HUDSON
INSTITUTE OF MEDICAL RESEARCH

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HUDSON NEWS

Cerebral palsy – improving outcomes at every stage in life

Melanie and Arlo's story

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Director's message

Professor Elizabeth Hartland

From discovering a new lung cancer treatment, to empowering young women to consider a career in science – the last six months have seen a number of wonderful and diverse achievements at Hudson Institute that I'm delighted to share with you.

Our strength at Hudson Institute lies in the breadth of our researchers' skillsets and our ability to approach a complicated issue from many angles. This issue's feature on cerebral palsy highlights the multifaceted approach we take when addressing complex diseases. Our scientists look at every stage of life for a person with cerebral palsy, considering how treatments and therapies can improve wellbeing and physical outcomes.

Lung adenocarcinoma is the most common form of lung cancer and the leading cause of cancer death worldwide. It is, therefore, no understatement to say the discovery by our researchers of a drug that can suppress tumours in lung adenocarcinoma is a medical breakthrough.

This very aggressive cancer has a survival rate of less than five years. The rapid tumour growth associated with this cancer renders radiation therapy ineffective and rules out surgery due to the size of tumours. The discovery by PhD student Mohamed Saad and Research Group Head Professor Brendan Jenkins of a drug that slows tumour growth has the potential to put these treatment options back on the table.

Gender equity is an important focus of Hudson Institute, not only bringing our own postdoctoral scientists through to the next level but also giving opportunities to young women in our community who are interested in pursuing a career in science.

In July we opened our doors to nine young women from secondary colleges in Melbourne's southeast to participate in a two-week immersive program, aimed at increasing the number of women in science. We need to engage with young women and get them enthusiastic about science early on. Through the program we are showing young women the types of jobs in a science career, and how they can make a difference to human health and our community.

We would like to see this successful inaugural program become annual, because it's only by investing early on that we can grow our female leaders of tomorrow.

I'm exceedingly proud of the work done by our researchers, and in this edition you will be introduced to one of our brilliant and upcoming stars, Dr Kate Lawlor. Dr Lawlor's research focuses on understanding and controlling cell death pathways. By controlling cell death, we can find therapeutic targets for a wide variety of diseases, ranging from bacterial and viral diseases, to chronic diseases like type 2 diabetes and arthritis.

You will undoubtedly hear this talented researcher's name in the future, as her work goes on to produce treatments that will benefit the lives of countless people.

Thank you once again to our supporters and community. Without you, our research wouldn't be possible. I hope reading about our research allows you to see what an impact your continued support has in creating profoundly positive real-life impacts across a broad spectrum of health issues.

We hope you will continue to support our research so that in turn we can continue to progress projects that will result in new discoveries and new life-saving treatments. Have a safe and relaxing festive season, and I look forward to sharing more research updates with you in 2020.

Professor Elizabeth Hartland
Director and CEO

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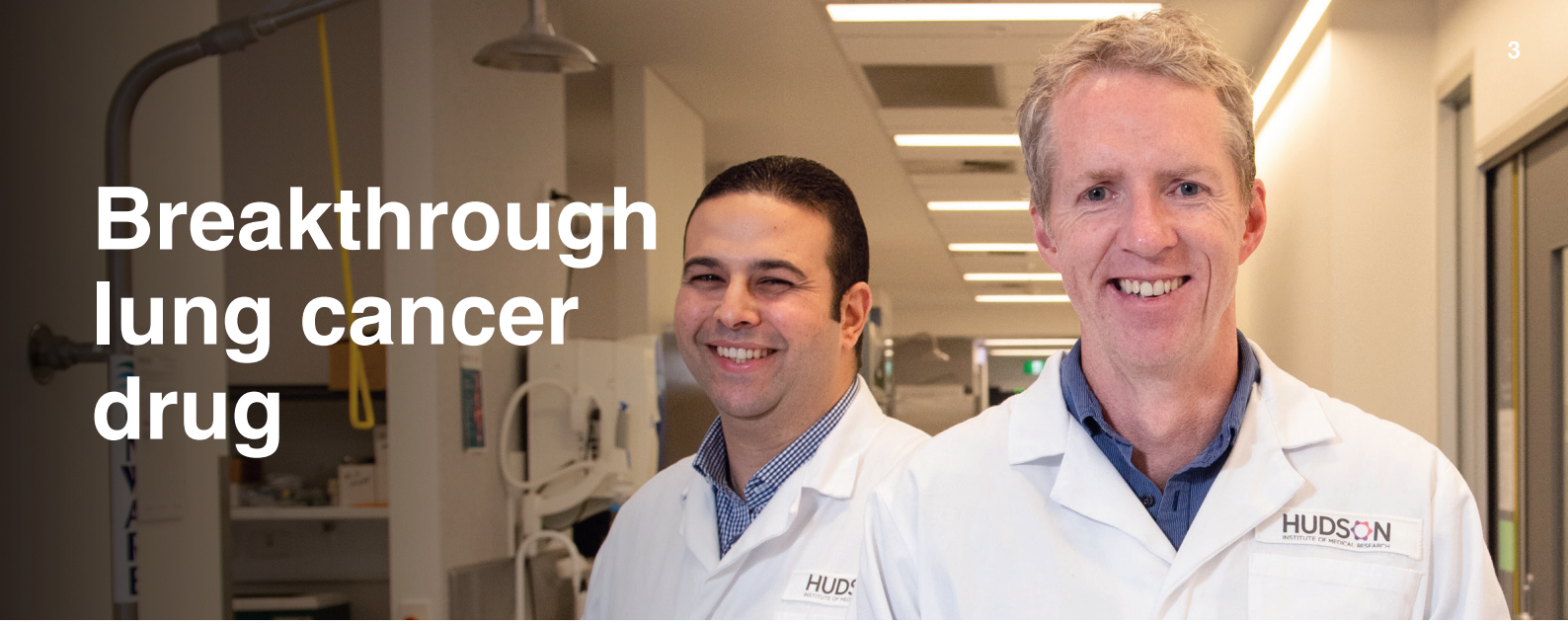
Breakthrough lung cancer drug



PhD student Mohamed Saad and Professor Brendan Jenkins

A drug that will supress tumour growth in the most common type of lung cancer may open up life-saving treatment options for the 1.8 million people worldwide diagnosed with the cancer each year.

Lung adenocarcinoma is the most common form of lung cancer and the leading cause of cancer death worldwide. It is associated with a high risk of tumour re-occurrence following surgery and treatments, such as chemotherapy, and has poor overall survival rates. Many patients are given five years to live, or less, when diagnosed.

PhD student Mohamed Saad and Research Group Head Professor Brendan Jenkins have made an important discovery, identifying a drug that slows down tumour growth by targeting an enzyme that makes cancer cells proliferate more rapidly.

Opening up new treatment options

Prof Jenkins said, “We have found a drug that rapidly slows tumour growth, which brings a lot more treatment options to the table. If we can slow down growth, we then open up the possibility that the size of tumours can reduce to a point where surgery could be more effective.

“In lung adenocarcinoma, the diagnosis is often late, progression is rapid, and life-expectancy outlook is very dire. Being able to drastically supress tumour growth gives a lot of hope,” he said.

“While chemotherapy, as well as radiation therapy, reduces the size of tumours in a number of different cancers, when people are diagnosed with lung adenocarcinoma, tumour growth is too advanced for these treatments to be much help.

“And while surgery may be an option for many cancers, it’s often not possible for lung adenocarcinoma as the size of the tumour is too large and has spread to other parts of the body. The implications for this drug, used in combination with other therapies, is very promising.”

Next steps

A Hudson Institute-led team is exploring the development of the drug in collaboration with colleagues at the Weizmann Institute of Science in Israel and support from Kiel University in Germany. Together they are looking to improve the drug that they have previously trialled to maximise its activity and stability, and find an easy way to administer it to patients.

Once the drug is ready for market, Prof Jenkins hopes the next stage could be a phase I trial, where the drug is trialled with chemotherapy to assess the extent of impact it could have for patients.

Collaborators: Garvan Institute, Kiel University (Germany), Monash University, Nagoya University (Japan), RMIT University, Weizmann Institute of Science (Israel).

Lung adenocarcinoma facts

Each year, 1.8 million people worldwide are diagnosed with lung cancer. About 85 per cent of the people diagnosed have non-small lung cancer and about 40 per cent of these will have lung adenocarcinoma.

How does the drug work?

The KRAS gene is a common cause of lung adenocarcinoma. When the gene mutates unexpectedly it can lead to the development and spread of cancer cells.

For many years, researchers have unsuccessfully tried to find a way to inhibit the KRAS gene to stop it creating cancer cells. Mohamed Saad and Prof Jenkins took a different approach, and decided not to target KRAS directly. Instead they looked for different interactions with the gene they could control.

Mohamed Saad said, “From our research we have found that a particular enzyme, ADAM17, when activated, amplifies the effect of the KRAS gene, causing it to also have greater activity and make more cancer cells.

“Based on this finding, we found a drug that reduced the activity of the enzyme ADAM17. This meant the enzyme was no longer putting KRAS in overdrive and telling cancer cells to grow faster than normal. By slowing down KRAS we were able to rapidly reduce tumour growth.”

“The drug needs some development before it is ready for patients, and we are working on this now with colleagues in Israel and Germany,” Mr Saad said.

Cerebral palsy – improving outcomes at every stage in life

Research into cerebral palsy at Hudson Institute is multifaceted, recognising that there are a number of points in an individual's life where intervention and treatment can significantly improve wellbeing and physical outcomes.

Pre-birth – preventing early brain injury

Strong evidence now suggests that much of the brain injury that underlies cerebral palsy occurs before birth. By identifying how abnormal conditions in the womb impact the developing brain, our researchers are finding ways to prevent cerebral palsy.

A leading cause of brain damage while in the womb is too much inflammation in a baby's blood and brain. Research by Associate Professor Tim Moss and Dr Robert Galinsky and their teams is aimed at identifying how the developing brain is affected by inflammation before birth and shortly after birth. By understanding how inflammation triggers abnormal brain development, they hope to identify therapeutic targets that will reduce the incidence and severity of cerebral palsy.

Dr Galinsky and his team, with collaborators at the University of Auckland in New Zealand, have discovered that blocking key inflammatory proteins that are over-expressed in the circulation system of cerebral palsy patients reduces brain inflammation and promotes healthy brain cell development and function.

Another common cause of cerebral palsy is fetal growth restriction (FGR), a condition where a baby stops growing in the womb and is born very small, usually due to the placenta failing to deliver the oxygen and nutrients required to meet the baby's needs.

Discovering how brain damage develops in growth-restricted infants is a key research area for Associate Professor Suzie Miller and her team. She is working to identify treatments that can be given during pregnancy to prevent injury. She has shown, in one promising study, that brain damage may be prevented if the 'sleep hormone' melatonin is given during pregnancy.

What is cerebral palsy?

Every 15 hours, an infant in Australia is born with a brain injury that underlies cerebral palsy. Most often injury to the brain occurs during pregnancy; however, it may also occur during childbirth or shortly after birth.

Cerebral palsy affects muscle tone, movement and motor skills. It is caused by abnormal development or damage to the parts of the brain that control movement, balance and posture.

Early diagnosis and intervention in children with cerebral palsy is critical for maximising their potential.

L-R: Dr Robert Galinsky, Associate Professor Graeme Polglase, Associate Professor Frances Milat, Associate Professor Tim Moss. Inset: Associate Professor Suzie Miller

Birth – stopping further damage

Prematurity is associated with higher rates of cerebral palsy, with 40 per cent of children with cerebral palsy born prematurely. While being born premature does not always result in cerebral palsy, it is classified as a risk factor because preterm babies encounter a number of stressors that make them vulnerable to brain injury.

The brain is still relatively immature when a baby is born preterm, and the altered environment that occurs with premature birth means the brain is very vulnerable to damage. In addition, the life-saving respiratory support they receive in hospital can be too much for premature newborns' under-developed lungs to cope with. This in turn can also lead to inflammation and injury in the brain.

Associate Professor Graeme Polglase's team are researching methods to support these tiny patients at birth. This includes optimising the timing of clamping and cutting the umbilical cord, finding ways to improve how respiratory support is delivered, and identifying ways to stimulate breathing, thus preventing the need for respiratory support.

In addition, A/Prof Miller's and A/Prof Moss's groups are tackling this issue by looking at novel treatments, such as stem cell therapies, that could be administered soon after birth to reduce brain inflammation and injury. These treatments would be suited to high-risk infants, such as those born extremely preterm or those exposed to inflammation in the womb.

Later in life – maximising potential

Research by Associate Professor Fran Milat and her team indicates that low bone density in adults with cerebral palsy is most likely a result of not building sufficient bone mass during childhood. Puberty is a critical time for building bone in cerebral palsy, as it is with typical adolescents.

This research supports the practice of early intervention in childhood and adolescence to promote better bone health for adults. A focus on intervention would ensure that people with cerebral palsy are able to remain mobile for longer and in turn reduce bone fractures.

A/Prof Milat's team are studying the factors that contribute to low bone density, including a lack of movement, nutritional deficiencies, use of anti-seizure medication and hormonal deficiencies. These findings will help inform clinical care that will allow for a better quality of life.

Maximising the potential of children with cerebral palsy is critical for providing the best quality of life. Intensive therapy programs studied by A/Prof Tim Moss in collaboration with families of children with cerebral palsy aim to allow children living with physical disabilities to thrive and reach once unimaginable levels of mobility and independence.

Read Melanie and Arlo's story on page 7

Cerebral palsy facts

- 1 in 700 babies are diagnosed with cerebral palsy
- 37 000 people are living with cerebral palsy in Australia
- The number of people with cerebral palsy in Australia is expected to increase to 47 601 by 2050

Researcher spotlight: Dr Kate Lawlor

Disease impact I Inflammatory and infectious diseases

Immunology expert Dr Kate Lawlor has spent the past 15 years studying how inflammatory and autoimmune diseases develop. By understanding how these diseases develop she is working on creating new therapeutic treatments that can target both chronic and infectious diseases.

What is your field of research?

Broadly, my research looks at how cell death contributes to infectious and inflammatory diseases. Cells are programmed to die all the time to maintain human health. My research looks at how we can either stop cell death, or cause cell death to treat diseases.

I got into this line of work because I wanted to understand the complex mechanisms that drive diseases. Basically, I like solving puzzles.

My growing research team focuses on translating this knowledge into repurposing anti-cancer drugs and designing new therapies to promote appropriate immune responses to clear infectious pathogens or dampen inflammation.

What research are you working on?

Type 2 diabetes is approaching epidemic levels in Australia, with 1.6 million people estimated to be affected. We already have promising data suggesting that inhibiting cell death could protect patients from the chronic inflammation that drives the development of type 2 diabetes.

My team is also tackling the growing problem of antimicrobial resistance and the emerging threat of superbugs. We are investigating whether we can repurpose or develop highly specific drugs to induce targeted death of infected patient cells, rather than attacking the bug itself.

What is the most exciting thing that's happened in your career?

It often takes years to see fundamental discoveries translated into clinical outcomes for patients, so it is exciting to see my research moving through this process. During my PhD I was looking at new ways to treat rheumatoid arthritis, and discovered that a protein, Granulocyte colony stimulating factor (G-CSF), was critical for disease progression.

Based on the discovery, the biotherapy company CSL has now developed an antibody that inhibits G-CSF's activity. The antibody is now in phase I clinical trials in Melbourne.

This work has fostered my interest in collaborating with companies to expedite new therapies entering the clinic. I find this process very rewarding as I'm passionate about seeing my discoveries turn into treatments that improve people's lives.

How cell death contributes to infectious and chronic diseases

In infectious diseases, such as Legionnaire's disease and gonorrhoea, the bacteria take over cells in the body in order to replicate. In these instances, we want to target infected cells and cause them to die faster and stop the spread of the bacteria. We can use newly developed, highly specific anti-cancer drugs to increase the rate of cell death.

In chronic diseases, such as diabetes or arthritis, too much cell death can cause inflammation. In this scenario, we want to regulate cell death. To do this we work to develop 'small molecule' drugs to limit cell death and inflammation.

Melanie and Arlo's story

Arlo is a bright, beautiful three-and-a-half-year-old boy who delights in musicals, including *Frozen* and *Moana*, and has an intense love of books.

Even though Arlo is non-verbal, when his mother Melanie tries to skip words or passages, he can certainly let her know that he's not impressed.

When Arlo was just six months old, his parents were told he had cerebral palsy. Cerebral palsy is measured on a scale of 1-5, 1 being the mildest form, and 5 being the most severe. As the months rolled on, Melanie and her partner, Rowan, were also told Arlo is a 5, and would be unlikely to ever walk. It was heartbreaking news that no parent ever wants to hear.

While many parents know throughout the pregnancy whether their child is a high risk for brain damage, Melanie's story reveals how cerebral palsy can come with no warning.

Reduced fetal movement

Arlo was four days past his birthing due date when Melanie noticed his movements had lessened, so she and Rowan decided to go to the hospital to make sure nothing was amiss.

"When I arrived at hospital everything looked okay, and I was prepped to be induced the following day. That next morning, just as my waters were about to be broken, Arlo's heart rate suddenly dropped. It virtually disappeared.

"The midwife scrambled about my belly with a stethoscope trying to find it, the emergency button was pushed, doctors flooded the room, and in an instant I was being whisked down a corridor to theatre," Melanie said.

This happens to others, not us

Arlo was born by emergency caesarean section in 10 minutes flat, but during that time his brain was deprived of oxygen, which made him a high risk for cerebral palsy. He was immediately placed on oxygen, and had to be cooled down to stop further brain damage. This meant Melanie and Rowan were not able to hold him for the first 72 hours.

"We were told that there was a chance he may have brain damage, and that the worst-case scenario would be cerebral palsy. However, at this point, we didn't think anything would be wrong.

"You always think, that's the sort of stuff that happens to other people. It doesn't happen to us. For six months we told ourselves everything would be okay, right up until Arlo was diagnosed with cerebral palsy. Quadriplegic cerebral palsy."

It takes a community

Now, Melanie, Rowan and Arlo have a great team of specialists that help Arlo thrive. His team includes two speech pathologists, a physiotherapist, an occupational therapist, a feeding specialist and a neurologist.

After being diagnosed as never able to walk, Arlo is now using a gate trainer to aid him getting about. His desire to play and keep up with his younger sister, Odette, spurs on his determination.

"His sight isn't affected and he isn't intellectually delayed, but he is non-verbal. We were told his brain damage meant he would only be physically affected. But, of course, using your tongue and mouth muscles is movement.

"We communicate with him on an augmentative and alternative communication, or AAC device, which lets the movement of his eyes communicate with us."

While Arlo's dedicated parents and superstar team of specialists are helping him reach his full potential, Melanie hasn't ruled out that medical advances, such as stem cell therapies, may help improve Arlo's quality of life.

"We've kept Arlo's sister Odette's umbilical cord stem cells, just in case."

Helping kids like Arlo

Cerebral palsy is a condition that can arise during pregnancy, during childbirth or shortly after birth.

Our research is working to help kids like Arlo, by providing developing therapies that can be given immediately after birth for babies who have been oxygen deprived and are a high risk for inflammation and brain damage.

Our teams research how early intervention in childhood and adolescence can promote better bone health for adults with cerebral palsy. They are studying factors that contribute to low bone density so their findings will allow for a better quality of life.

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Help us find better outcomes for children with cerebral palsy

One in 700 Australian babies are diagnosed with cerebral palsy. It has no known cause, no known cure – but our researchers are on a mission to change this!

2019 'Hudson Institute Young Women in Science' program attendees with CEO, Prof Elizabeth Hartland

Door to science opened for nine young women

This year as part of a new program, 'Hudson Institute Young Women in Science', the Institute opened its labs to nine young women from secondary colleges in Melbourne's southeast for a two-week immersive science program.

Gender equity is an important focus of Hudson Institute, not only bringing the Institute's own postdoctoral scientists through to the next level but also giving opportunities to young women in the community who are interested in pursuing a career in science.

The program included exploring a scientific research project in the laboratory, seminars, events, exposure to scientific technologies and attending forums to seek career advice from scientists and postgraduate students. To further their exposure to research careers, the young women also joined activities in the fields of embryology, cell therapies, microscopy and clinical trials.

The students were partnered with a female mentor, all volunteers from the Hudson Institute scientists. Over the two weeks, strong relationships were built that will extend to help and advice for the young women beyond the program.

At the close of the experience, the young women were most surprised by the breadth of jobs within science as well as by how interesting and flexible day-to-day lab life is. In addition, they appreciated the support and ongoing connection they will have with their mentors at Hudson Institute.

Several of the young women have already indicated that they would like to return for further work experience with their supervisor.

Based on the success of the inaugural program, Hudson Institute will be working to engage with government and philanthropists to invest in the program's future. By investing early on, we can grow our future female leaders.

Chelsea Campbell (15) from Wellington College spent her two weeks with mentor Dr Te-Sha Tsai, looking at what effects epigenetic changes in women's eggs have on their offspring.

Reflecting on the program, Chelsea said,

"I wasn't really sure about a career in medical research before, but seeing what the work is like and getting to experience it – it's definitely something I would consider."

'Thank you for your kind support'

Professor Elizabeth Hartland
Director and CEO, Hudson Institute