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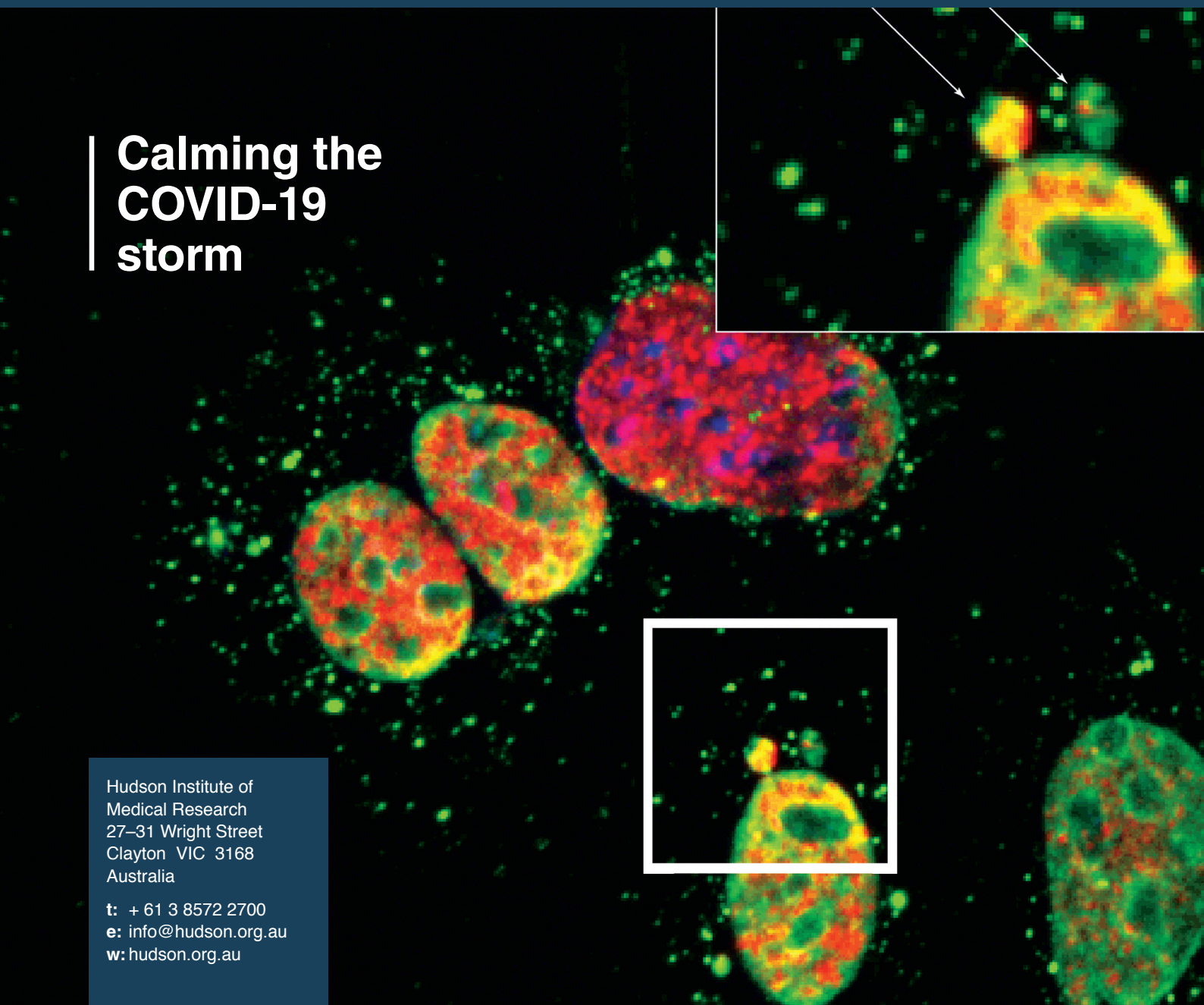
HUDSON NEWS

Calming the COVID-19 storm



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Director's message

Professor Elizabeth Hartland

Welcome to *Hudson News* winter 2020.

How life has changed in the six months since I last wrote. As the COVID-19 crisis unfolds before our eyes, it's having a devastating toll across the globe, not only in human health but also in social connection and economic loss. In doing so, the COVID-19 pandemic makes a case for the critical importance of medical research and scientific discovery—like never before. Research discovery saves and transforms lives, and humanity depends upon it.

I am proud to say that Hudson Institute is at the forefront of new preliminary treatments for COVID-19. Several of our research teams are working on different approaches to curb the hyper-acute inflammation that results from severe SARS CoV-2 infection.

In susceptible people, the inflammatory response during COVID-19 goes beyond what is helpful for the immune system to clear the virus and instead starts to cause widespread tissue damage in the lung, leading to acute respiratory distress. Our scientists are finding and testing new ways to dampen this inflammation to preserve lung function, stimulate immunity and keep people safe from the life-threatening consequences of SARS CoV-2 infection. You can read about this work on pages 3 and 4.

Because SARS CoV-2 is a new virus, there are still many things we don't understand; for example, why adults and children are affected so differently. We are part of a new clinical trial with Monash Health that will examine SARS CoV-2 infection in adults and children to compare those who have mild disease and recover, with those who suffer severe disease requiring intensive care. You can read about this trial on these pages.

We have been able to help our on-site partner, Monash Health, in other practical ways by offering laboratory support staff, personal protective equipment, diagnostic materials and producing our own hand sanitiser to back up domestic supply in the hospital during this crisis. Our gratitude and support go to all those at the front line of healthcare who are working long hours, often at risk to themselves, and to the scientists in our Institute and around the world working to rapidly advance COVID-19 research.

While the COVID-19 pandemic presents a challenging and uncertain time, we remain positive that the work of our dedicated scientists will improve the lives and health of many in our community. Despite the difficulty of having to slow the pace of some of our research programs due to COVID-19 restrictions, we continue to lead groundbreaking research on the gut microbiome, childhood brain cancer and pelvic organ prolapse. Once again, I am incredibly proud of the achievements of our researchers and I hope you enjoy reading about them here, in *Hudson News*.

Hudson Institute is inspired by the power of philanthropy. Our work would not be possible without your support, and any gift you can manage is greatly appreciated.

Stay safe and well this winter.

Professor Elizabeth Hartland
Director and CEO

Calming the COVID-19 storm

Our scientific teams with expertise in inflammation, infection and immunity hold vital clues to help tackle deadly virus outbreaks—like COVID-19.

Inflammation is a normal, protective reaction to infection—and a critical first step in activating the body's full immune response. However, if uncontrolled, inflammation can lead to a range of debilitating and life-threatening conditions—acute respiratory syndromes, sepsis, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus, pneumonia, endometriosis, infertility and even cancer.

The life-threatening acute respiratory distress syndrome (ARDS) in severe COVID-19 cases results from hyper-inflammation, similar to that seen during other SARS, MERS and avian influenza outbreaks. While most infections can be mild and cleared quickly, this is not true of all cases. The effect on our aged and immune-compromised communities has been devastating. Restricting this inflammation could help save lives before antiviral therapies and vaccines are developed and ready.

Several research teams at Hudson Institute are working on different approaches to curb this hyper-inflammation. In addition, we are investigating why some patients are affected more severely by COVID-19 than others—including the differences seen in adults and children.

When it comes to responding to a new infectious disease, there are many different pieces of the puzzle. In this issue, we look at some of the innovative approaches underway at Hudson Institute.

Cover image – see page 5

COVID-19 facts

- The coronavirus pandemic will affect millions globally
- The life-threatening acute respiratory distress syndrome (ARDS) in severe COVID-19 cases results from hyper-inflammation
- The infection is most severe in the aged and immune-compromised
- The SARS CoV-2 virus appears to have originated in bats and passed to humans via an intermediary mammal
- COVID-19 is the most severe global pandemic since 'Spanish' influenza in 1918–1919, which killed between 50-100 million people and infected about a third of the world's population.

Using our immune system to fight COVID-19

Professor Paul Hertzog, Centre for Innate Immunity and Infectious Diseases

There is something unusual about the initial—or innate—immune response to COVID-19 compared to usual influenza patterns.

The disease severity is surprisingly low in children, but high in older people. Our innate immune response provides early antiviral protection and shapes the immunity required later for vaccine responses. But, if uncontrolled, the resulting hyper-acute inflammation from excess cytokines can lead to potentially lethal ARDS.

A Hudson Institute and Monash Health collaboration between Professor Paul Hertzog, Dr Sam Forster, Professor Phil Bardin, Professor Marcel Nold and Professor Jim Buttery will study the innate immune response of COVID-19-infected patients admitted to Monash Health wards, comparing those who have mild disease and recover, with those who suffer severe disease requiring intensive care. The study will compare disease in adults and children.

This collaboration demonstrates the benefits of the Institute's location onsite at Melbourne's largest healthcare network, Monash Health—enabling this exciting translational project to occur.

How we are tackling acute inflammation

- Does the antiviral interferon response (inflammatory signalling proteins) align with disease severity?
- Which inflammatory cytokines influence development of severe lung disease?
- Does the immune cell response dictate protection, or drive long-term immunity?
- How does the lung microbiome influence the innate immune response including inflammation?

Why is research into the innate immune response needed?

"We don't understand why some people have mild disease and recover, while others develop life-threatening illness," Prof Paul Hertzog said. "This includes the apparent 'resistance' of young people and sensitivity of older patients." This study aims to study everything from patient genetics, to the nature of their immune cells and the molecules they produce.

Understanding early immune responses to COVID-19 will help scientists design vaccines to optimise successful protection.

Prof Hertzog said the response to the COVID-19 pandemic highlights the global scientific community's ability to work at pace, thanks to the latest cutting-edge technology and highly skilled scientists. "We have seen remarkable advances in the ability of the international scientific community to respond to a crisis such as this pandemic. The virus was isolated and its whole genome sequenced in three days, enabling tests to be available quickly, and vaccine projects to begin at an unprecedented pace," he said. "Nevertheless, a vaccine would take at least 12 to 18 months to develop."

In the interim, he said there was much more work to be done around the potential to harness innate immunity to fight pandemic and/or drug-resistant infections or respond to health issues by developing better immune biomarkers for disease diagnosis and surveillance, or immunotherapeutics and vaccines for treatment and prevention. The benefit of targeting the innate immune response is the existence of common elements regardless of the infection—COVID, SARS, EBOLA, and antibiotic-resistant bacteria. This complements approaches that do target specific infections, such as antiviral drugs, vaccines and antibiotics.

Professor Paul Hertzog
Centre Head, Centre for Innate Immunity and Infectious Diseases

Collaborators

Dr Sam Forster, Research Group Head, Microbiota and Systems Biology

Professor Phil Bardin, Research Group Head, Respiratory and Lung; Head of Unit, Respiratory and Sleep, Monash Health

Professor Marcel Nold, Research Group Head, Interventional Immunology in Early Life Diseases; paediatrician, Monash Health

Professor Jim Buttery, Head of Unit, Infection and Immunity, Monash Children's Hospital

Funders

This project requires funding for analysis.

Inflammation and infectious diseases

Dr Michelle Tate and Associate Professor Ashley Mansell

Severe COVID-19 infection presents as excessive lung inflammation, involving the build-up of cells and fluid in the lungs. This phenomenon, known as ARDS, restricts breathing and causes damage to the lungs. Severely affected patients will need ventilator assistance in intensive care.

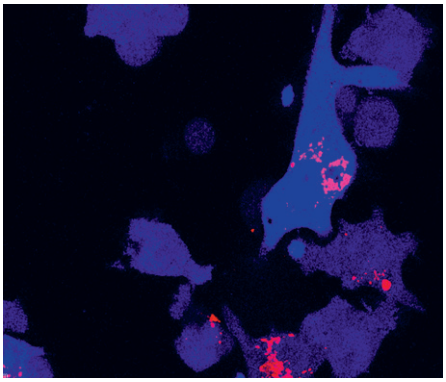
COVID-19 has similar characteristics to severe Influenza A virus (IAV) infections, including the damaging lung inflammation that causes ARDS. Associate Professor Ashley Mansell and Dr Michelle Tate are collectively using their knowledge of severe inflammation from IAV studies to repurpose and develop potential drugs to treat COVID-19. The team has been sought out by international biotech companies due to their specialist expertise.

How we are tackling acute inflammation

- Identifying the molecular mechanisms of SARS CoV-2 induced inflammation
- Examining how COVID-19 results in severe lung inflammation
- Developing and testing new, and repurposed, anti-inflammatory compounds to treat ARDS in COVID-19.

Why is research into inflammation caused by infectious diseases needed?

"At the moment there are no effective treatments to address the devastating effect of inflammation caused by COVID-19," A/Prof Mansell said. "There is a desperate worldwide need to identify and develop new therapies as quickly as possible."



COVID-19 has similar characteristics to Influenza A virus (IAV), including damaging lung inflammation. Here macrophages engulf an IAV peptide that induces inflammation. Activated cells are identified in bright blue.

Dr Michelle Tate added, "Inflammation is involved in nearly every disease known to humankind and yet we understand very little of how, why and where this occurs and what causes it. If we understand the how and why, we can try and target it to reduce disease."

A/Prof Ashley Mansell
Research Group Head, Pattern Recognition Receptors and Inflammation

Dr Michelle Tate
Research Group Head, Viral Immunity and Immunopathology

Funders

NHMRC, commercial partners

Further funding is needed for this team to pursue research into repurposing existing drugs and for the methods of delivery to patients, including inhalers and nebulisers.

Our experts say

COVID-19 may not be our biggest worry. There's still the threat of an avian influenza virus emerging, which may make COVID-19 look like a bad cough. The current pandemic highlights several concerning facts

- The world is poorly prepared for new and sudden emerging infectious diseases.
- While vaccines are highly effective, the timeframe to develop, test, make and distribute a new vaccine for an emerging disease like COVID-19 is at least 12-18 months.
- The world currently lacks approved and effective anti-inflammatory drugs to treat emerging inflammatory infectious diseases.
- It is impossible to contain an infectious disease in a global community without strict quarantine measures that severely damage the economy. We have to be prepared with strategies and treatments when pandemics arise. A range of measures is needed to tackle a new virus on the scale of COVID-19 and 'buy' time until a vaccine is ready.

Hyper-acute inflammation in COVID-19

Dr Michael Gantier

Sepsis is a hyper-acute inflammatory response leading to life-threatening organ dysfunction.

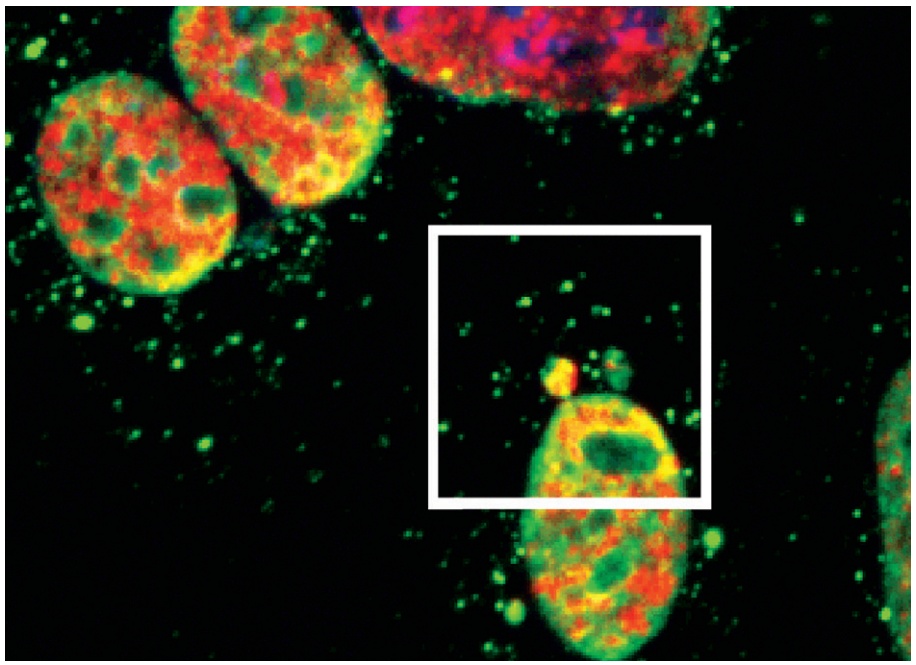
Sepsis is usually caused by bacterial infections; however, the COVID-19 pandemic illustrates that hyper-acute inflammation can also be part of viral infections. Many critical COVID-19 patients develop dangerous levels of hyper-acute inflammation, and this is associated with a high death rate.

The Nucleic Acids and Innate Immunity research group, headed by Dr Michael Gantier, is looking for treatments to help prevent chronic and hyper-acute inflammation.

Nucleic acids are the root cause of toxic inflammation in chronic diseases like lupus, or acute sepsis. This team is working with potential drugs targeting inflammation driven by nucleic acids, by validating the anti-inflammatory properties of these drugs in preclinical models of sepsis and chronic inflammation.

How we are tackling acute inflammation

- Selection of molecules that can be quickly repurposed as anti-inflammatory drugs to prevent chronic inflammation and sepsis
- Development of new treatments that build on 'good' inflammation to help the body's immune system successfully fight pathogens and cancer
- Understanding how chronic inflammation driven by nucleic acids controls cancer development.



The nuclei of mouse fibroblasts treated with a low dose of a chemotherapy drug for 2 days. The vesicles contain damaged DNA (revealed by the green and red overlay).

Why do we need to research life-threatening inflammation?

"It is clear that the world is not prepared to deal with the number of ARDS patients generated by COVID-19," Dr Gantier said.

The body's immune response to some infections can be toxic to patients, damaging major organs. This triggers a chain of responses that can ultimately result in organ failure and death.

"In critical COVID-19 patients, the progression from ARDS to death directly relates to out-of-control inflammation from damaged tissues," Dr Gantier said. "This progression is slow (over a week), allowing a window of opportunity to prevent the inflammatory storm and protect these patients. This is a primary focus for us."

Dr Michael Gantier
Research Group Head, Nucleic Acids and Innate Immunity

Funders

Noxopharm

Further funding is needed to pursue research into validating the drugs identified by this lab, to treat diseases driven by chronic and acute inflammation.

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Professor Paul Hertzog, Professor Elizabeth Hartland and Dr Sam Forster

Gut feeling leads to ground-breaking microbiome research

World-leading experts are uniting to investigate the interaction of the innate immune system with the microbiome and pathogens.

New and improved treatments for many serious conditions from inflammatory bowel disease (IBD) to chronic infections could be discovered thanks to a prestigious five-year NHMRC Synergy Grant, awarded to Hudson Institute scientists Professor Paul Hertzog, Professor Elizabeth Hartland and Dr Sam Forster, in collaboration with University of Melbourne's Professor Christine Wells.

In an era when antibiotic resistance threatens to limit treatments for bacterial infections, this leading research will develop alternatives, such as new ways of manipulating our immune systems to fight infections and distinguishing between 'good' bacteria and disease-causing 'bad' ones.

The pioneering project will explore new medical frontiers to probe how our innate immune system distinguishes 'friend from foe', how it interacts with resident microbes differently from pathogens, how these interactions control the immune system, and how the immune system shapes the microbiome—all the microbes, including bacteria, fungi and viruses that live on and inside our bodies.

This will improve our understanding of why an illness develops and how best to treat it.

The multidisciplinary team will use cutting-edge techniques and develop new ones that integrate genome sequencing, sophisticated computer analysis, microchip and microfluidics technology and a unique library of 'friendly' bacteria.

"We'll be generating enough information for thousands of projects," says Prof Hertzog. "Even though the amount of data to be generated is enormous, we now have computer systems that can actually make sense of it. It's amazing!"

The research will facilitate the development of new treatments across a range of diseases, including infections, inflammatory disease and cancers of many organ systems, including the gastrointestinal, reproductive, urinary tracts and lung.

The gut microbiome and IBD

In a second, separate study underway, our researchers are collaborating to identify common protective and inflammation-causing gut bacteria in children diagnosed with IBD, and to identify treatments that target those bacteria.

Up to 10,000 children in Australia suffer from IBD—an incurable lifelong disease that causes inflammation in the colon and rectum. Symptoms can be so severe that some people with the disease need to be hospitalised or undergo surgery.

The disease is currently managed using drugs that suppress the immune system—which become less effective over time and can have significant side effects, such as an increased risk of colorectal cancer and lymphoma.

Dr Sam Forster, Dr Jaclyn Pearson and Dr Edward Giles hope their research will lead to more targeted treatments, including faecal transplants, probiotics or immunomodulators.

Researcher spotlight: Dr Shayanti Mukherjee

Leading women's health scientist Dr Shayanti Mukherjee is developing new nanomaterials to help stem cell-based treatments improve the lives of millions of women worldwide with pelvic organ prolapse (POP).

What motivates you to come to work every day?

I was appalled to discover no safe and effective treatment for pelvic organ prolapse (POP) exists and that the condition worsens with age. I thought my background in materials engineering could make a real difference to women.

I work on developing new nanomeshes to treat POP. These are made with naturally therapeutic cells from a woman's womb. This incredible process protects women and provides a solution by avoiding harmful foreign body immune responses—and detrimental side effects—after surgery.

What is your biggest career highlight?

Being awarded my SIEF (Science and Industry Endowment Fund) Fellowship to support my stem cell research. I was new to Australia when I initiated this project idea with two of my now colleagues, whom I met at a conference. To have our plan come to fruition and be awarded such a competitive Fellowship was a game changer in my career.

What do you enjoy doing in your spare time?

Cooking dinner for my family and friends is one of my favourite things. In the past, I have been a Bollywood dance instructor. However, since the birth of my daughter last year, singing rhymes and playing in the park are my most favourite things to do. I also enjoy travelling and snorkelling in places with amazing sea life. I can't wait to be able to do this again once the COVID-19 outbreak is over!

At Hudson Institute the diverse research areas, support for early career researchers, equity, diversity and flexible work environment have made all the difference to my research and home life.

What is POP?

- POP affects one in four women worldwide, and up to 50 per cent of mothers over 50
- POP gradually develops due to childbirth when the muscles, tissues and ligaments supporting the pelvic organs (the uterus, bladder and bowel) are weakened or damaged.

Why the microbiome?

The human microbiome holds the key to how many ailments develop and play out in our body.

Humans are mostly made up of microbes—more than 100 trillion. Those in the gut, particularly in the large intestine, play an important part in health and disease.

Imbalances in our gut microbiome are known to contribute to complex conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome, allergies and obesity.

"Through our work, we have been at the forefront of understanding these complex communities. At Hudson Institute, we now have one of the most diverse collections of human isolated bacteria in the world," says Dr Forster.

"Ultimately, through this work we will find new treatments that will reduce suffering, minimise hospital visits and reduce the need for surgery, optimising growth and psychosocial outcomes for young people," said Dr Giles.

Shedding light on childhood brain cancer

Dr Dan Gough

Why is the most common form of childhood brain tumour seen more in boys than girls? In discovering the answer, Dr Dan Gough has identified an opportunity for less aggressive treatment.

What did you discover?

We found that a protein called STAT3 plays a key role in the male bias, seen in a type of childhood brain cancer, medulloblastoma. Medulloblastoma affects the cerebellum—the area at the back and bottom of the brain. It develops more commonly in boys than girls, but this is poorly understood.

When we blocked STAT3 in our preclinical study, males—but not females—were completely protected from developing a tumour.

We also discovered that patients with low STAT3 expression had a better survival rate versus those with high STAT3 expression.

This means STAT3 could be a biomarker for predicting patients with a good prognosis, who may benefit from less aggressive treatment. Directly inhibiting STAT3 would also be an effective new targeted therapy for boys with medulloblastoma.

How is medulloblastoma currently treated?

Surgery, radiotherapy and chemotherapy—but this has severe neurological, cognitive and developmental side effects on a young child's growing brain, with more than 90 per cent of patients needing long-term special education services.

What are the next steps to progress your research?

Our data suggests that clinical trials of STAT3-targeted treatment in children with medulloblastoma are now needed. These trials should also test the effectiveness of STAT3 as a biomarker to enable some patients to receive less aggressive treatment.

Future studies should also investigate the role of STAT3 in different subgroups of medulloblastoma.

Collaborators

Cancer Care Manitoba, German Cancer Research Center

Dr Gough is also striving to develop new therapies for small cell lung cancer and prevent spread of the disease—for which he was awarded a four-year Research Fellowship from the Victorian Cancer Agency.

'Thank you for your kind support'

Professor Elizabeth Hartland
Director and CEO, Hudson Institute

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