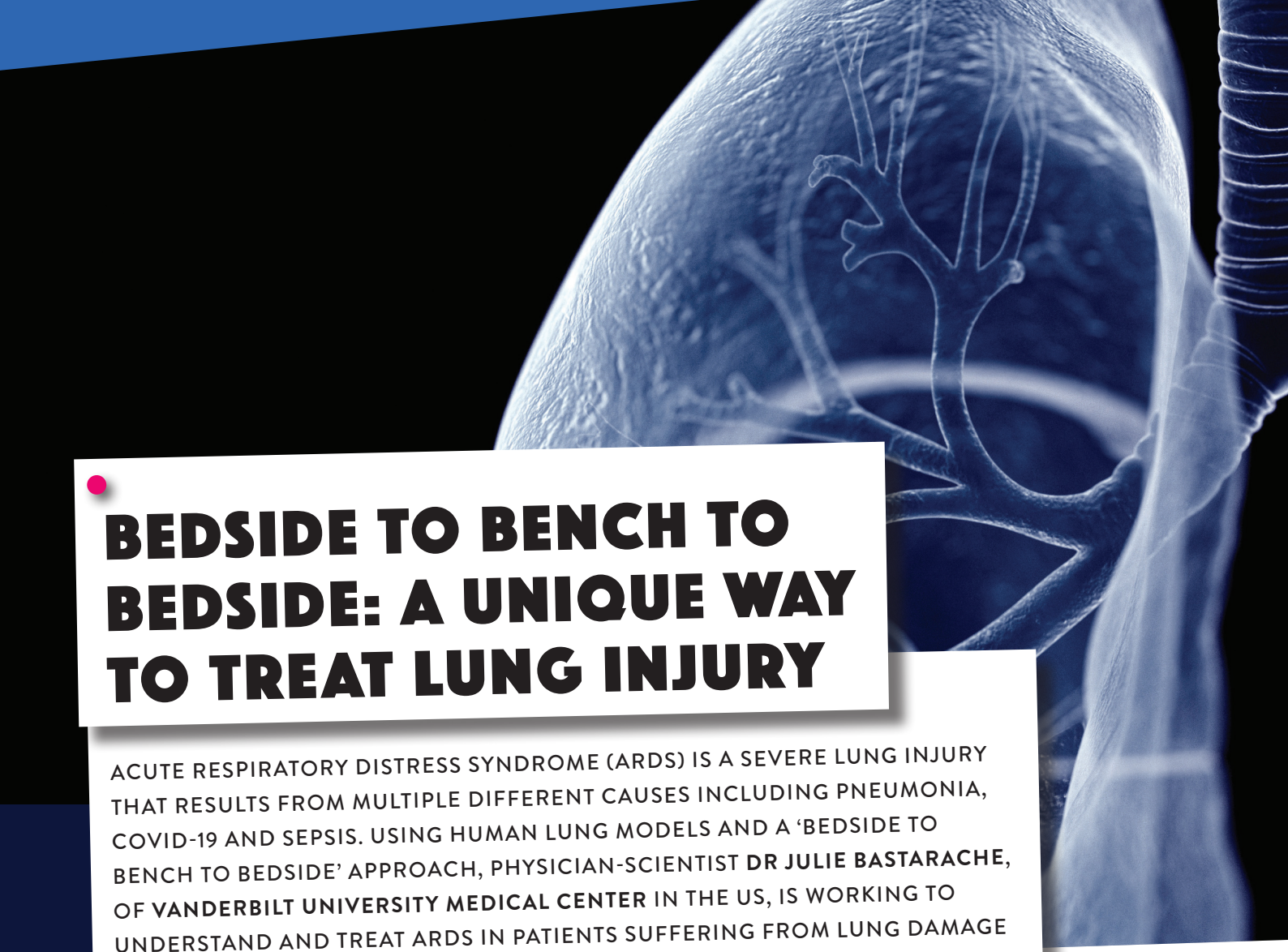


BEDSIDE TO BENCH TO BEDSIDE: A UNIQUE WAY TO TREAT LUNG INJURY

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) IS A SEVERE LUNG INJURY THAT RESULTS FROM MULTIPLE DIFFERENT CAUSES INCLUDING PNEUMONIA, COVID-19 AND SEPSIS. USING HUMAN LUNG MODELS AND A 'BEDSIDE TO BENCH TO BEDSIDE' APPROACH, PHYSICIAN-SCIENTIST **DR JULIE BASTARACHE**, OF **VANDERBILT UNIVERSITY MEDICAL CENTER** IN THE US, IS WORKING TO UNDERSTAND AND TREAT ARDS IN PATIENTS SUFFERING FROM LUNG DAMAGE

TALK LIKE A PHYSICIAN-SCIENTIST

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) – a cause of severe respiratory failure as a result of a serious injury or infection

CELL-FREE HAEMOGLOBIN (CFH) – haemoglobin leaked from red blood cells due to a weakening of the cell membrane after illness

HAEMOGLOBIN – an iron-containing protein in red blood cells which is responsible for carrying oxygen and carbon dioxide around the body

SEPSIS – an infection in the body that can lead to ARDS

Acute respiratory distress syndrome (ARDS) develops after a triggering event, such as pneumonia (an infection in the lungs), sepsis (an infection in the body) or severe trauma (like that caused by a car accident). Patients have difficulty breathing due to low oxygen levels in the blood and fluid collecting in the air sacs of their lungs. Many people experiencing ARDS end up in hospital, some needing mechanical ventilation to provide oxygen to the lungs. Despite being a common problem, many people still die from ARDS and currently there is no specific treatment.

Dr Julie Bastarache is physician-scientist at Vanderbilt University Medical Centre, working in a hospital as a medical doctor alongside working in a lab, researching the medical issues she encounters while on the ward. Using a 'bedside to bench' method, she observes human patients directly and then investigates her observations in the lab. Julie is using this method to better understand ARDS, and she hopes to develop a treatment that will enable doctors to prevent or reverse lung damage.

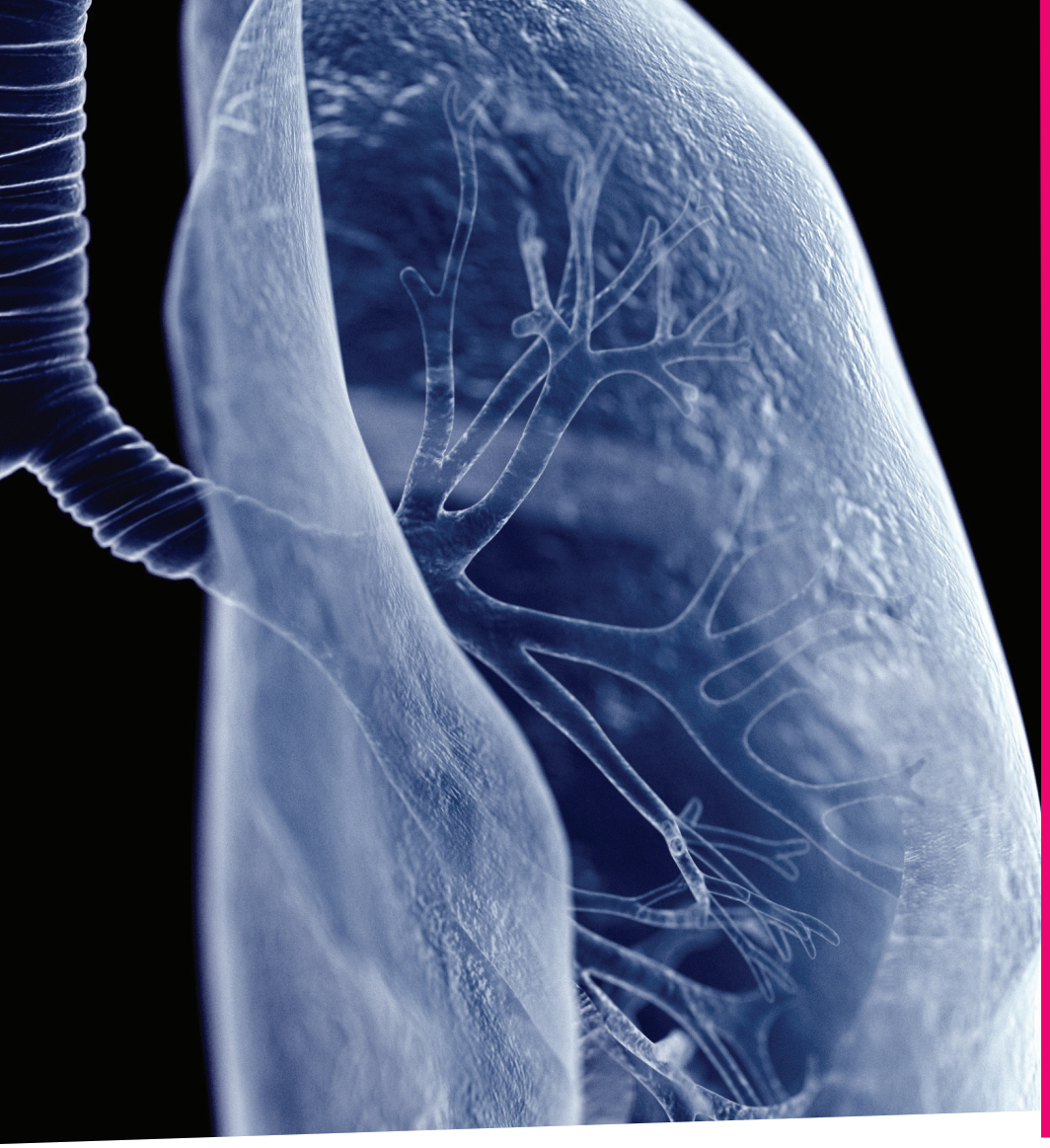
HOW DOES CELL-FREE HAEMOGLOBIN CAUSE ARDS?

Healthy red blood cells are full of a protein called haemoglobin, which carries oxygen and carbon dioxide around the body. The membrane of these blood cells is very flexible, allowing them to squeeze through very small blood vessels. However, when people are ill, for example with sepsis, this membrane becomes thinner and stiffer, causing the membrane to burst when it tries to fit through blood vessels. This releases haemoglobin into the bloodstream, producing cell-free haemoglobin (CFH) that is no longer contained within red blood cells.

Not only does CFH no longer bind oxygen, it also injures the cells that line the blood vessels (the endothelium) and the cells lining the air sacs in the lung (the epithelium). These layers become leaky, resulting in blood plasma entering the lungs and filling up the air sacs, causing inflammation and making it difficult for the patient to breathe and get oxygen into their blood.

FROM BEDSIDE TO BENCH

Julie describes her research methods as a 'bedside to bench' approach. Scientific discoveries begin as observations made at a patient's bedside, then the causes behind them are studied at a laboratory workbench. The hope



DR JULIE BASTARACHE

Vanderbilt University Medical Center, USA

FIELD OF RESEARCH

Physician-scientist

RESEARCH PROJECT

Studying the effects of cell-free haemoglobin on acute respiratory distress syndrome, in a dual role as a medical doctor and lab researcher

FUNDER

National Institutes of Health (NIH)

is that results can then be translated back to the bedside, to provide treatments for the patients.

"To make sure we are studying molecules and pathways that are important in human disease, many of our studies start with observations that we make in human patients," Julie says. She collects, with permission, blood and lung samples from patients suffering from ARDS, which are later studied in her research lab to find proteins and other markers that may be part of the disease.

Julie's discovery of the link between CFH and ARDS was an example of this 'bedside to bench' method. "In one of our studies, we found that blood and lung fluid from patients with ARDS had high levels of CFH," Julie explains. "We then took this observation back to the lab to study how CFH might be helping to cause lung injury." Using this method, Julie can start to understand the role that CFH plays in causing ARDS and hopefully develop a treatment to prevent it.

THE HUMAN LUNG MODEL

To develop treatments, Julie first needs to understand the biological pathways that cause CFH to damage the lungs. This requires the use of experimental models. "Experimental models allow the scientist to change variables to test the effects of those changes," explains Julie. No individual model is perfect, so these types of studies normally involve multiple models to focus on different aspects of a biological pathway.

This was the case in the experimental models set up by Julie. One of Julie's models cultured cells in a dish to study the molecular pathways of CFH effects, another used mouse models to test the effect of CFH in a living system. As well as this, a unique model of human lungs was used to test different therapeutic treatments in patients.

The human lung model is incredibly important in understanding how to treat ARDS. Only specialised research groups have access to human lungs, donated by people who allow their organs to be used for scientific purposes when they die. If the lung is not healthy enough to be transplanted into another person, the lung can be used by researchers like Julie for a more accurate way to test the effect of treatments on the lungs, which models in mice and cells cannot provide.

TREATING PATIENTS WITH ARDS

Once in the lab, Julie provides the lungs with oxygen, then studies what the effects of CFH are on the lung. During her research, Julie found that a very common over-the-counter medicine, acetaminophen/paracetamol, can fight the effects of CFH in patients with sepsis. Thanks to Julie's access to patients suffering from ARDS, she was able go back to the 'bedside' to do an early-stage clinical trial to see if this treatment works. "The results of this small study were positive," says Julie, "and we are now working on a larger study to test this in more patients." This link between laboratory research and patients is essential to quickly find a treatment that is effective at preventing ARDS.

Looking to the future, Julie hopes to continue learning more in the lab, focusing on understanding other biological pathways important in ARDS, as well as the genetic and environmental factors that may be important in causing ARDS. "Our hope is that we can take more things we learn in the lab and test them in patients with ARDS," she says. Julie's 'bedside to bench back to bedside' approach has, "established a natural cycle of scientific discovery". Physician-scientists are therefore essential in providing a link between hospitals and research labs, not only making it easier to quickly diagnose diseases, but also to develop treatments and cures.

ABOUT PHYSICIAN-SCIENTISTS

The unique feature of a physician-scientist is that they perform a dual role, working as a doctor in a hospital while also undertaking research in a laboratory. Physician-scientists are incredibly important in providing a link between patients in hospitals and research labs trying to treat the diseases these patients have. Without physician-scientists like Julie, many diseases would not be thoroughly researched, and research in labs may not lead to therapeutic treatments given to patients. Physician-scientists are, therefore, key figures in medical research.

WHAT DOES JULIE FIND MOST REWARDING AND CHALLENGING ABOUT HER ROLE?

Julie loves her dual role as a physician-scientist, though she found it difficult to switch between roles when she began. With more experience, the transition came more naturally, and each role motivates her for the other. "When I am working in the intensive care unit (ICU), I get excited about new clinical observations and questions that arise in the ICU that I can take back to the lab," she says. "And similarly, when I've been working in the lab for a couple of months, it's exciting to take a break from that and care for patients."

WHY IS COLLABORATION IMPORTANT FOR JULIE'S RESEARCH?

Julie is one of three principal investigators leading her lab. This is an uncommon set-up, despite the highly collaborative nature of science. Each principal investigator approaches the problem of treating ARDS in a different way, so Julie's work involves a lot of collaboration, without which a 'bedside to bench to bedside' approach would not work. "It's also incredibly fun to work so closely with my colleagues on a daily basis," says Julie. "I wouldn't want to work any other way!"

WHAT DOES THE FUTURE LOOK LIKE FOR PHYSICIAN-SCIENTISTS?

"Physician-scientists require work environments that value their special contribution to both medicine and science," explains Julie. Unfortunately, governments, hospitals and academic medical centres face financial pressures which make it difficult for them to support the unique position of physician-scientists. "It is important that the current and future generations advocate for support of physician-scientists at all levels, from international to national to local."

EXPLORE A CAREER AS A PHYSICIAN-SCIENTIST

There are several different paths to becoming a physician-scientist. These websites contain a lot of information, including funding opportunities available to support physician-scientists:

www.aamc.org/what-we-do/mission-areas/medical-research/physician-scientist

www.physicianscientists.org

Julie's lab, The Laboratory for Science and Translation in Critical Illness (**www.lstci.org**), hosts summer students through programmes run by her institution for high school and undergraduate students.

Talk to a physician-scientist to see what their job is like. Most work at large academic medical centres such as university hospitals. Don't be afraid to email and ask to meet them! You can contact Julie and her team through their website:
www.lstci.org

PATHWAY FROM SCHOOL TO PHYSICIAN-SCIENTIST

Alongside the traditional pre-medical courses needed to get into medical school in the US, Julie encourages students to take the subjects that interest them. "Everything you need to know to become a physician-scientist is taught during medical school and post-doctoral fellowship training," says Julie, "so pursue whatever interests you as a high school or undergraduate student." Julie majored in biology, but took other classes in English, art and music during her undergraduate degree.

To learn what subjects you should take at school to study medicine, visit the following links:

- US and Canada: **www.medapplications.com/pre-medical-programs**
- UK: **www.ucas.com/explore/subjects/medicine-and-allied-subjects**
- Europe: **www.mastersportal.com/articles/1801/what-are-the-entry-requirements-for-medical-schools-in-europe-and-the-us.html**

JULIE'S TOP TIPS

01 Work and study hard.
02 Keep an open mind.
03 Be curious and ask questions.
04 Take advantage of opportunities.
05 Step out of your comfort zone.

Julie runs her research group with two other principal investigators. Pictured here (left to right) are Dr Ciara Shaver, Dr Julie Bastarache and Dr Lorraine Ware.

Dr Jamie Meegan, a post-doctoral fellow in Julie's lab, works in the cell culture hood growing human lung endothelial cells.

HOW DID JULIE BECOME A PHYSICIAN-SCIENTIST?

WHAT WERE YOUR INTERESTS WHEN YOU WERE YOUNGER?

I always loved science as a kid. I had a chemistry set in the 1980s, when chemistry sets were allowed to contain actual chemicals. I loved going to the science museum and learning about science in any way I could. My favourite show was Mr Wizard's World, a show where Mr Wizard would do science experiments and demonstrations with kids. Although I loved science, I did entertain other careers such as becoming a magician or detective. Interestingly, being a scientist is kind of both.

WHO OR WHAT INSPIRED YOU TO BECOME A PHYSICIAN-SCIENTIST?

I grew up in a very small town and didn't know any physicians, let alone physician-scientists. I didn't even know that physician-scientists existed until I was finished with medical school and was a physician myself. As part of my fellowship training in pulmonary and critical care medicine, I had to do two years of research. I chose to work with Dr Lorraine Ware on a basic science project studying a blood coagulation protein called tissue factor. I completely fell in love with research and decided that I wanted to pursue a career as a physician-scientist.

HOW IMPORTANT HAS MENTORING BEEN IN YOUR CAREER?

Mentorship is probably the most important factor in a physician-scientist's success and happiness, even more important than the actual project. I was fortunate to have an amazing mentor in Dr Lorraine Ware. We had such a great working relationship that as I grew as a scientist, we decided to continue working together as colleagues. Then, my first mentee, Dr Ciara Shaver, made the same decision and stayed on as part of our group. Now, we are three physician-scientists who lead our large lab group.

HOW DO YOU SWITCH OFF FROM YOUR WORK?

I have young children so as soon as I go home, I become 'mom' and enjoy my time with family. When I had children, I made a conscious decision to spend as much time as possible with them when I was home. When I get home, it's family time and I don't do any more work until the kids go to bed. I also enjoy reading lots of non-fiction and jogging when I have time.

WHAT ARE YOUR PROUDEST CAREER ACHIEVEMENTS SO FAR?

Being a mentor is so rewarding. It is amazing to see my mentees succeed. I am also proud of the incredible group of students, technicians, research nurses and trainees in our lab. We have an amazing group and work hard to foster an inclusive, supportive environment in which people can thrive.