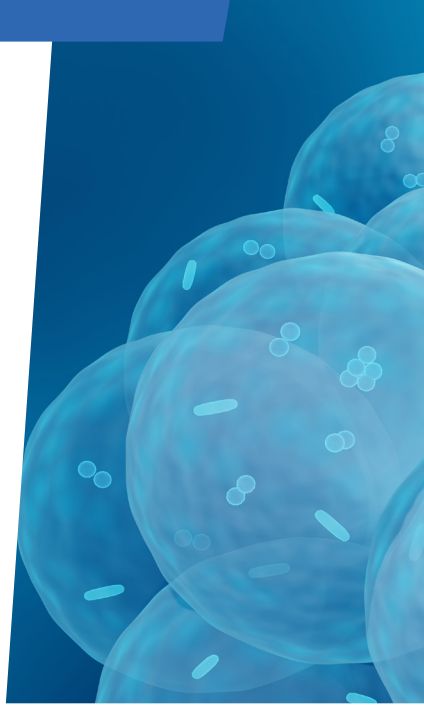
Breath by breath: how T cells protect our lungs from infection



Every day, we breathe in around 11,000 litres of air, full of microbes, dust particles and pollutants. Our lungs must work tirelessly to filter the air we breathe - so how do they keep us healthy despite so many potential threats? **Dr Anukul Shenoy** from the **University of Michigan Medical School** in the US, is investigating how immune cells that live inside our lungs – lung-resident T cells – detect danger, remember past infections and protect us from pathogens.

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Fields of research
Immunology, microbiology

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PROFILE

Talk like an ...

immunologist

Antimicrobial molecules — substances made by the body that kill or stop the growth of harmful microbes

Commensal — a microorganism that lives in the body without causing disease

Barrier epithelial cells — cells that form the outer layer of tissues and organs, creating barriers and regulating exchanges between body compartments

Immunocompromised — having a weakened immune system that makes it harder to fight infections

Pathogen — a microorganism, such as a bacterium or virus, that can cause disease

Pneumonia — a lung infection that causes inflammation and fluid buildup in the air sacs

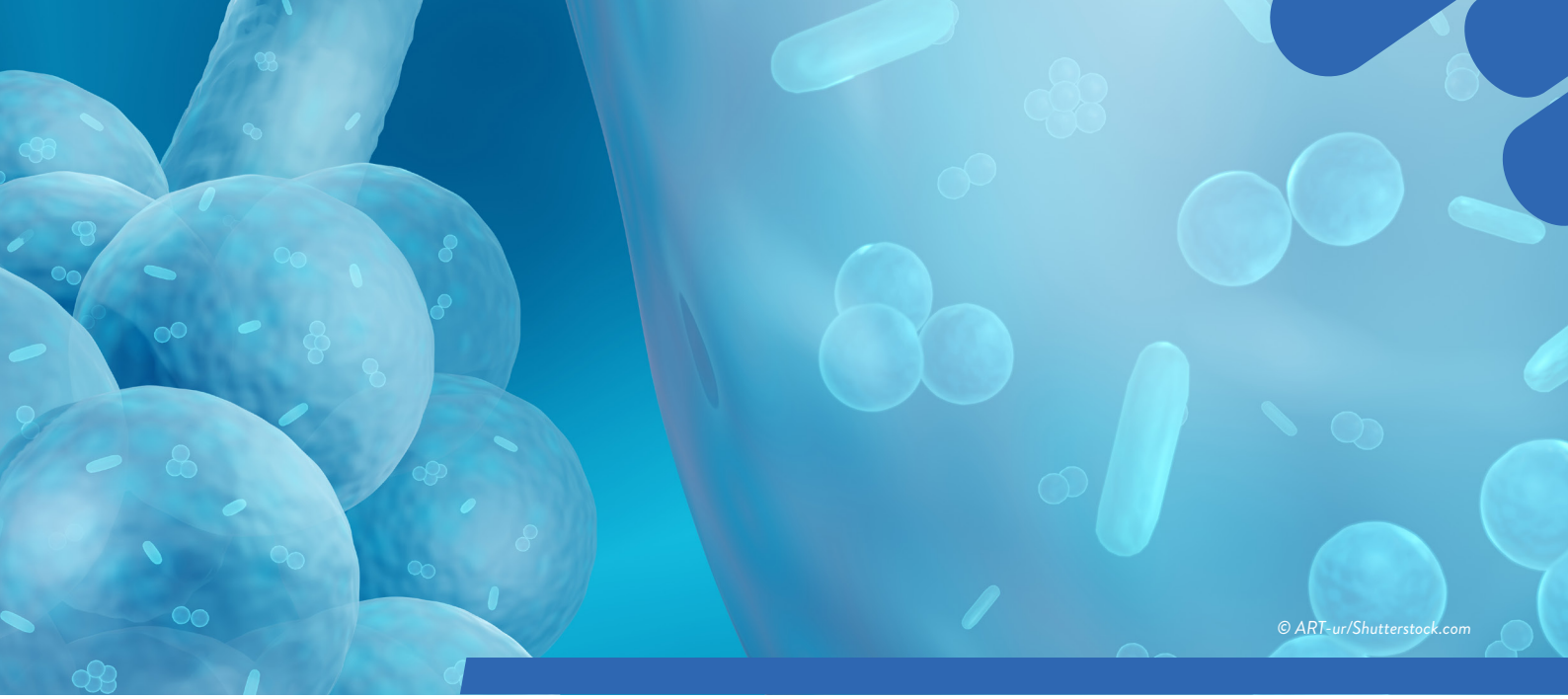
Sepsis — a life-threatening reaction that occurs when the body overresponds to infection, damaging its own tissues

T cell — a type of white blood cell that identifies and destroys infected cells and helps coordinate the immune response

Thymus — the organ where T cells mature and learn to distinguish foreign microbes from our own cells

Every breath we take connects our body to the outside world. With each inhale, air travels deep into our lungs, carrying dust, pollutants and countless microbes. To protect us, the lungs are lined with a thin layer of epithelial cells – a living interface between the external environment and the tissues within. This layer spans an area about the size of a tennis court, yet is less than one millionth of a metre thick, forming a delicate surface where oxygen enters the blood and carbon dioxide leaves.

"Barrier epithelial cells act as the immune system's eye, watching out for problems and triggering our immune response to keep us healthy," explains Dr Anukul Shenoy from the University of Michigan Medical School. Constantly exposed to the outside world, our lung epithelial cells must allow gas exchange while blocking harmful invaders. By producing mucus and antimicrobial molecules, and by working with immune cells, they keep the air reaching our lungs almost sterile. But what happens when something manages to get through this barrier?



T cells: the memory makers of the immune system

When something manages to slip past the lungs' epithelial defences, the immune system turns to one of its most specialised lines of defence: T cells. "T cells are a special type of immune cell that initially develop in our bone marrow but finish their development in the thymus, hence their name," explains Anukul. "They are capable of extraordinarily long-lasting memory and can remember pathogens for our entire lifetimes."

Once activated, T cells can become either helper T-cells, which release signals to coordinate the immune response, or killer T-cells, which destroy infected cells before the infection can spread. Another group, regulatory T-cells, helps to calm the immune system once the threat has passed, preventing unnecessary tissue damage.

Some T cells go a step further by taking up permanent residence in our tissues. In the lungs, these resident T cells remain after an infection has cleared, continually patrolling the airways and staying alert for returning pathogens. Acting as vigilant guards, they can recognise familiar threats, alert neighbouring immune and epithelial cells, and eliminate infection before it becomes serious. "Because of these layers of specialisation, T cells are important immune cells that are widely considered to be ideal targets for vaccines that could generate lasting protection from pathogens," says Anukul.

When bacteria take advantage: *Streptococcus pneumoniae*

One of the key focuses of Anukul's research is *Streptococcus pneumoniae* – a bacterium that quietly lives in the back of the nose and throat of many healthy children and adults. Most of the time, it coexists harmlessly with its human host. But, when inhaled into the lungs of people with weakened immunity, it can cause serious disease.

> ***"Our lab is deeply interested in understanding how epithelial cells perform so many key tasks beyond their basic specialised functions."***

"In a healthy person, our epithelial cells and immune cells team up and clear the inhaled bacteria without disease or symptoms," explains Anukul. "However, if the host is immunocompromised, this bacterium is no longer eliminated by the immune system, allowing it to multiply within our lungs." Once established, it can cause pneumonia, spread into the bloodstream to trigger sepsis, or even lead to meningitis (a serious infection that affects the brain and spinal cord). This ability to exploit weak immune systems, combined with its widespread commensal infection rate, makes it a leading cause of infectious deaths among infants, the elderly and immunocompromised individuals.

Part of what makes *S. pneumoniae* so difficult to control is its adaptability. It can quickly acquire new genes from its environment, helping it to resist antibiotics and disguise itself from immune cells and vaccines. For these reasons, the World Health Organization has classified it as a 'priority pathogen', requiring urgent research.

Anukul and his team in the Shenoy Lab take inspiration from the fact that most healthy adults carry *S. pneumoniae* without harm. "This suggests that healthy human lungs have all the adaptations and cell types required to keep this bacterium in its commensal state without causing severe disease," explains Anukul. "Thus, we are interested in understanding how lung-resident T helper cells, epithelial cells and other immune cells communicate to sense, respond to and clear *S. pneumoniae* without symptoms, which could guide the development of improved vaccines and therapies." Ultimately, Anukul's research aims to prevent infections in vulnerable populations and provide a framework for tackling other bacteria that are harmless in healthy people but pathogenic when immunity is compromised.

What does the future hold?

"Our lab is deeply interested in understanding how epithelial cells perform so many key tasks beyond their basic specialised functions," says Anukul. "These include detecting, eliminating and tolerating threats, recruiting immune help, guiding inflammation, building memories, and repairing barrier tissues." By exploring how lung epithelial cells balance these roles during infection and recovery, Anukul's team hopes to reveal new ways to strengthen tissue health. Their findings could help shape next-generation vaccines and therapies that target epithelial cells directly, improving the prevention and treatment of diseases such as pneumonia, asthma, long-COVID and even some cancers.

Confocal microscopy image of a mouse spleen, an organ with an important role in the immune system. © Shenoy Lab

About *immunology*

Immunology is the study of how the body defends itself against infection and maintains internal balance. Our immune system is made up of an extraordinary network of cells and molecules that communicate constantly to recognise and respond to threats such as bacteria, viruses and fungi. "Working in the field of immunology often feels like trying to solve a giant jigsaw puzzle that evolution has been building for millions of years," says Anukul. "Different immune cells and molecules have co-evolved to ensure the smooth functioning of our organs and tissues."

"Immunology is rewarding because our discoveries are broadly applicable to different disease states and organs," continues Anukul. "Given the limited number of genes we possess, it is very often the case that our immune system has repurposed the same cells, pathways and mechanisms to solve similar problems in different body sites."

However, studying such a complex system is not easy. The immune response involves intricate communication between different cell types within and across organs. "Such complex multicellular and multi-organ phenomena cannot be mimicked in a lab using simplistic systems, so we use animal models for experiments," explains Anukul. "To ask if a certain molecule is important in an immune circuit also requires the ability to delete or express that molecule specifically in one cell type or developmental stage, which demands genetically engineered mouse models that are expensive and time-consuming to create." Despite these challenges, each new insight reveals more about how the body protects itself – knowledge that could one day transform how we prevent and treat disease.

Pathway from school to *immunology*

In high school, build a strong foundation in biology, chemistry and mathematics.

At university, molecular biology courses, such as genetics, biochemistry, microbiology, animal physiology, cell biology and developmental biology, will be useful.

Take courses with a lab component, as they can help you become comfortable with scientific equipment and experimental techniques.

"Be proactive, be curious and do not shy away from asking questions," says Anukul. Look for research opportunities early; many universities offer summer internships where students can gain practical experience studying real biological problems. Asking teachers or professors about available placements is a great way to get started.

Explore careers in *immunology*

"For those looking to get more exposure, there are professional societies, such as the American Association of Immunologists (**aai.org**), the Society for Mucosal Immunology (**socmucimm.org**), the American Thoracic Society (**site.thoracic.org**) and the European Federation of Immunological Societies (**efis.org**), that have great resources to get you involved in immunology," says Anukul.

Explore what the leading researchers in the field are working on and discovering by listening to podcasts such as *Immune* (**microbe.tv/immune**), *The Immunology Podcast* (**immunologypodcast.com**) and the *Mucosal Immunology Podcast* (**socmucimm.org/resources/mucosal-immunology-podcast**).

For students seeking practical experience, the University of Michigan Health Sciences Summer Institute runs the Summer Pre-College Exposure Academy (**umhs.smapply.io**) which is designed to give highly-motivated high school students exposure to healthcare professions.

Meet *PhD students in the Shenoy lab*

"Just like a successful immunological response, science thrives on teamwork," says Anukul. "The scientific enterprise flourishes when individuals from all backgrounds, experiences and viewpoints are welcomed and empowered. Each unique perspective – shaped by personal history, culture and identity – adds a valuable piece to the grand puzzle of discovery. By creating an environment where every person is heard and valued, their curiosity is encouraged, and their questions are celebrated, scientific progress becomes more innovative, robust, and ever closer to revealing the profound beauty that underlies the complexity of the natural world and those studying it."

Meet *Olivia Harlow*

I am currently studying how *Streptococcus pneumoniae* makes the lungs more suitable for T cells to live there long-term so that these T cells can then help to protect against future *S. pneumoniae* infections.

I first worked in Dr Shenoy's lab as part of the University of Michigan's rotation scheme for biomedical sciences PhD students. This system allows students to try out a lab to see if they like the research, people and principal investigator. I was Dr Shenoy's first graduate student, so we made sure that we had good communication, aligned our expectations about the project, and planned for potential challenges during my PhD.

I've been interested in immunology since first learning about it in high school. My first science job was as a summer research fellow at my undergraduate institution, where I worked on a type of immune cell that is similar to those I work with now.

The first time I applied for a PhD, I didn't get into any school I applied to. I then worked as a post-baccalaureate research employee at the Mayo Clinic, where I learnt valuable technical skills (like working with research animals) and life skills (like living alone). That experience helped me consider what research I was curious in pursuing in graduate school, what school I wanted to go to and who I was interested in working with. I was then a more competitive applicant the next time I applied to graduate school!

To unwind from work, I like to go walking or running outside to enjoy the weather and clear my head. I also unwind by playing video games, watching TV or painting.

Olivia's *top tip*

Ask a lot of questions! Immunology is a dense subject that is not always straightforward. Even now, I ask a lot of questions in our lab meetings because I'm curious about all the immunological processes that could influence the work in our lab!

Meet *Sophie Maxfield*

My project involves asking questions about how the hygiene hypothesis works on a cellular and immunological level. The hygiene hypothesis is a theory which states that exposure to different microbes early in life can lead to protection against the development of allergic disease later on. To study this, my project is investigating mechanisms of how exposure to bacteria in the lungs can prevent the development of asthma.

Many of the most interesting aspects of immunology can be seen at the exact site where a pathogen actually makes contact with the host. This host-pathogen interface has always fascinated me, so working in a lung epithelial immunology lab felt like the perfect opportunity to start asking questions I'd had since I first started learning about immunology.

My favourite aspect of immunology is that rules can almost always be broken. While the field has established several core tenets of how we understand the immune system to function, we are frequently discovering new cell types, modes of intra- or inter-cellular communication, and their roles in health and disease.

As a low-income, first-generation college student, one of the largest hurdles I've faced is navigating academia to pursue the career I want. I've lacked guidance on how to apply for college, graduate school and jobs in the field, as well as how to build skills or reach benchmarks needed to advance my career at each of these stages. Through this, I've learnt that one of the most valuable skills is taking initiative and asking for help.

I like to relax by listening to and making music, working out, reading, cooking or watching TV with my cat. Creative hobbies help me recharge.

Sophie's *top tip*

Make sure not to neglect humanities subjects, as these will give you insights into how to better communicate your ideas and can help you understand how to address concerns from audiences at all levels of expertise.