CELL MAPPER Paving a way towards precision cancer treatment **p.129**

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ILLUSTRATIONS ADAPTED FROM GETTY

GLYCOBIOLOGY

Sweet success

Biologists are diving into sugar–molecule research thanks to new tools and techniques.

BY ESTHER LANDHUIS

Chemist Lingquan Deng was presenting a poster at a 2015 meeting of the Society for Glycobiology in San Francisco, California, when a career opportunity came knocking.

At the time, Deng was a research fellow studying platelet–bacteria interactions at Johns Hopkins University in Baltimore, Maryland. He had been searching for a faculty position close to Washington DC, where his wife worked as a lawyer.

Then, a fellow attendee at the meeting told him that his company was hiring and invited him to present his work there. The company was just outside Baltimore and Deng decided that a visit wouldn't hurt. A day after giving his presentation to GlycoMimetics, he received a job offer. And today, he works there as a research scientist, designing assays to evaluate compounds for preclinical testing for disorders such as blood cancers and sickle-cell anaemia. The skills he gained during his PhD and postdoc in synthesizing carbohydrates and studying their interactions with proteins were a perfect match with the job requirements, he says.

Deng is one of a growing number of scientists finding career opportunities studying the biology of glycans — the sugar molecules that often adorn the surface of cells. Glycans are involved in practically every area of biology, from helping cells to communicate to recognizing invading pathogens. But the field has taken a while to get off the ground, in part because glycans are dizzyingly complex and few tools were available to make them accessible to researchers.

But the situation is starting to change as funders have realized the importance of the field and begun to invest in it. In December 2009, the US National Institutes of Health (NIH) National Heart, Lung, and Blood Institute announced a programme to fund resources for studying glycans, as well as training through courses, workshops and annual retreats. In 2012, the US National Research Council warned that ignoring glycans would impair research in biomedicine. A better understanding of glycoscience, it added, would deepen researchers' understanding of cancer, infectious diseases, biofuels, alternative sources of carbohydrate-based energy and the development of new carbohydrate-based materials. And in the United Kingdom, IBCarb, a network of glycoscientists funded by the Biotechnology and Biological Sciences Research Council, hosts regular workshops and training sessions on glycocience research areas. Similar programmes have also sprung up elsewhere in Europe, as well as in Canada, Asia and Australia. Since 2015, the Common Fund of the NIH has awarded 49 grants totalling US$29.2 million as part of its glycoscience programme, for projects aimed at developing affordable methods to synthesize and analyse carbohydrates and at creating databases to store and share the findings.

As a result of all this investment, academic researchers have been empowered to develop services and tools that help to close the skills and technology gap, and glycoscience is emerging as a high-impact and enticing field. And job prospects are growing in industry, too. The global market for glycobiology is expected to double to $50.1 billion by 2021, according to market-research firm BCC Research in Wellesley, Massachusetts. There are now about a dozen glycomics centres around the globe that can conduct screens or create custom reagents using state-of-the-art commercial equipment.

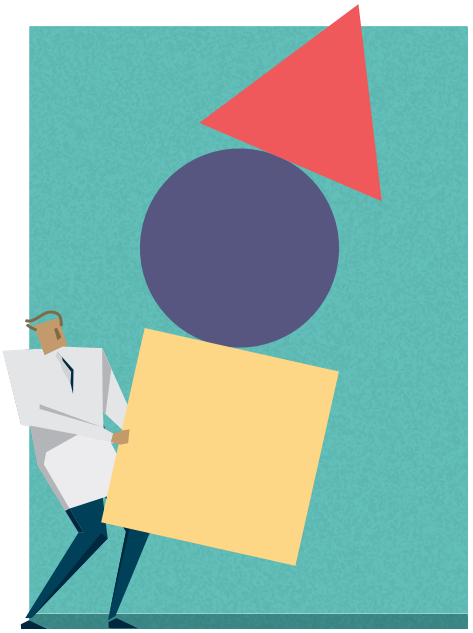
Glycans are so fundamental to biological ▶

processes that learning about them will help to give researchers a more comprehensive understanding of biology, even if they don't specialize in glycobiology, says Ajit Varki, who served as Deng's postdoc mentor and co-directs the Glycobiology Research and Training Center at the University of California, San Diego. It can also serve as a bridge into biomedicine for those who do not have a background in the life sciences — as was the case for Deng, who started off his research life with a bachelor's in materials science and engineering. "Glycobiologists are important in most biological drug programmes. It is a growing area," says Spencer Williams, a carbohydrate chemist at the University of Melbourne in Australia.

CRAZY COMPLEXITY

Researchers with an understanding of glycans have a wide choice of potential applications. Glycans attach to proteins and lipids through a chemical process known as glycosylation, and in doing so determine human blood type and facilitate the binding of sperm to eggs and mediate immune-cell interactions. Together with these other biomolecules, the glycome — or total set of glycans — forms a crucial interface that transmits signals between the cell's exterior and interior worlds.

Yet getting that understanding is hard. Researchers generally study biomolecules such as DNA and peptides by synthesizing them in the lab and then probing how they react to different circumstances. But DNA and peptides are linear molecules with no branches, and tools for analysing them took off in the 1970s and 1980s. Sugars, however, have numerous branching points and each of those linkages can exhibit left- or right-handed asymmetrical forms depending on the orientation of the attached molecule. They also have exponentially more potential configurations than do DNA or proteins, and that makes them much harder to synthesize in the lab, says Peter Seeberger, a biochemist at the Max Planck Institute of Colloids and Interfaces in Munich, Germany. DNA is made up of four nucleotides (G, A, T and C), so there are theoretically 4,096 possible ways to build a string of six elements, or a 6-mer. Proteins have more building blocks (20 amino acids) and can potentially assemble into 64 million different 6-mers. But 6-mer carbohydrates can adopt 193 billion possible configurations. As a result, tools for synthesizing sugars are about 35 years behind those for DNA and peptides, Seeberger says.



Investigating the biology of the molecules is also difficult. Researchers working on DNA can type the sequences they want into an online order form and receive them a few days later, Williams says. And for protein studies, online services can deliver custom-made antibodies in 6–8 weeks.

CORE SOS

Helping to bring people into the field are the increasing availability of core glycomics facilities, or centralized shared labs that offer access to specialized instruments, technologies and services for studying sugars. Decades ago, biologists wanting to know what carbohydrates a particular protein binds to would have to spend years doing tedious biochemistry experiments. Now, a core lab can run a protein sample across hundreds of carbohydrates immobilized on an array and rapidly detect which glycans the protein binds to. That allows researchers to move quickly onto functional studies and "cuts through years of difficult work", says Williams.

Emory University's core facility in Atlanta, Georgia, has proved crucial for Brian Robinson, a postdoc investigating the role of glycans in development and wound repair. The team there is helping him to harvest glycans from key target tissues and develop custom arrays to determine which glycans bind to several proteins he is studying. His research will help him to understand how those biomolecules regulate human metabolism and immune responses.

Glycan-array services are offered by about a dozen centres worldwide. The data they generate usually enter public databases, so that other researchers who study similar proteins can see the findings. For those wanting insight into the structure of particular carbohydrates, some labs and companies (see 'Extra help') offer mass-spectrometry and analytical chromatography methods. The advances are enabling researchers such as Robinson, an MD-PhD-trained pathologist, to study the biological role of glycans much more rapidly and in enough detail for future medical applications.

NEW TOOLS

Seeberger and his colleagues estimate that 90% of known molecules in the mammalian glycome can be synthesized from 45 basic structures. The team has managed to produce large quantities of about 40 such structures — now sold by GlycoUniverse, a spin-off company of his institute. The launch of the company reflects the unmet need for such technology and the entrepreneurial opportunities in the field.

To detect sugars and other biomolecules in living tissue, researchers often buy or make antibodies. However, conventional methods tend to work poorly for sugar-specific antibodies — in part because the glycan antigen can be tricky to make. Some labs are therefore working to create carbohydrates that are more likely to trigger an immune response, and thereby make antibodies — a critical research tool — easier to generate.

Carolyn Bertozzi, a chemist at Stanford University in California, has taken a different approach. She and her team feed cells with monosaccharides, or simple sugars, that sneak into biosynthetic pathways and are incorporated into glycans inside the cell.

Then, by chemically attaching tags or fluorescent dyes onto the building blocks of these sugars, researchers can visualize the glycans in their natural environment without

EXTRA HELP

Other sources of information

Researchers who want to familiarize themselves with the basics of glycobiology or learn about tools and support for working with glycans can check out these resources.

Science

- *Essentials of Glycobiology* is a textbook available free online (Cold Spring Harbor Laboratory Press, 2009)

Glycomics centres and core labs

- Consortium for Functional Glycomics in Boston, Massachusetts
- Glycosciences Laboratory, Imperial College London
- Emory Comprehensive Glycomics Core in Atlanta, Georgia
- Glycotechnology Core Resource, University of California, San Diego
- Copenhagen Center for Glycomics
- Alberta Glycomics Centre, Edmonton, Canada
- Institute for Glycomics, Griffith University, Brisbane, Australia
- Japan Consortium for Glycobiology and Glycotechnology Database E.L.

needing the hard-to-make antibodies.

For Julia Maxson, a cell biologist at Oregon Health & Science University in Portland, finding glycobiologists to get tips from and bounce ideas off was key. Several years ago, she was trying to determine how a gene mutation causes rare leukaemias. The mutation affects a receptor on the surface of immune cells by disabling where it attaches to a large glycan. Without the sugar, the receptor can trigger the cell to grow uncontrollably — a unusual cancer-causing pathway.

But when Maxson submitted the manuscript for publication, a reviewer wanted clearer evidence for the modification, called *O*-linked glycosylation. She wondered whether Bertozzi's labelling strategy might help and e-mailed her for advice on how to use it for her research.

With Bertozzi's counsel and a deeper understanding of how sugars can trigger rare leukaemias, Maxson won an NIH fellowship for postdocs transitioning to faculty positions. Today she works with Bertozzi to characterize sugar structures found uniquely on cancer cells. They hope that their findings can lead them to therapeutic strategies that precisely target tumour cells, which could pique industry interest and create research opportunities. Indeed, as scientists get a better handle on studying glycans in the lab, companies are exploring therapeutic ramifications, which should fuel growth in industrial research jobs.

"Glycobiologists are important in most biological drug programmes."

Most biologics — medical products derived from natural sources — are glycosylated, which drives interest in investigating how the sugar structures influence the safety and effectiveness of therapies being developed for cancer and other diseases, Williams says.

Analytical glycobiology is so crucial, in fact, that Deng's boss is looking to hire another researcher with these skills. And just as in his case, Deng says, it looks likely that such a candidate could land a job without even formally applying. ■

Esther Landhuis *is a freelance journalist in Pleasanton, California.*

CORRECTION

The Spotlight article 'China's Silicon Valley' (*Nature* **545,** S29–S31; 2017) erroneously stated that Ali Muhammad moved to Shenzhen from India. In fact, he moved from Pakistan.

TURNING POINT
Single-cell mapper

Biotechnologist Andrew Adey developed a high-throughput method for mapping the genomes of single cells. The advance, reported in January, allows for the identification of diverse cell populations in tumours, and so paves a path towards precision medicine. To develop it, Adey, now at Oregon Health & Science University in Portland, relied on HeLa cells, a prolific cancer-cell line biopsied in the 1950s from Henrietta Lacks, who had cervical cancer, and used widely in biomedical research without her consent.

MIKE LISKAY

How has single-cell biology advanced?

In the mid-2000s, next-generation sequencing was just starting, so today's version of single-cell biology was non-existent. Today, researchers can look at genome-wide properties or other aspects of single cells.

How did you use HeLa cells?

I knew nothing about the history of HeLa, just that it was a cancer-cell control line that grew really well. We wanted to understand how different copies of chromosomes influence cells. Once we developed technology to do this in normal cells, we set out to see how those copies act in cancer cells, and so applied it to HeLa. We learned more about HeLa — notably, that multiple copies of a genome can act differently — and worked out the genomic changes that enable an aggressive cancer to reproduce so readily.

What was your role in the privacy debate over publishing HeLa sequence information?

As we were readying a paper in 2013 (A. Adey *et al. Nature* **500,** 207–211; 2013), we didn't know how we were going to publish genetic information that could have consequences for Lacks's descendants. Ultimately, the US National Institutes of Health reached an agreement with the Lacks family that accompanied our paper, and that granted researchers access to the cells while maintaining the Lacks's privacy. HeLa is a unique case — one not only at the forefront of medical advances but also about the ethical informed consent that is crucial to medical practice.

Can you explain the technique put forth in your January paper?

Initially, our platform could fully sequence only the portion of the genome that regulates gene expression in single cells (S. A. Vitak *et al. Nature Meth.* **14,** 302–308; 2017). We wanted to progress to whole-genome sequencing from single cells. But when you target regulatory elements, you typically have access to only 1–4% of the genome. We had to work out how to free up the DNA to convert the entire genome into sequenceable molecules.

What were the main obstacles?

At one point, it seemed like we were playing 'whack-a-mole'. Every time we altered one fixed property of the protocol, something else that had been working fine would stop. It was challenging, because the genome is packed nicely into nuclei. We needed to destroy the proteins that packaged the DNA inside the nucleus, without destroying everything else. Most of the time, everything would just explode and we'd lose the ability to look at single cells.

What's next?

We've already improved our method from what we published in January. It's even more reproducible, and we can get more data from single cells. Half of my lab does technology development; the other half applies those methods to answer questions of interest. This method was the first step to examining other aspects at the single-cell level. We're now using these technologies to explore cell identity. For example, how does a cell respond when treated by a cancer drug?

How will your method affect cancer treatment?

With a single-cell focus, we can start to profile an individual's tumour and identify molecularly distinct subpopulations in a tumour. If we can then profile large cohorts and tumours at the single-cell level, we can learn how certain subpopulations will respond to specific drugs to better home in on effective treatments. ■

INTERVIEW BY VIRGINIA GEWIN

This interview has been edited for length and clarity.