HUDSON
INSTITUTE OF MEDICAL RESEARCH

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HUDSON NEWS

WWI antiseptic in frontline fight against 21st century viral infections

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Director's message

[Professor Bryan Williams]

The popular image of a medical researcher is that of a scientist in a laboratory, peering down a microscope to make discoveries. While laboratory research underpins everything we do at Hudson Institute, these days, this conventional image is only a component of medical research.

Our teams include microbiologists, immunologists and virologists—basic scientists who uncover the body's clues in microscopic detail; endocrinologists and neonatologists, both clinician-scientists who relay vital clinical knowledge to the lab to further improve the lives of patients; and bioinformaticians and medical genomics experts, who analyse and interpret the vast amounts of data generated by the human body (on computers—some rarely set foot inside a lab!).

All are integral to discovery, progressing scientific knowledge and improving healthcare for humankind through medical research.

Translational research leader

As a premier translational research institute, we work closely with our collaborators at Monash Health, Victoria's largest health service, and Monash University, Australia's largest university. Our scientists and students respond in real time to clinical need, relayed by doctors who are at the coalface of patient need.

We are constantly looking to outside of the lab for knowledge, and our collaborations extend to institutions across Australia and abroad, sparking novel ideas and 'unexpected' discoveries.

Professor Paul Hertzog and Dr Niamh Mangan worked with Deakin University scientists to combine our expertise in interferon epsilon and their expertise in HIV, resulting in possible new prevention strategies for HIV. Please take the time to read about this groundbreaking work, which has the potential to help millions of people (page 6).

Strengthened support

Government support remains integral to medical research. The exceptional quality of our work was recognised with the National Health and Medical Research Council (NHMRC)'s recent grants announcement, which provided a much-needed boost to a number of areas of our research.

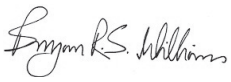
As I write this, our scientists have just concluded an intense three-month period 'at the desk', writing the next round of major grant applications for 2018. In all, they have prepared 61 NHMRC project grant applications. However, in a highly competitive research environment, only around 15 per cent of these grant applications Australia-wide are expected to receive funding.

Thank you to our supporters

For this reason, we are indebted to our supportive community and philanthropists who are passionate about ensuring that our research reaches and benefits those who need it most. We are especially grateful to

- A private donor, for establishing the the Kahli Sargent research studentship grant into cerebral palsy through a generous donation. This gift will progress vital research to prevent brain damage in preterm babies and newborns. The grant was established in memory of the donor's wonderful granddaughter, Kahli Sargent
- Gandel Philanthropy, which has established Gandel Genomics health research program within our Medical Genomics platform. The growth of 'big data' in medical research means genomics technology is increasingly crucial to our work. This new program will enable us to more readily take research discoveries into healthcare
- The Fielding Foundation, for its support of our best and brightest researchers through the Fielding Fellowship and Fielding Innovation Award. We are seeing the outstanding outcomes of this investment in science. Research by inaugural Innovation Award recipient, Associate Professor Marcel Nold, has led to a collaboration with Switzerland-based healthcare company, Roche, to develop next-generation treatments for autoimmune diseases.

I trust that you will enjoy reading about our exciting research in this latest edition of Hudson News, and I look forward to sharing more of our successes during 2017.



Best wishes,
Professor Bryan Williams

IN THIS ISSUE

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WWI antiseptic in frontline fight against 21st century viral infections

[Discovery impact: Common cold, viral infection, antibiotic resistance **]**

Nurses at the New Zealand Stationary Hospital, Wisques, France, 1918 - Archives New Zealand/Flickr

Our researchers have shown that a century-old topical antiseptic that was used to treat wounds and 'sleeping sickness' in soldiers in WWI activates the immune system to protect against viral infection, and could even be tested in the frontline fight against antibiotic resistance.

A study led by Dr Michael Gantier and Dr Geneviève Pépin in the Nucleic Acids and Innate Immunity group has shown that the antiseptic called acriflavine, made from coal tar derivative, protects against the common cold.

The findings of the study have been published in the prestigious journal *Nucleic Acids Research*.

The team believes the way acriflavine activates the immune system could also offer a useful tool in the fight against viral pandemics and potentially superbug resistance.

In the study, the team showed that pretreating human lung cells with acriflavine protected the cells against rhinovirus infection (the common cold), by triggering an antiviral immune response.

Whole picture revealed

Dr Gantier, Head of the research group in the Centre for Innate Immunity and Infectious Diseases, says acriflavine was used to treat everything from gonorrhoea to urinary infections prior to WWII, but a whole picture of its mechanism of action has evaded scientists—until now.

"Acriflavine was heavily used during WWI as a topical antiseptic to treat wounds. Early scientific literature notes its antibacterial qualities in test tubes, but its very effective action on the skin has never been fully defined," Dr Gantier said.

"We have shown, for the first time, that acriflavine binding to cellular DNA could activate the host immune system, unleashing a powerful immune response on a potentially broad range of viruses.

"The effect is two-fold—acriflavine directly affects the bacteria, and then you get the activation of the immune system through the 'STING' pathway, which helps to clear the infection," he said.

Acriflavine (also known as trypaflavine) was first identified as an antiseptic by German scientists in 1912. It was used by soldiers in WWI to treat wounds and kill parasites that cause sleeping sickness. Australia's volunteer nurses in WWII also had acriflavine in their kits.

War on superbugs

Dr Pépin, first author on the paper, says acriflavine could be used during a viral outbreak to trigger a baseline immune response to an infection, such as SARS or influenza, in at-risk groups and could one day potentially offer a safeguard against drug resistance.

"Acriflavine was used in the first half of the 20th century as a topical antibacterial, before being supplanted by penicillin. Now, antibiotic-resistant superbugs are a growing threat to human health," Dr Pépin said.

"Our study indicates that acriflavine stimulates the host immune system, rather than simply killing bacteria, suggesting it wouldn't be as likely to drive mutations in bacteria—providing a safeguard against the growing problems of antimicrobial resistance and a potential alternative to current antibacterial drugs," she said.

Next, the team will use preclinical models to test how well acriflavine mobilises the immune system in more virulent strains of infection.

Dr Gantier says acriflavine, a drug that has largely been out of use for the last 50 years, is showing strong potential against viral and bacterial infections and their newest challenges in the 21st century.

ACRIFLAVINE FACTS

Acriflavine (also known as trypaflavine) was first identified as an antiseptic by German scientists in **1912**. It was used by soldiers during WWI to treat wounds and kill the parasites that caused 'sleeping sickness'. Australia's volunteer nurses in WWII also carried acriflavine in their kits.

Front page L-R: Dr Jonathan Ferrand, Miss Charlotte Nejad, Dr Geneviève Pépin, Dr Michael Gantier, Professor Philip Bardin, Dr Belinda Thomas

Acriflavine bottle from the collection of Geoffrey Kay Museum of Anaesthetic History (Australian and New Zealand College of Aneasthetists).

Hope for babies starved of oxygen at birth

[Discovery impact: Cerebral palsy]

Kahli Sargent loved going fast in a car or boat, everyone knew she loved it—which is surprising, because her mother was told by doctors at birth that she would never communicate.

"Kahli's laughter was unreal, she might not have been able to talk, but she certainly could communicate with everyone around her. She was a strong and courageous girl," said her mother Kendra.

Kahli was starved of vital oxygen at birth, resulting in massive brain damage and cerebral palsy.

Her love of life and everything fast became even clearer after the family moved to Echuca when she was seven, to escape life-threatening infections from colds and flus brought on by Melbourne's winters.

"Kahli loved the warmth and the freedom of not wearing layers of clothing in her wheelchair, and, of course, speed. We could drive freely down the highways in Echuca and go out on a speed boat on the Murray River—the faster we went, the more she giggled.

"Even at home, the faster her brother pushed her in the wheelchair, the more she laughed," said Kendra.

"They say a mother instinctively knows what her child needs, but it was more than that. Kahli communicated with everyone—her teachers, other kids and neighbours. People would always look to me for help when they first met Kahli, but it never took long before they were communicating directly with her," she said.

Sadly, Kahli passed away in 2012, aged just 17.

"If Kahli could have been given a treatment in those early hours, her condition and quality of life could have been better. Those early hours are crucial, anything that can be done to prevent further damage matters for the child and the family," Kendra said.

Kahli Sargent research studentship grant

To improve outcomes for other young people with cerebral palsy and their families, and in memory of Kahli, her grandparents have established the Kahli Sargent research studentship grant at Hudson Institute.

The studentship will support a PhD student to undertake medical research that will assist in understanding the brain injury that underlies cerebral palsy, and in finding new therapies that could decrease the severity, or even cure cerebral palsy.

"When Kahli was born, we wondered about medical research and if it could help her," said her grandmother.

"As she grew and things got worse for her, we often thought that if there had been something better for her in the early days it would have helped. Kahli didn't get that chance, but if there's hope for other children and families to have a better future, we want that," she said.

"This was an inheritance from my mother, Kahli's great-grandmother. She made and donated many patchwork quilts to the Royal Children's Hospital and Echuca Regional Hospital, so this would make her happy."

Promising treatment

Madison Paton, a PhD student at The Ritchie Centre, is the recipient of the the Kahli Sargent research studentship grant.

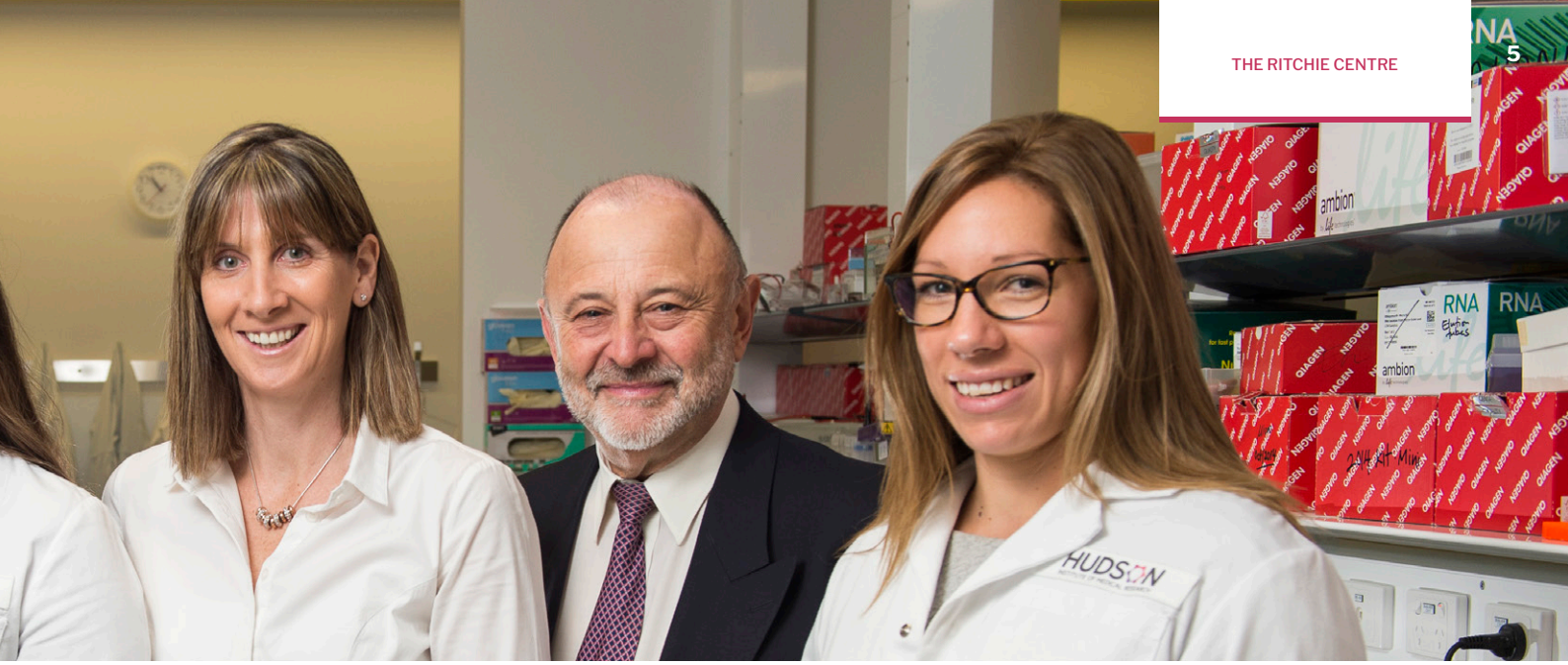
Madison's work is focused on umbilical cord blood stem cells, which are providing a promising treatment for preterm brain injury caused by infection during pregnancy, referred to as chorioamnionitis. Infection during pregnancy is a large contributor to the brain injury that leads to cerebral palsy, particularly in babies born preterm.

"We are extremely hopeful that umbilical cord blood stem cells could be a treatment option, not only for preterm babies exposed to infection, but also for those starved of oxygen at birth, like Kahli," said Madison.

"There is a critical need to develop a treatment for babies exposed to infection during pregnancy and to protect their brain soon after birth. All research to date indicates that umbilical cord blood stem cells may protect the immature brain from the long-term effects of exposure to infection during critical periods of development. If we can show that these cells are beneficial in preterm babies with brain injury, we can start to understand how stem cells can be used to prevent cerebral palsy.

"My PhD studies will establish how beneficial umbilical cord blood stem cells are at reducing the progression of preterm brain injury and potentially whether, one day, cerebral palsy could be cured or prevented with a cell treatment."

Madison is completing her PhD under the supervision of a team of experts at The Ritchie Centre, including Associate Professor Suzanne Miller, Professor Graham Jenkin, Dr Courtney McDonald, Dr Beth Allison and Associate Professor Michael Fahey, who leads the Paediatric Neurology clinic at Monash Health.



L-R: Dr Beth Allison, Professor Michael Fahey, Miss Madison Paton, Associate Professor Suzie Miller, Professor Graham Jenkin, Dr Courtney McDonald

What is cerebral palsy?

Cerebral palsy is an umbrella term that refers to the motor and postural impairments associated with damage to the developing brain. Cerebral palsy can result from injury sustained *in utero*, at or around the time of birth, or up until one month of age. These times correlate with critical periods of brain development, and when disrupted, this can lead to damage.

In Australia, a child is born with a brain injury that underlies cerebral palsy every 15 hours. It is the most common disability in childhood. While the causes of brain injury can vary, the largest contributor to cerebral palsy is preterm birth. In addition, up to 70 per cent of these preterm births have been complicated with an infection during pregnancy. The effects of a baby being exposed to infection, born too early and with no current treatment options, has meant that rates of cerebral palsy have remained static for decades.

Children with cerebral palsy not only have difficulty with movement, but also experience a range of other impairments, including difficulty talking, or with vision, sleeping and behaviour.

Stem cells and what makes them so special?

The human body is made up of more than 200 different kinds of specialised cells, such as muscle, nerve, fat and skin cells. All specialised cells originate from stem cells.

Stem cells are different from other cells in the body in two main ways. They can

- Make copies of themselves, or self-renew
- Differentiate or develop into specialised cells.

Stem cells are found in bone marrow, blood or umbilical cord blood, in blood vessels, skeletal muscles, skin and the liver.

What is stem cell therapy?

Stem cell therapy is a treatment that uses stem cells to replace or repair a patient's cells or tissues that are damaged. The stem cells might be put into the blood, or transplanted into the damaged tissue directly. These transplants can be from the patient's own cells or from a donor.

How will stem cell therapy be used in cerebral palsy research?

When a baby is growing in its mother's womb, the umbilical cord is a vital source of life, transferring oxygen and nutrition from the placenta to ensure the baby develops healthily.

Umbilical cord blood is a rich source of stem cells that can be used in research and in the clinic to treat diseases of the blood and immune system.

In a world-first study, our scientists are examining whether umbilical cord blood stem cells, given intravenously, could protect the brain from damage and 'kickstart' the process of repair after exposure to infection *in utero*.

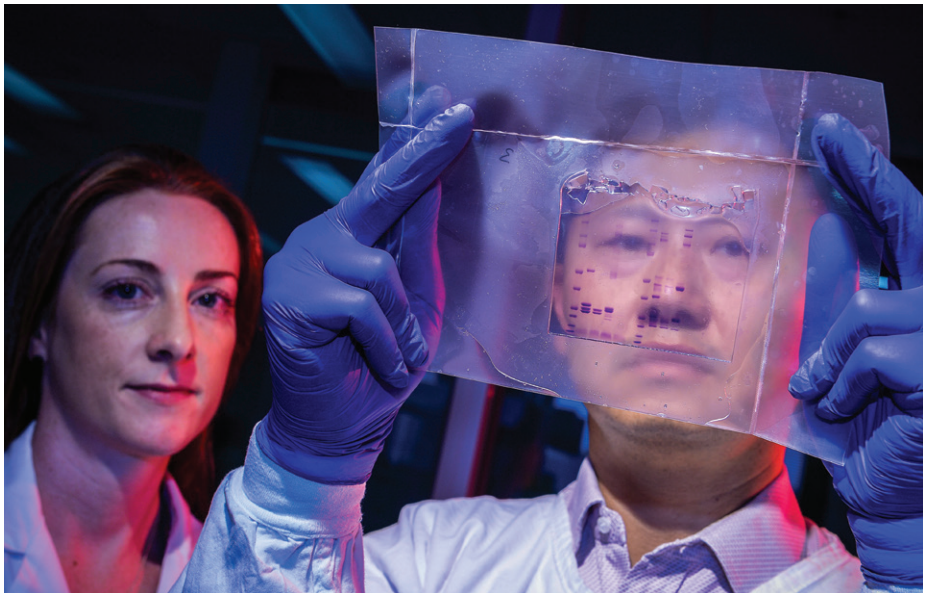
For babies like Kahli born at term, it is feasible that their own cord blood could be used for treatment of brain injury. However, preterm babies would require a donor, as they are often born small and therefore collection volumes of blood are low. Finding healthy donor cells to treat the preterm brain following injury is an ideal therapeutic strategy and uses blood from the umbilical cord, which is discarded soon after healthy babies are delivered.

CEREBRAL PALSY FACTS

- Around **10 per cent** of all babies in Australia are born preterm.
- Worldwide, an estimated more than **15 million** babies are born preterm and one million die ever year as a result.
- Up to **70 per cent** of these babies were exposed to infection during gestation.
- In developed countries like Australia, a lack of oxygen at birth can occur in up to **six of every 1000** births. The risk that the child will develop cerebral palsy is very high.
- Nearly **half of all** babies treated with the current best-practice therapy of whole-body cooling, to reduce inflammation and interrupt brain injury, will still die or suffer lifelong disability.

HIV barrier: protein found in the female reproductive tract could halt spread of the virus

[Discovery impact: HIV]



Dr Niamh Mangan and Deakin University collborator, Professor Johnson Mak
Image credit: Justine Mcmanus/Fairfax

In the past 30 years, the prevention and treatment of HIV has been revolutionised by the advent of strategies such as pre-exposure prophylaxis (PrEP) with antiretroviral drugs, which attack the virus in different ways to stop it from replicating and taking hold.

These 'one pill a day' prevention strategies mean that for many HIV-positive people living in the developed world, HIV is now akin to a chronic condition such as diabetes or high blood pressure that is manageable with medication.

However, more than 95 per cent of the 2.5 million new HIV infections each year occur in developing countries, where sustainable access to PrEP and other prevention strategies is limited. There is a clear need to develop alternative, female-administered HIV prevention strategies for at-risk populations that can prevent the spread of HIV.

Protective defence

A team led by Professor Paul Hertzog in our Centre for Innate Immunity and Infectious Diseases has discovered the body produces a naturally occurring cytokine, interferon epsilon, which is found exclusively in the female reproductive tract and may provide defence against HIV infection.

Working with Deakin University scientists, the team pretreated human cells with a pure form of interferon epsilon made in Prof Hertzog's lab before the Deakin team infected the cells with HIV. The results were exciting.

"We found that interferon epsilon reduces HIV viral replication in human cell lines and induces many of the mechanisms known to block HIV infection. This protection occurred at several stages across the replication cycle of the virus," Dr Niamh Mangan, a senior scientist and Fielding Fellow at Hudson Institute said.

The findings of this collaborative study have recently been published in the Nature Publishing Group journal, *Immunology and Cell Biology.*

L-R: Professor Paul Hertzog, Dr Niamh Mangan, Dr Nicole de Weerd

Boosting natural immunity

The team is now looking at ways to boost base levels of this natural defence in the female reproductive tract.

Current HIV prevention strategies, such as PrEP, primarily attack the virus by chemical means. Interferon epsilon works differently by taking advantage of our natural immune system to suppress viral replication.

"The wonderful thing about interferon epsilon is that it's made naturally by the body. It boosts natural immunity. We know it acts quickly, we know it acts effectively and we know it's there all the time in the reproductive tract of premenopausal women. Boosting the levels of this protein could help to protect women against HIV infection," Dr Mangan said.

Impacts beyond HIV

Prof Hertzog's team first discovered and characterised interferon epsilon in 2013, showing that it had similar effects in blocking the viral replication of other sexually transmitted infections, including chlamydia and herpes simplex virus. This work prompted the HIV study.

Interferon epsilon is regulated by the female hormones oestogen and progesterone, meaning levels fluctuate throughout a menstrual cycle. Susceptibility to HIV is higher when interferon epsilon levels are low, suggesting this cytokine may help to protect against HIV infection in women.

"The next part of this study would likely be further characterisation of the interaction between the HIV virus and cells. We would also like to look at the impact of interferon epsilon on other stages of the HIV life cycle, including its role in latent infection," Dr Mangan said.

The study has implications for the spread of other sexually transmitted infections, including Zika virus, which is linked to an unprecedented increase in the birth of babies born with microcephaly.

The Hertzog group are also investigating the role of interferon epsilon in other reproductive tract diseases such as ovarian cancer and endometriosis.

HIV FACTS

- More than **33 million** people are living with HIV. While huge advances in treatment have been made, the number of newly infected people each year outnumbers those who gain access to treatment by two to one.
- There are **2.5 million** new HIV infections each year, with 95 per cent in developing countries.
- More than **300 000** children are born with HIV each year. Half won't reach their second birthday.

A gift in your Will is a legacy that leaves the world a healthier place for this and future generations.

"Our research focus is on finding new cures for diseases to enhance the quality of life for this and future generations."
Professor Bryan Williams

You can leave a legacy to support an area of medical research that is important to you. It's a simple process. For a confidential discussion or to receive a copy of our bequest brochure, please contact Hudson Institute fundraising department:

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Promising treatment for incurable lung disease in premature babies at birth

[Discovery impact: Bronchopulmonary dysplasia]

L-R: Dr Claudia Nold, Dr Ina Rudloff, Associate Professor Marcel Nold

Babies who are born preterm are often placed on essential and lifesaving respiratory support immediately after birth. This helps their immature lungs get crucial oxygen to the heart and survive.

An unfortunate side effect of this lifesaving care is that up to 60 per cent of premature babies will develop bronchopulmonary dysplasia (BPD) soon after birth. This inflammatory lung disease is caused by severe injury to the lung tissue and prevents normal lung growth.

BPD affects the alveoli, the tiny sacs in the lungs that enable the entry of oxygen into the bloodstream, and the clearance of carbon dioxide from the body.

Researchers from The Ritchie Centre have discovered a safe and effective treatment for BPD, which could save preterm babies from the severe lifelong effects of this incurable premature lung disease.

Babies with BPD often suffer lifelong, severe complications, including impaired neurodevelopment, and are highly susceptible to airway infections that may lead to death. As a result, some will require ongoing medical care into childhood, some even into adulthood.

Timing of treatment is key

The researchers, led by Associate Professor Marcel Nold and Dr Claudia Nold together with senior scientist Dr Ina Rudloff, showed that an anti-inflammatory drug, interleukin 1 receptor antagonist (IL-1Ra), could be given as a preventative measure in the hours after birth to prevent the development of BPD. The findings of the study have recently been published in the *Journal of Cellular and Molecular Medicine*.

The Nolds' laboratory had previously shown (*PNAS* 2013) that IL-1Ra was effective in preventing BPD, but the optimum timing to offer maximum protection was not clear. This study has proven that IL-1Ra is most effective at protecting newborns against BPD when given at moderate doses and when administered early, ideally within 12 hours of delivery.

"This anti-inflammatory drug worked best to prevent the development of BPD when it was given immediately after birth, before chronic inflammation could establish itself, and at a lower, rather than higher dosage," Dr Claudia Nold said.

Double hit

The team also investigated in the study whether protein C, an anti-inflammatory and anti-coagulation medication, could prevent the development of BPD. They were able to show that the two drugs target different inflammatory pathways that cause BPD, and may complement one another when used together.

The two drugs are well tolerated, and are already used to treat various inflammatory diseases in adults and children.

"Both drugs are well tolerated and are shown to be safe in children, so it appears likely that they could be safe to use in preterm babies as well. This will have to be confirmed by clinical trials, which we hope to begin soon," Dr Rudloff said.

Safe and effective

The safety profiles of both IL-1Ra and protein C are markedly more favourable than those of corticosteroids, which are currently the only drugs available to treat, but not prevent, BPD.

"We are very hopeful that alone or in combination, IL-1Ra and protein C could one day be introduced as a safe therapy and prevention strategy for at-risk premature infants," Dr Nold said.

"With otherwise no safe or effective treatment for these babies, this work provides families with new hope and a healthier lifelong outlook."

How does IL-1Ra work?

IL-1Ra is a natural protein and is the inhibitor of IL-1, one of the most important inflammatory cytokines. The body uses IL-1Ra to curb excessive inflammation. In some diseases that involve chronic inflammation, such as rheumatoid arthritis, the patient often does not produce enough IL-1Ra, and in these cases IL-1Ra can be used to supplement the body's natural stores and act as an anti-inflammatory drug.

Next steps

Before they can commence a first-in-human trial of the drug in premature babies, the team must undertake an important preclinical study.

Having this treatment available will make a world of difference to premature babies and their families. This is a major breakthrough that will result in better understanding and prevention of BPD. This is a huge step forward in ensuring better outcomes for babies," Life's Little Treasures Foundation, Co-Founder/CEO, Shusannah Morris said.

BPD FACTS

- Almost **1 in 10** babies in Australia are born premature.
- Up to **60 per cent** of preterm babies will develop BPD.
- The anti-inflammatory drug IL-1Ra has been used safely by more than **150 000** patients since its introduction to clinical medicine in 1993.

Support life saving research by making a tax deductible donation today.

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