Heart healer

Dr Enzo Porrello leads an ambitious research group in the School of Biomedical Sciences at the University of Queensland who are investigating the regenerative capacity of the neonatal heart, aiming to find a way to enable the adult human heart to heal itself following a heart attack

To begin, what provided the inspiration for your interest in the molecular mechanisms guiding heart growth and development during the neonatal period?

The neonatal period is one of the most important times in our lives and the heart undergoes a number of critical transitions during this physiological switch to life outside the womb. My PhD thesis focused on the neonatal origins of cardiac hypertrophy (abnormal heart enlargement) and I have been fascinated with this developmental period ever since. During the course of my PhD it occurred to me that while the molecular mechanisms governing embryonic heart development and adult heart disease were relatively well-documented, we knew very little about the molecular underpinnings of heart development during the neonatal period. When I began my postdoctoral research at the University of Texas (UT) Southwestern Medical Center in 2009, I decided that I wanted to analysis the mechanisms that might regulate cardiac regenerative capacity during the neonatal period. I have been particularly interested in the role that non-coding RNAs, such as microRNAs, might play in this process.

How has pre-existing knowledge on non-human animals guided your current assay? How effectively can research on mice be translated to humans?

Our work was inspired by earlier studies in model organisms such as the zebrafish and newt. These remarkable organisms can regenerate entire limbs, fins and even their heart following injury. We wanted to understand why mammals had apparently lost this incredibly useful capacity for organ regeneration during evolution. Pre-existing work in rodents also provided us with a clue that something very important was going on in mammals during neonatal life. These landmark studies in non-human animal models as diverse as fish, amphibians and mice provided us with the rationale to ask whether mammals might also be able to undergo heart regeneration during early life. The significance of these findings for humans is still unclear but there is no reason to believe that the human heart would not retain similar properties during neonatal life, and there are indeed some case studies that suggest this might be so.

Do you envision this study having an impact on investigations of other organs in the human body?

I think there is a good possibility that developmental windows of regeneration also exist in other organs in the body. It will be interesting to see whether other groups pick up on our work related to the heart and extend these observations to other organ systems in the future.

How important is collaboration to your research?

Collaboration is a vital component of our research programme. The need to collaborate and form partnerships is somewhat born out of necessity in Australia, where scientific resources for individual labs are much more limited than in the US. We continue to collaborate with old friends at the UT Southwestern Medical Center and we have also established new collaborations within Australia (Baker IDI Heart and Diabetes Institute and Australian Institute for Bioengineering and Nanotechnology) as well as overseas partners.

Who has been of particular influence in your career as a biomedical scientist?

My formative years as a scientist were most influenced by my PhD thesis mentors, Professor Lea Delbridge and Professor Wally Thomas. They not only helped to train me as a scientist and developed my research and professional skills, but also continue to provide me with advice and mentorship to this day. In more recent times, my postdoctoral mentor Dr Eric Olson has had a tremendous influence on my career. Eric created such an incredible environment in his lab enabling me to 'think big' and to answer the most pressing questions in the field. I think that this experience has forever changed my scientific mindset and it will undoubtedly influence the way that I approach research in my own lab.

What is your ambition for future research and development? Do you have any new projects on the horizon?

The overarching goal of our research is to identify the key molecular mechanisms that govern cardiac regenerative capacity in mammals during neonatal life. We hope to ultimately be able to use this knowledge to re-awaken innate regenerative responses in the adult heart following a heart attack. We have a number of projects in the lab that focus on understanding the molecular mechanisms that lead to silencing of regenerative genes after birth. There are many open questions in the field and we believe that this work is going to keep us fairly busy for a while.

Secrets of the heart

A team of researchers at the **Laboratory of Cardiac Regenerative Biology** in Australia is uncovering the genetic mechanisms behind the remarkable regenerative ability of the neonatal mouse heart

FOLLOWING A HEART attack, millions to billions of heart muscle cells called cardiomyocytes die within the space of a few hours and the majority of these cells are not regenerated. As a consequence, these contractile cardiomyocytes are replaced with non-contractile scar tissue and the heart's pumping capacity is compromised, which ultimately leads to heart failure. Although the adult mammalian heart has very limited regenerative capacity, certain fish and amphibians can regenerate organs and body parts, including the heart, throughout life. These organisms have been the subject of a number of landmark studies which have inspired the inception of a new research group focusing their studies on the regenerative capacity of the mammalian heart during the neonatal period.

THE NEONATAL HEART

Based at the University of Queensland (UQ) in Australia, the Laboratory of Cardiac Regenerative Biology is trying to unravel the molecular mechanisms that regulate cardiac regenerative capacity in mammals. Led by Dr Enzo Porrello – who only recently completed his postdoctoral training at the University of Texas (UT) Southwestern Medical Center under the mentorship of Dr Eric Olson, a preeminent figure in cardiac biology – the team is collaborating with scientists in the US, Germany and Australia to investigate the critical mechanisms required for cardiac regeneration.

During his postdoctoral research at UT Southwestern, Porrello discovered that, in contrast to the adult mammalian heart, the neonatal heart harbours a remarkable intrinsic capacity for regeneration. Similar to the zebrafish and newt, he found that the neonatal mouse heart can instigate a robust regenerative response following injury, which appears to be driven by the proliferation of resident cardiomyocytes rather than the activation of stem cells. Mammalian cardiomyocytes lose this ability to divide shortly after birth and cardiac regenerative capacity is subsequently lost.

The molecular mechanisms that regulate this cardiomyocyte proliferative potential and cardiac regenerative capacity are currently poorly understood, and Porrello's lab is aiming to identify the critical pathways that lead to the silencing of regenerative genes after birth. Their ultimate goal is to find a way to reactivate these processes in the adult heart following a heart attack.

MICRORNAS

Porrello previously identified a microRNA that regulates this regenerative process in neonatal mice. MicroRNAs are small pieces of genetic material that play an important role in regulating gene expression and are unique because they do not encode proteins. Due to their very small size and the fact that they do not produce any protein products, microRNAs escaped the attention of biologists for a long

LABORATORY OF CARDIAC REGENERATIVE BIOLOGY

OBJECTIVES

To unravel the molecular mechanisms that regulate cardiac regenerative capacity in mammals. More specifically, to decipher the complex mechanisms by which large gene regulatory networks are altered in the heart shortly after birth and to understand how these changes contribute to cardiomyocyte maturation and regenerative arrest. Ultimately, the aim is to discover the key mechanisms that bestow the neonate with regenerative potential and to reactivate these processes in adulthood.

KEY COLLABORATORS

Professor Eric Olson; **A/Professor Hesham Sadek**, University of Texas Southwestern Medical Center, USA • **Dr Paul Gregorevic**; **A/Professor Assam El-Osta**, Baker IDI Heart and Diabetes Institute, Australia • **Professor Justin Cooper-White**; **A/Professor Ernst Wolvetang**, Australian Institute of Bioengineering and Nanotechnology, Australia • **Professor Walter Thomas**, The University of Queensland, Australia • **Professor Lea Delbridge**; **Professor Stephen Harrap**, The University of Melbourne, Australia • **Dr Shizuka Uchida**, Institute for Cardiovascular Regeneration, Germany

FUNDING

National Health and Medical Research Council (NHMRC) of Australia

National Heart Foundation (NHF)

CONTACT

Dr Enzo Porrello
NHMRC/NHF Postdoctoral Research Fellow
Head, Laboratory of Cardiac Regenerative Biology

Room 722, Otto Hirschfeld Building (81)
St Lucia Campus
School of Biomedical Sciences
The University of Queensland
Brisbane, Queensland 4072
Australia

T +61 7 3365 2402
E e.porrello@uq.edu.au

DR ENZO PORRELLO received his PhD from the University of Melbourne in 2009. He subsequently undertook postdoctoral training at the University of Texas Southwestern Medical Center (USA) in the laboratory of Dr Eric Olson. Porrello relocated to the University of Queensland in 2012 to head the Laboratory of Cardiac Regenerative Biology.

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Drugs might be able to reactivate neonatal regenerative mechanisms in the adult heart following a heart attack

time until they were first discovered in worms in the early 1990s. However, it is only in the last five to 10 years that the importance, diversity and functional significance of microRNAs have really come to the fore. Porrello explains that they have now been implicated in almost every biological process, where they play key roles in fine-tuning the expression of large networks of genes: "One of the most exciting aspects of microRNA biology that has emerged in recent years is the realisation that these small snippets of genetic material might also be good pharmacological targets for heart disease and cancer".

The group is now working on a large family of microRNAs, known as the miR-15 family, which is activated in the heart shortly after birth and participates in shutting down the machinery required for proliferation of cardiomyocytes and regeneration of the heart. In collaboration with miRagen Therapeutics, they have recently shown that inhibiting this microRNA family in the adult mouse heart improves heart function following ischaemic injury.

STEM CELLS

Part of the focus of the Laboratory of Cardiac Regenerative Biology centres on stem cells, which represent a potentially infinite source of cardiomyocytes, and therefore hold enormous potential for heart regeneration. A number of stem cell trials are already underway in humans but the beneficial effects reported to date have been fairly modest, and the observed increases in heart function do not appear to be the result of actual cardiomyocyte regeneration, but rather due to the secretion of beneficial growth factors from the stem cells.

There are a number of bottlenecks that still need to be overcome if stem cell therapy for heart disease is to become a reality. For example, heart regeneration requires: that the estimated 1 billion dying cardiomyocytes are replenished after a heart attack; that the tissue is resupplied with oxygen and nutrients to keep the cells alive; and that the cardiomyocytes then mature to a level that is sufficient to enable proper contractile function of the heart without any risk of arrhythmia.

The standard approach that has been taken by many groups in their attempts to regenerate the heart using stem cells involves the injection of millions of these cells into the heart following a heart attack, most of which die following injection. The idea of this technique is that the remaining stem cells will differentiate into the right cell types in exactly the right place and at exactly the right time: "There are also issues of selecting the right stem cell type for the job, overcoming immune rejection and limiting unwanted side effects," reveals Porrello. There are no guarantees that stem cell therapy will work at all, and a long way to go before any such therapy, if possible, becomes a reality, so in the meantime Porrello is ensuring he explores every avenue of investigation: "Stem cells might prove to be the magic bullet for heart regeneration, but I think there is also merit in looking into alternatives".

SCIENTIFIC SUCCESS

Although Porrello's group is still some way from realising any direct translational implications of their work for human cardiac regeneration, they believe that their findings in mice indicate that a similar window of opportunity for heart regeneration might also exist in humans. One obvious outcome of their work could be the development of drugs that might be able to reactivate neonatal regenerative mechanisms in the adult heart following a heart attack. In addition, their work could help inform paediatric surgeons with regards to optimal timing for surgical interventions in humans.

Porrello's findings have been published in some of the world's most prestigious publications, and a major part of this success comes from his collaborators, both past and present: "I am really fortunate to have worked with some great people in an incredible scientific environment that encouraged creativity and boldness," he reflects. "Like any scientific discovery, our progress involved a combination of a lot of hard work and late nights in the lab with a stroke or two of luck along the way." Despite his success, he will not be resting on his laurels: "As Eric used to tell me, you're only as good as your next publication, and there is still a huge amount of work to be done – a whole career's worth I hope!".