughs in immunology owe a lot to major strides in lab technology. Advances in cameras, microscopes and imaging systems have provided researchers with insights into how the immune system works *in vivo*. Studying genes, proteins, messenger RNA and metabolites in samples has become progressively easier: techniques that just a few years ago required large, expensive machines have now become routine. Until the past few years, such analyses mostly involved averaging data gathered across many samples, but today's immunologists are gaining access to a range of technologies for single-cell analysis. This opens up both big opportunities and significant challenges. "These technologies generate vast amounts of data and the big hurdle is often on the analysis side," says Coles.

This data-rich environment means that immunologists need training in how to handle large data sets. Graduate and postgraduate training programmes at various institutions are adapting to this state of affairs to different extents.

"Early-career biologists now have to be able to cope with complex data sets that require machine learning and other techniques," says Coles. "You don't have to do four years of maths, but if you are working with others, you need to understand what has happened with the analysis of your data. The average university degree does not necessarily include the required skill set."

One place getting to grips with the big-data revolution, with characteristic Silicon Valley steam, is the University of California, Berkeley. There, undergraduates of all disciplines have been encouraged to take data-science courses since 2015. Students of immunology are, for example, taught how to use publicly accessible databases such as the one curated by the Immunological Genome Project, which is building a collaborative data bank of gene expression for all known immune cells in mice.

"From an immunological perspective, there are so many different cell types, functions and differentiation states," says Berkeley immunologist Nilabh Shastri. "The idea is to give students an understanding of what kind of information they can extract from the available data."

These rapid technological advances have also helped to drive interdisciplinary working. A generation ago, an immunologist's lab would have looked very different from the labs of an oncologist or a neuroscientist. Today, the same equipment is used across disciplines, helping to break down barriers and stimulate conversations between researchers.

The emphasis on collaboration across fields and sectors more generally means that those who are good at networking and remain receptive to outside influences are most likely to thrive. "You have to be open to new ideas," says Maiti. "Being dogmatic around a particular hypothesis or belief system is more detrimental now than it was 10 or 15 years ago. The field is moving quickly." ■

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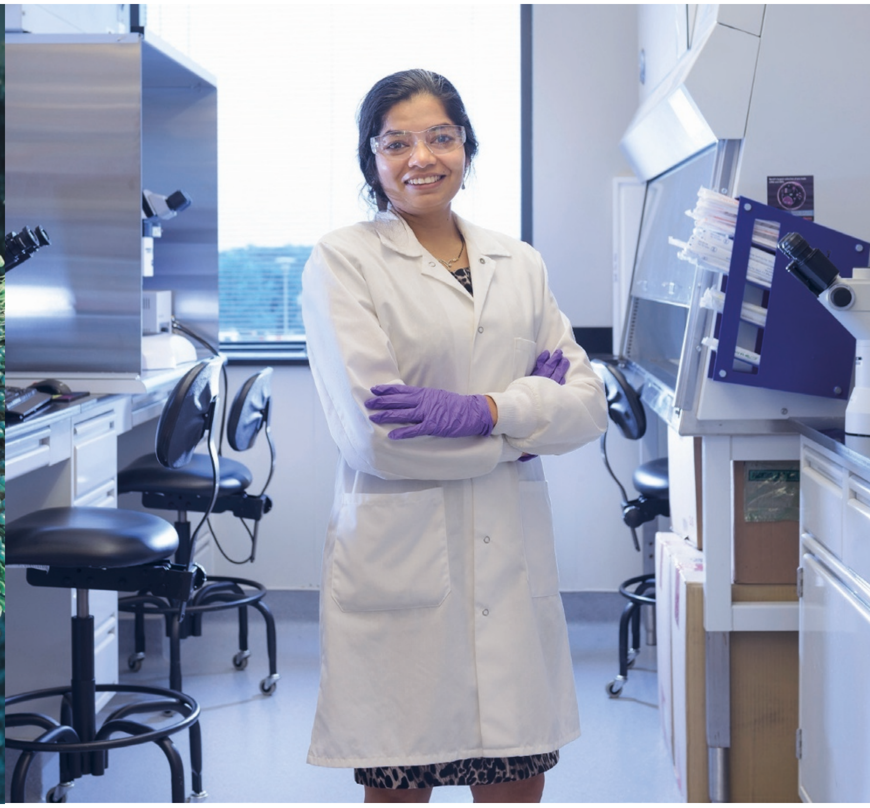
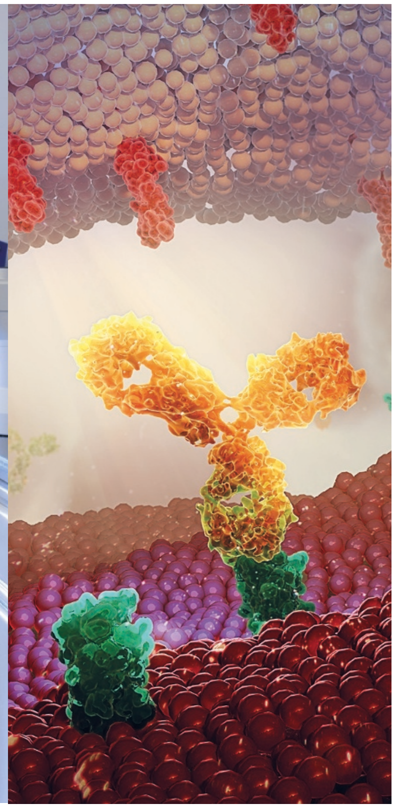

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