Q&A: Arunima Chaudhuri

Arunima Chaudhuri is a postdoc at Yale University in New Haven, Connecticut, where she studies membrane fusion using microscopy. Here, she talks about the need for interdisciplinarity in her work, the importance of being flexible, and what it takes to make it in the job market.

What do you work on?

Super-resolution microscopy. It's a way of observing subcellular components in their natural state. I study proteins, such as synaptotagmin-1, that are part of the membrane fusion machinery. Synaptotagmin-1's basic function was discovered in the 1990s through experiments in mice with the protein 'knocked out'. But the current view is that deleting a protein and looking for changes doesn't necessarily give you a holistic view of what the protein does. There's redundancy built into biological systems. So, if you want to study the entirety of what a protein does, you need different approaches — such as detailed structural observations from living cells.

What's a typical day in the lab like?

I basically spend the whole day talking to people, because I work with so many different kinds of expert. I use a custom-built microscope, so I rely on physicists to tune it. I need chemists to make fluorescent molecules able to tag the protein that I'm studying, and programmers to handle the enormous amounts of data my project generates. If something doesn't work, I have to go back to these people, talk it through and try something else.

How did you come across your postdoctoral programme, and what's next for you?

I've switched around a lot academically — I studied human physiology, then marine biotechnology and then, finally, did a PhD in membrane biology. But I really worked on my CV as a graduate student: I published papers and did presentations to enable me to aim for the big labs. I also received a Fulbright fellowship, which meant that I brought a postdoc stipend with me for two years — that helps! I'd like to make it in academia, to get my own lab and faculty position. So, in a few years, I see myself applying absolutely anywhere on Earth — wherever I can really use my skill set. ■

INTERVIEW BY ANNA PETHERICK

This interview was edited for length and clarity.

The advancements have opened up the field of membrane science to researchers in other areas. No longer are membranes the preserve of cell biologists and biochemists; Zhang started his career as a chemical engineer — a discipline that, in his words, "used to be geared towards the oil business". But training in an area that emphasized chemical purification, mass and heat transfer — not to mention an engineer's instinct to deconstruct and design — has served him well as a membrane investigator. Today, his lab houses every flavour of bench researcher, from immunologists to material scientists. And as the range of specialities that are finding a place in membrane research has broadened, so, too, has the geographical spread of leading labs, most notably into China.

Zhang turns the conversation to poison. "If you look at the toxins that attack red blood cells, currently we know of about 80 toxin families, and they each do it in different, specific ways," he says. Some attack by binding to protein receptors on the surface of red blood cells, gaining a foothold that makes them almost impossible to shift, he explains. Others interact with the phospholipids that constitute the membrane, a process that tears the cell apart. This variance has hindered the development of any kind of 'cure-all' solution. "Basically, creating a synthetic material that could simultaneously target 80-odd families of toxin would be an impossible task, because many of these toxins work completely differently," says Zhang.

Zhang's lab has developed something they call a nanosponge, which mops up all kinds of haemolytic — red-blood-cell-rupturing — poisons, from animal venom to the fluids produced by infectious agents such as methicillin-resistant *Staphylococcus aureus* (MRSA). The nanosponge is made of a polymer core that serves as structural support within a red-blood-cell-membrane wrapping. Each sponge is more than 3,000 times smaller in surface area than a red blood cell, but can soak up tens to hundreds of haemolytic poison molecules. It operates as a decoy, drawing toxins towards itself and away from living cells (C.-M. J. Hu *et al. Nature Nanotechnol.* **8**, 336–340; 2013). "The only way to produce a complete solution is to use natural cell membrane," says Zhang. "It has all of the components the toxins can target."

A molecule of poison is just one of hundreds of thousands of chemicals that a cell might encounter over its lifetime. The membrane holds the cell together, and works as a barrier to the outside world. If anything on the outside wants to manipulate cell behaviour — perhaps by preventing cell reproduction or changing cell metabolism — it has to get the message through the membrane first. This is true for both natural and synthetic processes; roughly 60% of prescription drugs target membrane proteins.

METHODOLOGICAL OUTREACH

In the early 1980s, Johann Deisenhofer, Robert Huber and Hartmut Michel determined the structure of the photosynthetic-reaction centre of a bacterium, for which they shared the Nobel Prize in Chemistry in 1988. By bouncing X-rays off a crystallized sample — a technique at the time already well established in the orderly world of inorganic chemistry — and doing the mathematics to interpret the diffraction patterns, they built a map of the proteins involved (J. Deisenhofer *et al. J. Mol. Biol.* **180,** 385–398; 1984).

Crystallization was a major step forward for protein characterization, but it's not well suited to membrane proteins. When layered as a membrane, lipids apply lateral pressure that can hold an embedded protein in a particular conformation. Rip a protein from its spot in a plane of fat molecules — something typically needed for X-ray scientists to get the crystalline samples they crave — and you might change its shape, which could mask what the protein does and how it works.

One method exciting the field is cryo-electron microscopy (cryo-EM). The technique helps scientists to elucidate molecular structures by bouncing beams of electrons over a sample, after freezing the structures to stop them from jiggling around. "Cryo-EM has become very popular as a means to determine membrane-protein structure," says Ronald Clarke, a chemist at the University of Sydney, Australia, who studies ion pumps — proteins that transport ions across membranes.

Once the technology behind cryo-EM was fine-tuned, flash-freezing proved much more structurally respectful of the delicate associations between protein subunits than turning them into crystals and zapping them with X-rays. "Now, membrane-protein structures are being solved quite regularly," says Clarke. "That means lots of theoreticians have been entering the field, because it's now possible to carry out simulations of molecular dynamics. From structural clues, they model how membrane proteins function." In other words, membrane science is slowly being permeated by computer science.

Being able to determine the detailed architecture of membrane proteins is a big deal. Today, the Protein Data Bank, an online repository for known 3D structures of biological molecules, holds just one membrane protein for about every 300 non-membrane ones, despite the fact that membrane proteins make up about one-quarter of the total roster of different proteins in the body.

Biophysicist Tao Xu has personally experienced how developing a technique can spur

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