HUDSON
INSTITUTE OF MEDICAL RESEARCH

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HUDSON NEWS

Sarah Maree's story

Clues to the cause of endometriosis uncovered

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Director's message

Professor Elizabeth Hartland

Hudson Institute's medical research programs are continually pushing the boundaries of knowledge to bring new and innovative treatments and cures to patients. Our work spans the full spectrum of discovery and translational research to clinical trials.

As part of a vibrant medical innovation hub, our scientists work alongside Monash Health clinicians and staff, building a fundamental science-clinic-patient connection. This means our scientific discoveries are informed by patient need and positioned for clinical development. Throughout this issue, you will see the game-changing outcomes of those essential connections.

The reality of life for the one in 10 women with endometriosis is one of crippling pain that affects every part of life – personal, family and work. I am extremely grateful to Geelong K rock 95.5 FM radio presenter Sarah Maree Cameron for sharing her experience of this invisible disease to raise awareness about the need for progress.

Hudson Institute is at the forefront of research into endometriosis. Professor Caroline Gargett's research is putting the pieces of the endometriosis puzzle together with a very clear end game – to find new treatments and early diagnosis tools to help women. Our results are extremely promising but this work needs more funding to progress rapidly. If you are able to help, please give generously to this appeal.

Dr Sam Forster, a ground-breaking researcher studying the human microbiome, and Dr Jaclyn Pearson, leading work on gut responses to bacterial infection, are collaborating with Monash Children's Hospital to investigate the role of usually 'friendly bacteria' in Inflammatory Bowel Disease. Together, the team have one goal – to find new treatments for this incurable disease that affects up to 10,000 Australian children.

A further example of our leading-edge work is helping our smallest patients. A clinical trial based on Hudson Institute research will help determine whether a simple delay in cord clamping could have life-saving benefits for babies with breathing difficulties. The results could change the way clinicians help all newborns to breathe after birth.

We are so proud of the hard work done by all our researchers. In this issue, we introduce Dr Rebecca Lim, whose work on the clinical applications of placental stem cells has put Australia on the medical world map. Without the generosity of our supporters, Dr Lim's innovative cell therapies would not be possible, so we thank you and look forward to sharing more updates with you as our work progresses.

Professor Elizabeth Hartland
Director and CEO

Front cover and page 3 | Tissue image shows the location of human endometrial epithelial progenitor cells deep in the uterine lining. There are two types: the most primitive epithelial progenitor cells (red and blue) and more mature epithelial progenitor cells (green and blue). These progenitors produce the fully matured gland cells that provide nutrition to the implanting embryo and nourish it for the early weeks of pregnancy as the placenta develops.

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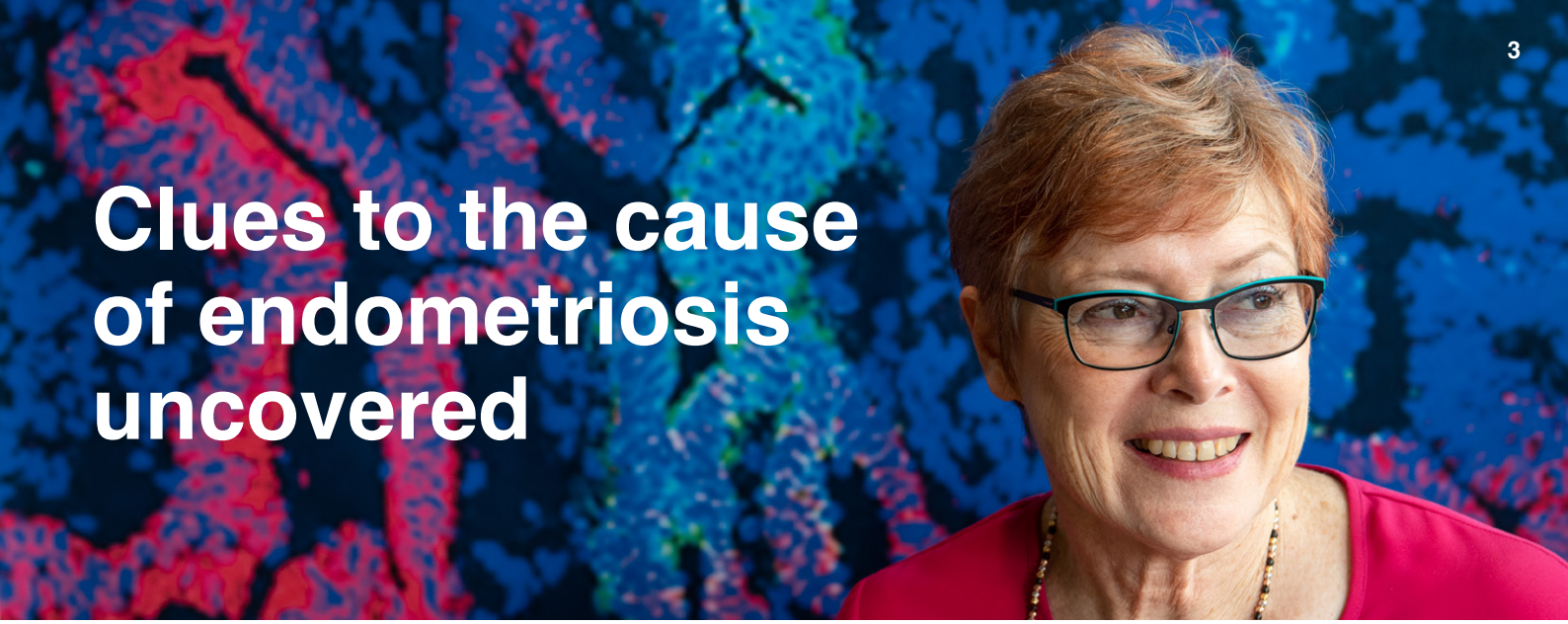
Clues to the cause of endometriosis uncovered



Professor Caroline Gargett

Endometriosis is a debilitating disease affecting one in 10 women, but its cause is unknown and there is no cure.

Sadly, many women with endometriosis experience infertility and, despite many suffering crippling pain, it takes on average seven to 10 years for a diagnosis. Besides the financial and emotional cost to patients and their families, endometriosis costs Australia around $5 billion in lost productivity and around $2.5 billion in healthcare every year.

Hudson Institute's world-leading endometrial stem cell expert, Professor Caroline Gargett, has discovered that highly regenerative cells called endometrial epithelial progenitor cells could lead to the abnormal cell growth in endometriosis.

In a study published in the journal *Human Reproduction*, Prof Gargett and collaborators from the UK examined endometrial samples from 102 women, and found that women with endometriosis had endometrial epithelial progenitor-like cells mixed with cells in the part of the womb lining that is shed during menstruation.

"These progenitor-like cells come from a deeper basal layer in the endometrium and generally shouldn't be shed during menstruation. These are highly regenerative cells so it's entirely possible that, in the wrong place, they could initiate endometriosis lesions," Prof Gargett said.

"We believe that these cells may be related to an endometrial epithelial progenitor cell we discovered in the endometrium several years ago. Together, they could form an important piece of the endometriosis puzzle, helping us understand the complexity of the progenitor cells in the endometrium and their likely role in endometriosis."

While this brings researchers closer to understanding how the endometrium works, more research is needed to find out the actual cell of origin for endometriosis. Hudson Institute research is seeking to generate this knowledge so new targeted treatments can be developed for patients.

World-renowned expert

Prof Gargett leads the Endometrial Stem Cell Biology Group at Hudson Institute. In 2004, she made the world-first discovery of two different stem cells in the endometrium. Her research aims to determine the role of stem cells in the development of endometriosis so that non-hormonal treatments can be developed to prevent or halt the disease.

In 2017, Prof Gargett's team discovered that a protein called N-cadherin could be used as a marker to identify and isolate endometrial epithelial progenitor cells in the uterus. The discovery has meant that scientists can now investigate the role of these adult stem cells in conditions such as endometrial cancer, endometriosis, adenomyosis and Asherman's syndrome, which are not well understood.

Collaborators: University of Liverpool, UK

ENDOMETRIAL EPITHELIAL PROGENITOR CELLS

Endometrial epithelial progenitor cells are types of adult stem cells found in the lining of the uterus or womb that are responsible for maintaining the tissue. They can divide and renew themselves and also differentiate to form more mature cells of the tissue.

WHAT IS ENDOMETRIOIS?

A condition that affects women of reproductive age. It occurs when cells that line the uterus (or endometrium) grow in other parts of the body, usually the pelvic cavity.

These endometrial cells may stick to organs such as the ovaries, fallopian tubes, peritoneal lining, bowel or bladder, where they may grow to form patches, plaques, lesions or cysts.

Endometriosis lesions have also been discovered on the heart, knee and brain.

Although these cells are not in the uterus, they are still responsive to the female reproductive hormone oestrogen and may bleed during menstruation, causing inflammation, internal bleeding and scar tissue.

Adenomyosis

A condition where cells that normally line the uterus also grow in the muscle wall of the uterus.

Could bacteria change the paradigm of IBD treatment?

L-R: Dr Sam Forster, Dr Jaclyn Pearson, Dr Edward Giles

Leading researchers from Hudson Institute, Monash Health and Monash Children's Hospital are combining their expertise to find new treatments to help young people with Inflammatory Bowel Disease (IBD).

In Australia, one in 200 people, including up to 10,000 children, suffer from IBD. It's 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.

Dr Sam Forster is a specialist in the microbiome, world-renowned for his research into gut bacteria. His study into new species of gut bacteria has been described as 'game-changing' for research worldwide.

Dr Forster is collaborating with Dr Jaclyn Pearson and Dr Edward Giles to combine expertise in clinical disease, genomics and immunology. Together, they are working to identify common protective and inflammation-causing gut bacteria in children diagnosed with IBD, and to identify treatments that target those bacteria.

The physical and emotional toll of IBD

There is a real need for new treatments for children with IBD. Currently, the disease is managed using drugs that suppress the immune system, but these become less effective over time and can have significant side effects, leaving patients with an increased risk of colorectal cancer and lymphoma.

The disease not only impacts physical health, but also social and emotional wellbeing. Having IBD can cause severe embarrassment and disruption to a young patient's education, employment and relationships. Isolation and stress experienced can also result in anxiety and depression.

Focus on friendly bacteria

The research program will focus on the role of gut bacteria in IBD. Already, the team have grown almost 2500 bacteria and identified around 20 of these bacteria that associate with bowel damage to proceed with more in-depth research.

"If we can understand how these key bacteria initiate the disease symptoms, this research has immense potential to change the paradigm of IBD treatment," said Dr Pearson.

The team hope their work will lead to more targeted treatments including improved faecal transplants, probiotics or immunomodulators.

"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.

A baby-led approach to umbilical cord clamping

L-R: Dr Douglas Blank, Associate Professor Graeme Polglase, Professor Stuart Hooper

Newborn babies will remain connected to their mother via the umbilical cord until their breathing stabilises, as part of a Melbourne trial aimed at helping clinicians determine the safest time to cut the cord.

More than five per cent of babies born worldwide need help breathing immediately after birth and 800,000 die due to breathing problems.

Researchers want to determine whether a simple change in the timing of umbilical cord clamping could improve outcomes for these babies.

The trial is based on a feasibility study led by researchers from Hudson Institute, Monash University and the Royal Women's Hospital.

The study, called Baby Directed Umbilical Cord Clamping (Baby DUCC), published in the journal *Resuscitation* found that newborns with breathing difficulties after birth could be safely helped by medical staff while remaining connected to their mother via the umbilical cord.

In these babies, their oxygen level and heart rate were more stable, and the dangerous drop in heart rate often observed following clamping cord was avoided.

The clinical trial will take place at Monash Health and the Royal Women's Hospital and involve around 1000 newborn babies born after 32 weeks.

Clinicians will use a baby's vital signs as the deciding factor on when to cut the umbilical cord, rather than relying on a set time.

Hudson Institute and Monash University PhD student Dr Douglas Blank said the technique harnessed the natural power of the mother and placenta.

"This study may change the way clinicians help all newborns to breathe after birth, with no need for new equipment, just a change in timing. If successful, this technique could be used in virtually any setting."

A larger trial is underway to determine whether the technique can also be used to reduce death and brain damage resulting from birth asphyxia, which can occur when a newborn is deprived of oxygen during the birth process.

Collaborators: Monash University; Royal Women's Hospital; The University of Melbourne

FACTS

- More than five per cent of newborns born worldwide need help breathing immediately after birth.
- Worldwide, more than 800,000 newborns die annually because they do not breathe well after birth.
- The majority of newborns that die are born in developing countries, but are born at full-term and are otherwise completely healthy.
- Birth asphyxia is a result of a newborn being deprived of oxygen for long enough during the birth process to cause physical harm, usually to the brain.
- Babies with mild or moderate birth asphyxia may recover fully. Babies who have long periods of asphyxia may develop permanent injury, which could affect their brain, heart, lungs, kidneys or other organs.

Researcher spotlight Associate Professor Rebecca Lim

Cell therapy leader Associate Professor Rebecca Lim's incredible work is putting Australia on the map as a leading research hub. In March she was ranked among Australia's top scientists in the National Health and Medical Research Council's Research Excellence Awards.

A/Prof Lim has dedicated more than 10 years to understanding how stem cells from the amniotic sac could reverse the downward spiral of life-threatening diseases. Now she has translated her breakthrough scientific findings into world-first clinical trials to help extremely sick babies and acute stroke patients.

What difference has your research made to the health of Australians?

For over a decade, I have dedicated my research to understanding how stem cells from the amniotic sac, which surrounds the baby during pregnancy, could alter the progression of life-threatening diseases.

I developed a method for producing these stem cells that complied with national regulatory standards and could be used in patients. Now, my research has brought world-first cell therapy to extremely premature babies with severe lung disease and acute stroke patients.

Describe a turning point or defining moment in your research career.

I still get goose bumps thinking about it. The day when I discovered that the amniotic stem cells release tiny nanoparticles of biological material that mimic the actions of the parent cell. I double-checked the data. I asked another scientist in our team to repeat the experiment. I gave a sample of these nanoparticles to a colleague to test.

When I discovered that the observation was real and reproducible in the hands of multiple scientists, I just about cried. Here was a 'eureka moment' in its true essence.

What excites you about your research?

The potential to improve the lives of patients suffering from debilitating diseases. We are continually exploring the boundaries of cell therapies and improving our understanding on the way they work and how we can provide safe and effective treatments for patients.

Amniotic stem cells offer the simplest of treatments – they don't need to be matched to the patient's blood type or tissue type, and can be delivered by the simple procedure of an intravenous line, taking about an hour.

How do you see your research impacting the field?

For a long time, Australians have struggled to access approved cell therapy clinical trials. As stem cell researchers continue to develop cell therapies for serious diseases, access to approved treatments will grow. And, conversely, by progressing the science of stem cell treatments I hope there will be a reduction in Australians seeking potentially dangerous, unapproved therapies overseas and falling victim to stem cell tourism.

What are the next steps?

The high cost and labour-intensive manufacture of cell therapies mean few patients have benefited from cell therapies. Breaking down these barriers with technology that reduces manufacturing costs will mean that more patients will be able to access the benefits of cell therapies. That will be a game-changer for patient health.

How is your work putting Australia on the map?

One of the first things we hear from our colleagues in Europe and North America, when we present our findings, is "Wow! Never heard of that before, where are you from?" This work is putting Melbourne and Australia on the map as a leading research hub for stem cell research.

WHAT ARE AMNION EPITHELIAL CELLS?

An amniotic epithelial cell is a stem-like cell extracted from the lining of the inner membrane of the placenta. They have the ability to grow into any cell in the body, in a similar way to stem cells. Each placenta produces about 150-200 million amnion cells.

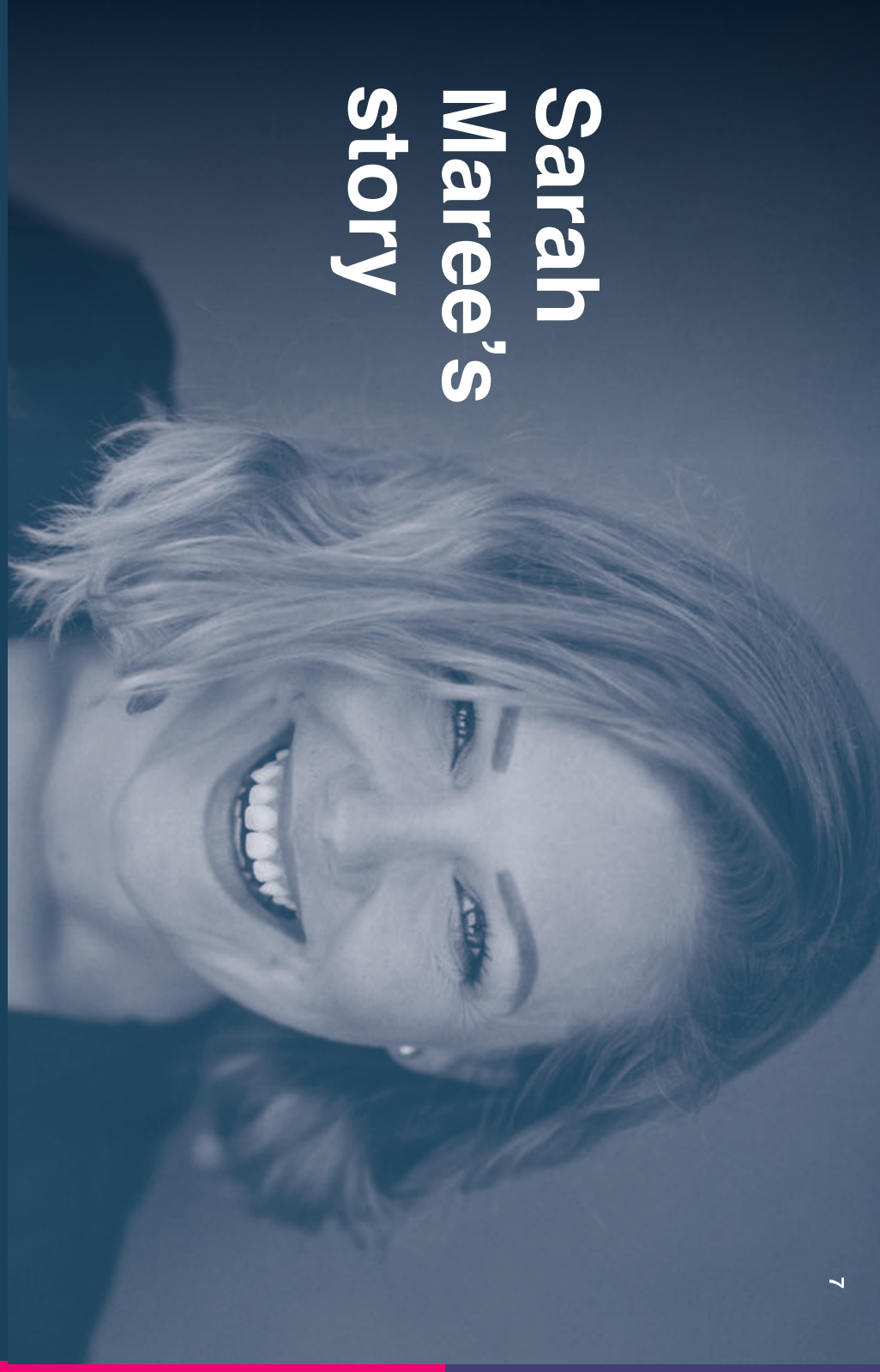
WHAT ARE CELL THERAPIES?

Cell therapies are an emerging medical treatment that uses living cells to treat a range of diseases. They aim to replace or regrow diseased or dysfunctional cells with healthy, functioning ones. Examples include whole blood transfusions, cancer immunotherapies and stem cell therapies.

The oldest form of cell therapy is bone marrow transplantation, where living blood stem cells are given to patients to treat diseases such as cancer.

Regenerative medicine uses technologies such as cell therapies, biomaterials and/or drugs to help damaged organs or tissues to repair. This can include bioengineered bone grafts impregnated with growth factors (naturally occurring substances like proteins and hormones) to speed up repair.

Sarah Maree's story



Imagine being in so much pain that you can't do the things you love – like running, surfing and going for long swims. Imagine what it feels like to be known at work for always being 'off sick', rather than for being good at your job.

For Geelong K rock 95.5 FM radio presenter and comedian Sarah Maree Cameron, this was the reality of life with endometriosis, the 'invisible disease'. Every day she would put on a brave face to the world, masking the crippling pain she was feeling as a result of endometriosis. Now, as an ambassador with Endometriosis Australia, Sarah-Maree is raising awareness of this debilitating disease and the need for research.

Sarah Maree was diagnosed with endometriosis in 2010, after experiencing symptoms for a number of years. At the time, she didn't know much about the disease, so she didn't immediately seek treatment, but it got to the point where she was in immense pain every single day.

"You don't notice when something slowly takes hold, which is why I wasn't initially as proactive with managing it, as I am now."

Multiple surgeries were required, as the endometriosis spread to different areas of Sarah Maree's body. As Sarah Maree also had adenomyosis, a painful condition in which the endometrium breaks through into the muscle wall of the uterus, doctors eventually recommended a hysterectomy.

Sarah Maree says the decision to have a hysterectomy was made slightly easier in her circumstance because she didn't want to have children.

"While I completely understand that a hysterectomy does not cure endometriosis, it cured my adenomyosis and has improved my quality of life to a point that I couldn't have even imagined," said Sarah Maree.

These days, living with endometriosis is manageable because Sarah Maree has explored and found other options that help.

"I use acupuncture, yoga, exercise and a low FODMAP diet to control my endo. The benefits they bring have been vital to my management. I truly believe it has contributed to why I haven't had an operation in two years.

"It has taken an entire community of people and specialists to give me the knowledge I needed to manage my treatment plan and I'm eternally thankful to have met each person along the way of my journey."

Sarah Maree says there is a need for a non-invasive early diagnostic test for endometriosis, so that this debilitating disease can be picked up and managed earlier. She also wishes there was better awareness of the condition – among medical practitioners and the general population.

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Help us find new solutions for women with endometriosis

“It’s everyone’s problem when we have this many women suffering. Earlier diagnosis would really help – but funding is needed to progress research and new treatments.”

SARAH MAREE CAMERON

Understanding the impact of men’s health on future offspring

Dr Patrick Western, Dr Jessica Stringer

When it comes to conception, it has long been accepted that a mother’s lifestyle choices can affect a child’s development. But could a father’s behaviour be just as important?

Hudson Institute scientists have identified a new pathway of non-genetic inheritance that could one day link a father’s lifestyle choices, including diet, alcohol, drugs, smoking and medications, to the development of his children.

The study, led by Dr Patrick Western and Dr Jessica Stringer, looked at epigenetics – heritable marks in the DNA that act like a set of instructions, or ‘road-map’, that defines cell types in the body.

These pathways can be disrupted by exposure to lifestyle factors like diet, drugs and chemicals, providing a means by which health and lifestyle of a parent can affect his or her future children.

In the study, Dr Western and Dr Stringer found that an epigenetic modifying complex, called PRC2, regulates non-genetic information transmitted from a father to his offspring.

“For the first time, we demonstrated that altered function of PRC2 in mouse sperm, before eggs are fertilised, caused epigenetic effects on development and gene expression in the father’s offspring,” Dr Stringer explained.

The study is a big step forward in our understanding of how a parent’s diet and lifestyle can affect children. Research has previously suggested that if a parent has a poor diet, they significantly increase the risk of obesity for future generations – including in children and grandchildren. However, in many cases the specific epigenetic factors at play have been unclear.

“Now we’ve shown that PRC2-dependent epigenetic changes in sperm can be ‘inherited’ by offspring from their fathers, we can start to look at whether specific foods or chemicals might positively or negatively affect PRC2 function and, therefore, development in children.

“For example, in future work, we will look at how specific drugs, diets or environmental factors affect the sperm epigenome and provide up-to-date information to men wanting to become fathers. Similarly, further work may explain how environmental factors mediate inter-generational health impacts where genetic mutations are excluded.”

For now, Dr Western said that fathers needed to be mindful of their role in conceiving a healthy child.

“When thinking of starting or adding to their family, both mum and dad should try to be as healthy as possible,” Dr Western said.

Collaborators: Monash University; University of Adelaide; University of Melbourne

WHAT IS EPIGENETICS?

Epigenetics refers to heritable marks in the DNA that determine whether a gene can be ‘switched’ on and off, changing how cells read genes, without causing changes in the underlying DNA sequence.

The epigenome provides a layer of complexity on top of our DNA. It’s like a set of instructions or ‘road-map’ that defines cell types in the body.

Epigenetic control of genes is part of what allows a tiny cluster of identical cells in the womb to grow into a fully formed baby. By regulating different sets of genes that can be switched on and off, some cells become heart cells while others become brain cells.

Importantly, epigenetic pathways can be disrupted by exposure to lifestyle factors, like diet, drugs and chemicals, providing a means by which health state in a parent can affect his or her future children.

‘Thank you for your kind support’

Professor Elizabeth Hartland
Director and CEO, Hudson Institute