ABOUT THE AUSTRALIAN REGENERATIVE MEDICINE INSTITUTE

ARMI is Australia’s first research institute dedicated to the important new field of regenerative medicine. ARMI was opened in 2009 to deliver on this medical field’s promise, at a time when only four such centres existed worldwide.

While an important centre for Australia, ARMI’s reach extends globally with important global research linkages. In 2017, ARMI and its partners worked towards building opportunities and programs for CCRM Australia that will ultimately form part of an international network specialising in regenerative medicine.

The Institute continues to explore new research methods to test new ideas that position ARMI to bring revolutionary breakthroughs from bench to bedside at a faster pace. To help achieve that goal, 2017 saw the early success of the Monash Transgenic Quail Facility increasing our technological capabilities with four proof-of-concept transgenic quail lines plus two commissioned lines genetically engineered for research projects.

ARMI’s research and knowledge base covers heart disease, muscular dystrophy, diabetes, multiple sclerosis, brain injury and autoimmune disorders. In 2017, ‘Organ engineering and synthetic biology’ was added as a new research pipeline for ARMI, reflecting the latest in cutting-edge research with the potential to translate discoveries to solve clinical problems.

Established through a joint venture between Monash University and the Victorian Government, with additional funding from the Australian Government, ARMI is an Institute within Monash University’s newly formed Faculty of Biomedical and Psychological Sciences, located at one of the world’s largest regenerative medicine and stem cell research centres.

ARMI’s research programs seek to answer some of the fundamental questions of growth, repair and regeneration:

- How do some human tissues (skin, blood, cells and the lining of the digestive tract) naturally regenerate?
- What determines the regenerative ability of cells? What switches regeneration on and off?
- How do newts regrow their tail or limbs, or fish regenerate their fins or heart? What biological and molecular processes make this happen?
- Do the parts of the body that do not regenerate (such as the brain and heart) retain a latent ability to do so?

This understanding will enable researchers to develop techniques in tissue regeneration that can be used in human medicine, including:

- inserting cells that are capable of regeneration and are usually derived from adult or embryonic stem cells into tissues
- preventing cell death that would otherwise occur from disease or injury
- recruiting a person’s own cells or molecular processes to induce tissue regeneration
- preventing inflammation and scarring in tissues.

ARMI has adopted a multidisciplinary highly specialised approach to the investigation of the science of regeneration, designed to seed and foster collaboration, and to pursue rapid translation of basic research into clinical knowledge and treatments.

At ARMI’s core is the development of the scientific leaders of the future. ARMI provides talented young researchers opportunities to accelerate their careers, nurture their talents and secure a career pathway.

Expert mentoring and state-of-the-art core research infrastructure and facilities provide a rich and inspirational research environment. After this extraordinary start, group leaders move to other institutes – a practice that deliberately enhances ARMI’s flexibility and disseminates this highly supported and creative research culture to other institutions.

The Institute’s dynamic and collaborative research culture promises to redefine how regenerative medicine is approached worldwide, as ARMI scientists address fundamental regenerative biology questions and provide the knowledge base to move beyond current therapies into combination-therapy standards.

The Institute’s research group leaders, recruited from around the world, represent a broad range of disciplines that contribute to a shared vision for the development of regenerative therapies, capturing new opportunities for international collaboration.

The functional integration of key research platforms at each level of enquiry – molecular genetics, stem cell biology and animal modelling – aims to deliver technologies with medium-term to long-term application for treatment of diseases of social, medical and economic importance and unmet clinical need.

ARMI is also a major resource for members of the public, policy makers, industry, and undergraduate and school students to learn about and engage with the concepts of regenerative medicine and the people undertaking the pursuit of new knowledge and tools.
INTRODUCTION TO REGENERATIVE MEDICINE

Regenerative medicine is a new approach to understanding development, ageing and disease.

Over the past 100 years, medical research has transformed human lives. People are living longer and better. Children rarely die of preventable infectious diseases; cancer survival rates are improving and people can live for decades after a heart attack.

However, although scientific discoveries have enabled doctors to replace organs or use drugs to compensate for organ disease, medicine still can’t provide treatments that help hearts to repair themselves or help nerves to regrow after a spinal cord injury.

As a relatively new field of research, regenerative medicine seeks to unlock the body’s remarkable innate ability to repair, restore and replace various tissues and organs damaged by age, injury or disease. The US Department of Health and Human Services has called regenerative medicine the ‘next evolution of medical treatments’.

Regenerative medicine approaches aim to regain the remarkable regenerative capacity humans have before birth. The techniques include injecting or implanting cells that can regenerate or re-engineer tissues to stimulate endogenous stem cell pools or reprogram existing differentiated cells to proliferate.

Researchers in this exciting and unique field of science look to exploit the body’s own capacity to heal and repair. Exploring this fundamental biological challenge is enriched in an extraordinary environment that brings together different science disciplines working in tandem.

The animal kingdom provides inspiration for what is possible. As Australia’s first institute dedicated to regenerative medicine, ARMI’s work studying axolotls has identified the critical role that an immune cell plays in the animal’s ability to regrow limbs and regenerate spinal cord, brain and heart tissue. Meanwhile, the zebrafish is also revealing how it regenerates new fins, skin, heart and brain.

ARMI’s unique transgenic quail facility has already begun providing more opportunities to leverage the unique characteristics of birds to help researchers understand potential regenerative therapies for humans, especially in skeletal muscle. In its first year of operation, four genetically engineered quail lines were produced as proof of concept and two additional transgenic quail lines were produced for researchers.

From exotic animals to therapeutic application, regenerative medicine holds the promise of assisting human cells, limbs and organs to do the same as these animals. Moreover, it has the potential to revolutionise health care for an ageing population facing many years living with degenerative conditions.
Australian Regenerative Medicine Institute (ARMI) has created the following themes to ensure maximal results for the Institute’s research and people.

**REALISING REGENERATIVE MEDICINE**

Regenerative medicine represents a revolution in human health and has the potential to reverse tissue damage, repair traumatic injuries and improve the health of an ageing population. It seeks to repair, replace, restore and regenerate tissues and organs damaged by age, injury and genetic and degenerative conditions.

**HARNESSING SCIENTIFIC PASSION**

ARMI actively recruits young, creative scientists from all corners of the world to share and inspire differing approaches to some of the most perplexing biological questions of the 21st century. They are highly motivated and nurtured in a collaborative working environment to approach complex biological problems with ingenuity and passion.

**FOSTERING INTERNATIONAL LINKAGES**

In late 2016, ARMI established the Centre for Commercialisation of Regenerative Medicine (CCRM) Australia. CCRM Australia will ultimately form part of an international network with the original organisation in Canada and future hubs in in Europe, Japan, Singapore and Israel. In 2017, ARMI and its partners worked towards building opportunities and programs.

ARMI group leaders, Associate Professors Edwina McGlinn and Mikaël Martino, are part of the Victorian Node of the European Molecular Biology Laboratory (EMBL) Australia. These links provide unique access to the best science in Europe and a new way to approach scientific endeavour.

**BUILDING A RESEARCH COMMUNITY**

As a global biotech life science centre situated at Monash University, ARMI is an integral presence in the broader Melbourne research and medical ecosystem. Its state-of-the-art core scientific facilities are maintained by outstanding infrastructure and technology.

**ENGAGING WITH THE PUBLIC**

ARMI is a significant part of the fabric of Melbourne through its outreach programs and engagement with the general public.
ARMI’S FIVE DISCOVERY PIPELINES

FIVE INTEGRATED DISCOVERY PIPELINES DRIVE ARMI’S RESEARCH FINDINGS FROM THE LABORATORY BENCH TO THE PATIENT

The pipelines exploit the evolutionary and developmental diversity of research platforms and systems biology approaches within the Institute to explore specific aspects of the regenerative process. These specific aspects will include disease targets such as the heart, muscle and nervous systems, to more general features of regeneration such as stem cells and the immune system.

Each pipeline engages established leaders of international standing who support young groups at a creative stage in their careers. The model has proven successful in driving the most innovative research at EMBL.

HEART AND MUSCLE DEVELOPMENT AND REGENERATION

Cardiovascular disease kills one Australian every 12 minutes and the crippling effects of traumatic injury are often permanent. ARMI researchers are studying animals with highly regenerative qualities in heart and other tissues to develop cures for diseases such as muscular dystrophy, traumatic injury and heart disease.

IMMUNITY AND REGENERATION

Soon after birth, human immune systems mature and we lose our capacity to respond to damage with scar-free healing. ARMI scientists are exploring the relationships between immunity and regeneration in the animal kingdom to enhance tissue repair in patients with wounds or degenerative diseases.
STEM CELLS AND REGENERATION

Stem cells are important to human embryonic development and persist in adults as essential building blocks for our bodies. ARMI studies embryonic stem cells as a window on the mechanisms of human development, and as an essential part of the tool kit of regenerative medicine.

ARMI is devising methods for growing stem cells that can be used to: repair damaged tissue, investigate particular diseases, test drug candidates for therapeutic safety and effectiveness, and develop ways to enhance the intrinsic mechanisms of stem-mediated repair.

NEURAL REGENERATION

Our researchers are unlocking the regenerative potential in the central nervous system so it can be harnessed to treat neurodegenerative disorders.

ARMI scientists are tackling the fundamental obstacles in neural repair for diseases such as multiple sclerosis and Alzheimer’s by uncovering neural regenerative potential across the animal kingdom.

ORGAN ENGINEERING AND SYNTHETIC BIOLOGY

ARMI is exploring a number of innovative techniques to enhance function and form that is lost as a consequence of ageing and degenerative diseases.

These advanced techniques explore various aspects of tissue engineering and include:

• organoid and organ-on-a-chip technology
• bioactive biomaterials and biointerfaces that simulate the cellular microenvironment at the micro and nanoscale
• functional biomaterials and synthetic and biological matrices for tissue engineering and transplant development.
WHY STUDY AT ARMI?

• Our Higher Degree by Research (HDR) and Honours programs attract talented students from Australia and abroad.

• Our students reflect ARMI’s international perspective with students from Malaysia, Singapore, The Netherlands, Mexico, Iran and Sri Lanka.

• The highly collaborative, interdisciplinary nature of the ARMI research program exposes students to cutting edge science in our laboratories.

• Students are supported to engage in career building opportunities in Australia and overseas.

ARMI’S VISION IS FOR TODAY’S STUDENTS TO BE TRAINED TO AN EXCEPTIONALLY HIGH STANDARD, TO BE THE NEXT GENERATION OF SCIENTIFIC LEADERS.
### Heart and muscle development and regeneration

We use the basic rules of animal regeneration to unlock regenerative potential in patients for treatment of a range of currently untreatable disorders.

**Project areas:**
- discovery of the basic rules that govern formation of muscle stem cells in the embryo and adult
- better understanding of how stem cells are used during muscle regeneration
- treatments for muscular dystrophy using zebrafish models
- making the heart a better regenerating organ by stimulating specific signaling pathways.

**Research Groups:**
- Currie Group
- Marcelle Group
- Ramialison Group
- McGlinn Group

### Immunity and regeneration

We exploit the immune system as a new player in regenerative medicine, which can be manipulated for therapeutic gain.

**Project areas:**
- understand the role of the immune system in scar-free healing
- determine how immune cells form and are continually replenished
- define the immune system as a critical component of tissue regeneration
- understand the difference in immune regulation between the regenerative and non-healing context
- harness the immune system for delivery of therapeutics to regenerating tissues.

**Research Groups:**
- Lieschke Group
- Martino Group

### Stem cells and regeneration

We use knowledge gained from highly regenerative tissues and animal models to generate human cells that can treat a range of degenerative disease, and learn how to manipulate cell populations in the body to repair more effectively.

**Project areas:**
- define how the genome is read and packaged to form a stem cell
- understand how a stem cell-like state is maintained and regained in induced reprogramming
- identify what environment cues (niche) and other cell systems (immune) interact to influence stem cell function
- enhance endogenous stem cell-mediated repair of injured tissues
- make therapeutically relevant cell types from stem cells to treat disease.
- Unravelling microtubule dynamics at the single cell level using live imaging.

**Research Groups:**
- Polo Group
- Nilsson Group
- Laslett Group
- Hobbs Group
- Nagy Group
- Zenker Group

### Neural regeneration

We work on stimulating regeneration of the mammalian nervous system after damage and degenerative disease.

**Project areas:**
- define how the brain and spinal cord respond after injury and what innate regenerative potential exists in the nervous system of mammals and non-human primates
- make neural cells from stem cell
- identify genes needed to make the brain form normally
- formation of neural stem cell populations in regenerating systems such as the zebrafish brain
- characterise relative regenerative differences in spinal cord of zebrafish and mammals.

**Research Groups:**
- Bourne Group
- Kaslin Group
- Merson Group
- Nillegoda Group

### Organ engineering and synthetic Biology

ARMI is exploring a number of innovative techniques to enhance function and form that is lost as a consequence of ageing and degenerative diseases.

These techniques explore various aspects of tissue engineering including organoid and organ on a chip technology, bioactive biomaterials and biointerfaces that simulate the cellular microenvironment at the micro and nanoscale, functional biomaterials and synthetic and biological matrices for tissue engineering and transplant development.

- Characterising the local cell-autonomous and nonautonomous responses to an injury, including the production and role of alarm signal(s) and the response of stem/progenitor cells
- Exploring the impact of the discovered injury response pathways on the buffering of developmental noise (random perturbations during normal development)

**Research Group:**
- Janovjak Group
- Rosaló-Díez Group
HOW TO APPLY FOR HONOURS AT ARMI

Students from the following fields of study are encouraged to apply to do an Honours project at ARMI Biomedical Sciences:
- Science
- Medical Science
- Health Science
- Engineering
- Pharmacy.

The next step is to contact the Group Leaders to discuss the project further.

Current projects are listed below in this booklet or to suggest your concept for a project, please contact one of our research group leaders. All are happy to meet with potential honours students.

Once you and your supervisor have agreed on a project:

1. Your supervisor will need to fill out an ARMI Honours EOI undertaking to be your supervisor and stating the name of the project.

2. Prepare a copy of your transcript highlighting the subjects you wish to be considered for entry.

3. Submit completed ARMI Honours EOI, Faculty and transcript to the ARMI Honours Coordinator for approval.

4. Complete the relevant faculty’s online application form
   - BMS Students: www.med.monash.edu.au/biomed/honours/
   - Science Students: www.monash.edu/science/current-students/science-honours/

STUDENT RESEARCH PROJECTS 2019
ELIGIBILITY CRITERIA FOR HONOURS

Completion of a Bachelor’s degree in either Science or Biomedical Science.

If you are a BSc student, you need an average of at least 70% in four relevant third year units.

BMS students need an average of at least 70% across BMS3021, BMS3042 and the two highest level 3 electives.

How to apply:

BMS students must enrol directly through the Med Faculty for BMS Hons.

An application form can be found at: http://www.med.monash.edu.au/biomed/honours/

BMS Honours Students must enrol for the following units:
- BMS4100 Biomedical science research project
- BMS4200 Advanced studies in biomedical science.

BSc students enrol through the Science Faculty for BSc Hons.

Application details can be found at: http://www.monash.edu/science/current-students/science-honours

BSc Honours Students must enrol for the following Regenerative medicine units:
- MIS4100 Regenerative medicine research project (36 points)
- MIS4200 Advanced studies in regenerative medicine (12 points).
RESEARCH GROUPS
HEART AND MUSCLE DEVELOPMENT AND REGENERATION

CURRIE GROUP
The Currie group use zebrafish embryos to learn about muscle cell types. In particular, they are interested in how specific muscle cell types are determined within the developing embryo, how they grow and how they regenerate after injury.

Research Themes:
- Dissecting molecular mechanisms that act to pattern the vertebrate embryo
- Discovering how specific muscle cell types are determined within the developing embryo
- Discovering how different muscle cell types have evolved
- Determining how muscle types cells grow and regenerate after injury
- Large-scale mutagenesis of the zebrafish genome to produce different classes of mutations which disrupt gene function.

Currie Lab Honours Projects
Contact
Peter.currie@monash.edu

Project 1
Molecular investigation of cardiac and Hematopoietic Stem Cell (HSC) using zebrafish mutants
Emery-Dreifuss Muscular Dystrophy (EDMD) is a rare genetic disorder characterized by mild but progressive degeneration of specific skeletal muscles and the heart. The cardiac conduction defects and arrhythmias in EDMD patients are the most severe and life-threatening clinical manifestations of this disease. Mutations in six genes, including emerin (EMD), lamin A (LMNA), nesprin1 (SYNE1), nesprin2 (SYNE2), four and half LIM domains 1 (FHL1) and transmembrane protein 43 (TMEM43) are known to cause EDMD. We have generated two mutants (LMNA and Emerin) in zebrafish to investigate the role of these genes during development. We will assess differential gene expression between mutant and wild type fish, as well as perform chromatin accessibility and chromatin modification assays to find potential regulatory regions in the genome that impact on cardiac and HSC defects. Together, these transcriptional and epigenetic data sets will provide insight into the molecular pathways in which LMNA and Emerin function, a finding which has implications for understanding EDMD disease etiology.
Project 2. 
Brief Muscle Project Outline:

It is easy to look at distantly related vertebrates and recognize anatomical variants of the same structure. This observation, however, begs the question “how does anatomical diversity arise over the course of evolution, and can we gain insight into the mechanisms that shape this diversity by studying development?” Here we explore this question in the context of vertebrate appendage evolution, with a particular focus on one of the great transformations of the vertebrate body plan, the fin-to-limb transition. Early in development, the tissue buds that give rise to fins and limbs are remarkably similar, even in vertebrates as distantly related as sharks, ray-finned fish, and mice. However, as development proceeds, these early tissue buds diverge, giving rise to lineage specific variation. The earliest morphogenetic event unique to fin development is folding of the distal ectoderm into an apical fold, which elongates to form a fin-fold. While the relative timing of fin-fold formation has long been posited to have a critical role in fin-limb evolution by modifying the signalling environment of the distal appendage, investigating this role has been hampered by a lack of understanding of the mechanistic basis of distal appendage patterning and ectodermal folding. In our previous work, we identified a novel population of migratory somitic cells that invade the distal ectoderm of fin buds and induce formation of the apical fold. Remarkably, we also found evidence that these “apical fold inducing cells” entered the fin AER earliest and in greatest number in sharks, with a trend towards gradual reduction in ray-finned fish and then lobe-finned fish, broadly reflecting differences in the size of the fin-fold (and dermoskeleton). Together, the discovery of AFIC’s not only provides a tissue-level mechanism for the formation of a fin-specific morphology, but also supports a new mechanistic paradigm for the role of somitic cells in dermoskeleton loss and endoskeleton expansion in the lineage leading to tetrapods. The goal of this project is to explore how AFIC’s arise during development and the genetic basis for their function. This work will inform our understanding of the evolution of fin and limb specific structures, and more broadly, how changes in developmental systems underlie the evolution of morphology.

Project 3. 
Zebrafish models of muscular dystrophy

Muscular dystrophies are inherited diseases of progressive muscle weakness and wasting. Patients with muscular dystrophy are often wheel chair bound from a young age. Currently there are no treatments for these devastating conditions. Here we investigate the mechanisms that lead to disease pathology, using the zebrafish as our model organism of choice. We have projects that focus on diverse areas of interest from stem cells, myotendinous junction formation, wound healing pathways and physiology. We offer an opportunity to study muscle using cutting edge imaging, genetic, physiology and biochemistry techniques. These techniques are used during the early stages of the zebrafish’s ex-utero development to answer fundamental questions about how muscles develop, in order to better understand muscular dystrophy disease progression.

Key Techniques: Confocal Microscopy, CRISPR, Force Measurement, Micro Injection & qPCR.
RESEARCH GROUPS
HEART AND MUSCLE DEVELOPMENT AND REGENERATION

MARCELLE GROUP

The Marcelle Group is interested in understanding how functional skeletal muscle arises from a group of unspecialised mesodermal cells. They do this by studying chick and mouse embryos during the first few days of development. This period is crucial to development because the fate of individual cells are decided, extensive cell migration occurs and tightly regulated cell division takes place.

The focus of the group is to understand the cellular and molecular mechanisms at play during this complex process.

Research Themes:
• Observe the cellular events that take place during muscle formation
• Understand the molecular mechanisms underlying muscle fusion
• Identify gene networks implicated in the maintenance and differentiation of muscle stem cells.

Project Description:
Towards a molecular understanding of the spatial organisation of skeletal muscles
Supervisors: Prof Christophe Marcelle, Dr Olivier Serralbo and Nadège Véron.

The early vertebrate skeletal muscle is a remarkably well-organized tissue. For instance, muscle fibers are all parallel and aligned along the future limb axis, long before any skeletal structure (bones or cartilage) is present. Functionally, this is crucial so that all muscle fibers within a same muscle contract in the same direction. How this is molecularly regulated is unknown.

Some years ago, we uncovered that signalling molecules of the WNT family were implicated in the spatial organization of muscles in the trunk of the chicken embryo (Gros et al. Nature 2009). We want now to understand whether a similar network of genes is at work in limbs. The chicken embryo is particularly well adapted to those studies as it is accessible to observation and manipulation. Moreover many aspects of embryonic development are virtually identical in birds and mammals. This is particularly true in the skeletal muscle system, where this similarity extends to the gene networks, the morphogenic movements, the contribution of stem cells to growth and repair, etc.

The techniques that will be used are the in vivo electroporation of various constructs, in situ hybridization, confocal analyses, etc. We will also take advantage of a transgenic quail facility (unique in the world) that we are developing at Monash to extend the findings to generate a quail transgenic line that will allow observing using real-time imaging the organization of muscle fibers in normal and mutant conditions.
RAMIALISON GROUP

The Ramialison group focuses on applying systems biology (the study of biological components, be it molecules, cells, organisms or entire species) to reconstruct the cardiac gene regulatory networks and to work out not only what leads to proper heart formation, but what are the causes of congenital heart disease. Since gene regulation is as important as gene function itself, investigating this complex process is crucial for understanding normal heart formation as well as congenital heart diseases.

Research Themes:
- Dissecting cardiac gene regulatory networks in healthy and diseased hearts
- Combining ‘wet’ and ‘dry’ lab: Using bioinformatics to decipher the regulatory code of vertebrate heart development
- Investigating the mechanisms of heart development and evolution
- Identifying candidates for human congenital heart diseases
- Role of ubiquitous transcription factor (compensation?) in heart disease

Project Description:
Decoding the heart: Discovering new players during cardiogenesis.

1% of Australian babies are born with Congenital Heart Disease (CHD), manifesting as anatomical heart defects that are detrimental for the newborn. Despite its prevalence, the aetiology of more than 80% of CHD cases remains unknown, making diagnosis and evaluation of the risk of the disease inheritance difficult. Our team has a long-standing interest in identifying the specific gene sets required for the formation of a healthy heart based on the principle that perturbations in these genes will impair normal development, resulting in anatomical cardiac defects. Thousands of genes are expressed in the heart at any given time point during development, but which of these genes are critical for heart formation and play a significant role in CHD? To address this, we designed bioinformatic pipelines to identify novel players in three layers of the cardiac gene regulatory network (transcription factors, downstream effectors and cis-regulatory modules). The Honours project will consist in investigating the function of novel genes and regulatory elements during heart development using a combination of wet-lab (zebrafish model organism) and dry-lab (computational biology) technologies.
RESEARCH GROUPS
HEART AND MUSCLE DEVELOPMENT AND REGENERATION

MCGLINN GROUP

The McGlinn Group is particularly interested in critical developmental regulators, the Hox genes, and how microRNAs shape Hox functional output during formation of the vertebral column and spinal cord.

They use elegant mouse genetics coupled with cutting edge functional genomics technologies to unravel novel gene networks and mechanisms of regulation.

Research Themes:
- microRNA control of Hox gene networks
- Genomic/epigenomic regulation of axis elongation and vertebral patterning
- Formation and patterning of spinal cord circuitry
- Evolutionary acquisition of microRNAs shapes developmental networks

Project Descriptions:
Revealing new players in the networks driving vertebral column formation
The developmental modules that control total vertebral number and those that control vertebral shape have largely been considered as separate. Our work has shown the importance of the miR-196 family of microRNAs in integrating these developmental modules. We complement high level mouse genetics (fluorescent knock-ins, straight knockouts) with more high throughput analyses afforded in zebrafish, to build the gene networks driving this process. This project will focus on a number of novel miR-196 target genes we have identified, to understand how they regulate key developmental signals during formations of the vertebral column and thus may contribute to congenital malformation.

Key techniques: Mouse genetics, zebrafish experimentation, in situ hybridisation, immunofluorescence, microRNA-target analyses.

A novel function for Hox gene networks in establishing spinocerebellar circuitry
In the spinal cord, Hox genes have been shown to direct correct topographic connectivity of motor neurons, though there is little appreciation for their role in wider neural networks. The McGlinn Lab has recently uncovered a novel role for Hox gene regulatory networks in spinocerebellar neurons. These neurons project from the spinal cord all the way to the cerebellum, relaying information regarding the relative positioning of body components such as the limbs as well as the sense of effort and force associated with movement (proprioception). In this project, we will use our extensive series of novel mouse fluorescent reports lines to investigate the genes expressed in these neurons as they arise developmentally, and how they establish correct topographic connectivity.

Key techniques: Mouse genetics, histology, immunofluorescence, FACS, transcriptomics.
LIESCHKE GROUP
The Lieschke group studies the haemopoietic system and leukocytes. The haemopoietic system is a collection of organs and tissues (bone marrow, spleen, lymph nodes etc.) responsible for the production of blood in the body.

Leukocytes (white blood cells) are the keys cells involved for counteracting foreign substances and disease. They also play a major role in determining whether tissue repairs and regenerates rather than scars after injury.

Using the zebrafish as a model organism, the Lieschke group study blood cell development and function. They also look at mutant zebrafish with faulty blood cell development to find insights into the genes that regulate the haemopoietic system. Mutant zebrafish also assist with understanding the role of leukocytes in inflammation and healing. This information is used to create infection models that stimulate leukocytes in action, which helps the group investigate the host-pathogen response.

Research Themes:
• Discovery of genes critical for white blood cell development
• How the inflammatory response is regulated
• How modulating the inflammatory white blood cells might tip the outcome to favour regeneration rather than scarring
• Investigating how white blood cells keep out and contain micro-organisms.

MARTINO GROUP
The Martino group is focused on combining knowledge of immunology, stem cells, and bioengineering, to understand how the immune system modulates tissue repair and regeneration. By leveraging discoveries from the lab, the group aims to engineer effective strategies for repairing and ideally regenerating damaged tissues.

To make regenerative therapies a more widespread reality, we must better understand the interactions between the multiple actors that shape a regenerative microenvironment. In particular, tissue injury is generally associated with the activation of our immune system, which is a key regulator of the healing response. For example, excessive inflammation often leads to scarring/fibrosis and loss of functions. In addition, our immune system most likely affects the regenerative capacities of transplanted stem cells and pro-regenerative molecules such as growth factors.

The primary goal of the group is to reveal mechanisms by which the immune system modulates tissue repair and regeneration, by using genetically modified and chimeric mice. Several types of tissues, including bone, muscle, and skin are used as models.

Ultimately, the group aims to engineer efficient regenerative medicine strategies that integrate a control of the host immune system.

Research Themes:
• Dissecting how the innate immune system affects tissue-resident/transplanted stem cells and growth factors activities.
• Understanding the immune modulations of stem cells and regeneration by T lymphocytes.
• Developing effective systems for delivering stem cells and cytokines/growth factors, using biomaterials and protein engineering.

Project Descriptions:
ENGINEERING OF AT CELL-RECRUITING HYDROGEL TO PROMOTE TISSUE REGENERATION

Background: While tremendous progress has been made in understanding the cellular and molecular mechanisms of tissue repair and regeneration, it remains unexplained why mammals have a tendency for imperfect healing and scarring rather than regeneration. There is ample evidence in different model organisms that the immune system is crucial to determine the quality of the healing response, including the extent of scarring, and the restoration of organ structure and function. A wide spread idea deriving from findings in diverse species supports a correlation between the loss of regeneration capacity and maturation of immune competence.

Usually, an immune response directly follows tissue injury. The first phase of the immune response involves components of the innate immune system, which provide defence against potential pathogens invading the damaged tissue. Even in the absence of pathogens, the body responds to tissue injury with a so-called “sterile inflammation”. The innate immune response is then followed by the activation of the adaptive immune system, which was originally thought of as being secondary actors in the healing process. However, the adaptive immune response to tissue injury – in particular the activity of T lymphocytes (T cells) – most likely plays a critical role during tissue repair and regeneration.

Project and output: The goal of this project is to engineer a biomaterial hydrogel (based on fibrin) with molecules (e.g. cytokines) able to induce regeneration by mobilizing pro-regenerative T cells at a site of tissue injury. Using molecular cloning and rational protein engineering methods, cytokines will be engineered and recombinantly produced, in order to be incorporated into the hydrogel. Then, the ability of the newly created hydrogel to recruit T cells will be assessed in vitro and in vivo. Ultimately, the hydrogel system will be tested in mouse models of tissue regeneration such as skin, bone, and muscle defects. The output of this project will be integrated into a larger project aiming at reprogramming to immune system (immunoengineering) to stimulate tissue regeneration. This type of approach has the potential of being the next generation of regenerative therapies and this Honours project could evolve into a PhD project.

Contact: mikael.martino@monash.edu

Hypothesis

<table>
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<tr>
<th>TISSUE INJURY</th>
<th>Adaptive immune response:</th>
<th>Secreted factors</th>
<th>REGENERATION</th>
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<tr>
<td></td>
<td>“antiregenerative” T cells</td>
<td>Stem cells</td>
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<td></td>
<td>“proregenerative” T cells</td>
<td>Special Treg ?</td>
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Current regenerative strategies

Uncontrolled immune system → Low efficacy...

Novel hydrogel platform controlling T cells

Integrate a control of the pro/antiregenerative T cells → Immune system controlled

References:
ENGINEERING EFFICIENT AND SAFE MORPHOGENS FOR REGENERATIVE MEDICINE

Background: Morphogens such as growth factors and cytokines are key molecules involved in tissue repair and regeneration. They stimulate key cellular processes such as stem cell mobilization, proliferation, and differentiation. Therefore, they have an enormous potential in regenerative medicine. However, their translation to clinical use has been very modest. Although few growth factors and cytokines have entered clinical practice, they are used at enormous doses and with regulatory warning of cancer risk and other side effects. These issues are likely associated with high dosing and the lack of appropriate delivery systems. Other promising growth factors have unfortunately failed in the clinic, such as vascular endothelial growth factor in chronic wounds and transforming growth factor β3 in prevention of dermal scars.

Project and output: The objective of this project is to develop a new generation of growth factor and cytokine variants that are effective and safer for patients. The approach is to engineer growth factors to provide them a very strong binding affinity to endogenous extracellular matrix (ECM) molecules, which surround cells in tissues. Thus, we can use the native tissues as a delivery system for morphogen immobilization and presentation. In this work, the targets are chronic wound repair, dermal scar prevention, bone regeneration and eventually myocardial preservation and repair following infarction. First, we will use rational protein engineering, molecular cloning, and recombinant protein methods to design and produce fusion proteins between morphogens and ECM-binding domains. Then, we will test the ability of the engineered morphogens to bind ECM proteins and the native tissues where the growth factors are delivered. Finally, we will evaluate the regenerative efficacy of the engineered morphogens in mouse models of wound repair, bone regeneration and eventually myocardial preservation. This Honours project has the potential to evolve into a PhD project.

Contact: mikael.martino@monash.edu

References:

Clinical need

- Damaged tissue
  - Liver
  - Heart
  - Skin
  - Bones
  - Joints

Mechanisms of tissue repair/regeneration

- “Building blocks”
  - Stem cells
  - Progenitor cells, ...

- Extracellular matrix
  - Stiffness
  - Remodeling, ...

- Immune regulations
  - Cytokines
  - Immune cells, ...

Regenerative medicine strategy

- Stem cells
- Biomaterials
- Growth factors
- Tissue constructs, ...

Clinical translation

- Tissue regeneration

*Adv Wound Care (New Rochelle)*
UNDERSTANDING THE ROLE OF THE NEURO-IMMUNE AXIS DURING TISSUE REGENERATION

Background: Neurotransmitters propagate essential information that regulates the intensity of the host response to infection and tissue damage1. For instance, the so-called “inflammatory reflex” is a neural circuit that regulates the immune response to both tissue injury and infection. This reflex has a sensory afferent arc, which is activated by cytokines such as IL-1, and an efferent arc in the vagus nerve that leads to the release of neurotransmitters such as acetylcholine (ACh), which dampen the secretion of inflammatory cytokines from immune cells. Because tissue repair and regeneration is in part regulated by the immune system, the nervous system – in particular the inflammatory reflex – could regulate tissue regeneration via its immunomodulatory activity. Indeed, while the mechanisms have not been revealed yet, it has been shown that regeneration of some mammalian tissues greatly depends on nerves2,3. In this project, we hypothesize that the release of neurotransmitters by nociceptive sensory neurons can promote a regenerative microenvironment. Moreover, neurotransmitters could directly control the regenerative function of tissue-resident or transplanted stem cells.

Project and methods: The primary goal of this project is to determine to which extent sensory neurons modulate regeneration of bone skin and/or cardiac tissues. Ultimately, we seek to design regenerative strategies integrating neurotransmitters. The main experimental model will be the following: Sensory neurons in mice will be ablated using a mouse genetic model (NaV1.8cre/DTA mouse)4,5. Then, tissue defects (bone defects, skin wounds, and/or cardiac defects) created in these mice will be treated with or without adult stem cells delivered within a hydrogel (such as fibrin). The analysis of the healing process using microCT for bone and histology for skin and cardiac tissues will reveal to which extent sensory neurons influence regeneration. Finally, we will test the regenerative capacity of nociceptive neurotransmitters (ACh, substance P, calcitonin gene related peptide, etc.) delivered alone or in combination with stem cells in bone defects and skin wounds and/or cardiac defects. This Honours project could evolve into a PhD project.

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The neuroimmune-regenerative axis hypothesis

Control of the neuro-immune axis

Co-delivery of neurotransmitter(s) with stem/progenitor cells or growth factors

References

POLO GROUP

The Polo group is interested in the transcriptional and epigenetic mechanisms that govern cell identity and cell fate. It has a particular focus on pluripotency and the reprogramming of somatic cells into induced pluripotent stem (iPS) cells and other mature cell types.

Being able to reprogram any specific mature cell into a pluripotent state and then back into any other particular cell gives the group a unique tool to study the molecular and cellular events that permit the conversion of one cell type to another.

Moreover, iPS cells and the reprogramming technology are of great interest in pharmaceutical and clinical settings, since the technology can be used to generate animal and cellular models for the study of various diseases as well as provide (in the future) specific patient tailor made cells for their use in cellular replacement therapies.

The Polo group are dissecting the nature and dynamics of the process using a broad array of approaches through the use of mouse models and a combination of different molecular, biochemical, cellular techniques and genome-wide studies.

Research Themes:

- The kinetics and universality of the epigenetic and genomic changes occurring during reprogramming
- The composition and assembly kinetics of transcriptional regulation complexes at pluripotency genes
- How the cell of origin influences the in vitro and in vivo plasticity potential of cells generated during the reprogramming process
- The epigenetics changes occurring in adult stem cells as a consequence of changes in their environment.

NILSSON GROUP

The Nilsson Group is currently involved in a number of research projects that focus on understanding haemopoietic stem cells (HSC). Haemopoietic stem cells are responsible for the production of blood and immune cells.

They are a very important part of the body as they are constantly renewing blood. They create billions of new blood cells each day. They are located in the bone marrow, which is the flexible tissue inside most bones.

The main objective of the group’s research is to characterise the microenvironment in which blood stem cells reside. They also look at blood stems cells at a cellular and molecular level, as well as analysing how they create new blood cells.

Learning more about normal and diseased stem cells will lead to better prevention, clinical diagnosis and treatment. This will ultimately improve human health. An example of this is better bone marrow transplantation outcomes in cancer patients.

Research Themes:

- Understanding the role of the endosteal niche in the regulation and function of haemopoietic stem cells
- Characterising the role of megakaryocytes in the endosteal niche and haemopoietic stem cell regulation
- Isolating bone marrow sinusoidal endothelial cells and characterising their role and potential
- Understanding the role of key extracellular matrix molecules in the adult bone marrow microenvironment in foetal haemopoietic development
- Understanding the role of regulatory T cells in the bone marrow
- Design and synthesis of novel haemopoietic stem cell mobilisation agents
- Characterising adult cells that have been directly differentiated into hemopoietic stem cells.
- Functionally assessing embryonic stem cell subpopulations whose differentiation has been directed towards hemopoietic stem cells.
LASLETT GROUP
The Laslett group investigate the biology of human pluripotent stem cell lines, including embryonic stem cells (hESC) and human iPS cells. Collectively they are known as human pluripotent stem cells (hPSCs) and have the ability of indefinite self-renewal and to differentiate into all types of human adult cells.

Further comprehension of human pluripotent stem cell lines will lead to the development of tools and novel cell lines that will be required for the safe use of these cell types in future cell-based industries.

This is important because although there is a huge potential for the treatment of diseases and injuries, it also creates a number of risks when producing cell populations to be used for cell therapy.

Research Themes:
• The production and characterisation of monoclonal antibodies that detect live human pluripotent stem cells
• Functional uses for monoclonal antibodies that detect live human pluripotent stem cells
• The development of “disease in a dish” models using human induced pluripotent stem cells
• Investigation of culture substrates for the maintenance and differentiation of human pluripotent stem cells.
HOBBS GROUP

Adult stem cells are found in living organisms. They are undifferentiated cells found throughout the body after development. Their main role is to maintain and repair the tissue in which they are located by a process of cell division to replenish dying cells. Discovering the mechanisms behind this will provide invaluable information to medical science.

The primary research aim of the Hobbs group is to identify and define the critical molecular mechanism underlying adult stem cells by using germline stem cells from the mouse testis as a model system.

The Hobbs group aims to uncover the self-renewal capabilities of adult stem cells, which will have importance to the fields of fertility, tissue regeneration and cancer.

Research Themes:

- Identify and characterise novel molecular mechanisms underlying adult stem cell function using germline stem/progenitor cells from the mouse testis as a model system
- Define downstream targets of Plzf in SPCs and their role in SPC function, which is achieved using a combination of mouse genetics, flow cytometry analysis and in vitro SPC culture techniques.

Project Description:

Transcriptional networks controlling germline stem cell fate

Supervisors: Dr Robin Hobbs, Dr Ai-Leen Chan, Dr Julien Legrand

Maintenance of an array of adult tissues is dependent on a resident population of stem cells that self-renews plus generates differentiating cells. Regulation of stem cell self-renewal and differentiation is critical for tissue homeostasis and disruption of the balance between these processes can contribute to tissue degeneration or cancer.

In adult testis, there is a pool of germline stem cells (spermatogonial stem cells; SSCs) that are required for life-long production of spermatozoa and fertility. SSC maintenance is critically dependent on crosstalk between cell-intrinsic factors and growth factors produced from a specialized stem cell niche within the testis. We have identified key transcription factors and growth factor signalling pathways involved in self-renewal versus differentiation decisions of SSCs. Through use of mouse models carrying targeted deletions in these factors, we aim to define central pathways required for stem cell self-renewal.

The project will focus on characterizing mechanisms regulating SSC function with particular emphasis on components of key transcription factor networks and their downstream targets. This work will involve use of mouse models, isolation and in vitro culture of SSCs, flow cytometry and cell/molecular biological techniques. These studies can have particular relevance to the stem cell and fertility fields.

NAGY GROUP

The Nagy lab is focused on combining knowledge of developmental biology, stem cells, immunology and genetic engineering to create successful therapeutics for regenerative medicine applications. Our research program aims to tackle several major challenges facing the translation of cell therapies to the clinic, such as eliminating risks of tumorigenesis and allograft rejection, and improving the effectiveness of therapeutic cells. Towards these goals, we are establishing underlying technologies to engineer “designer cells” with important novel functions and validating these in pre-clinical animal models.

Research Themes:

- Transferring and establishing our patented safety and immune “cloaking” technologies in non-human primate pluripotent stem cells
- Developing protocols to differentiate pluripotent stem cells into therapeutic cell types
- Combining cell and gene therapy to target key cytokines involved in central nervous system autoimmunity
- Functional validation of cells engineered with our immune “cloaking” system
- Testing designer cells in pre-clinical models of stroke and multiple sclerosis
Project description:
Immune-cloaking to prevent rejection of allogeneic cell products

Supervisors: Dr Natalie Payne, Prof Andras Nagy

Immune rejection of cells from a different genetic background remains a critical barrier for cell therapies. This is because the immune system has evolved a complex set of mechanisms to recognise and eliminate “non-self” cells that express specific protein fragments that differ between donor and recipient. The current solution to preventing allograft rejection is treatment with broadly-directed immunosuppressant drugs, which act systemically and ultimately leave patients immunocompromised.

To overcome this issue and allow the development of universal cells for therapeutic applications, we have identified a set of eight immune-modulating genes involved in allograft tolerance and rejection. Expression of these immune-cloaking transgenes in mouse embryonic stem cells (mESCs) allows the development and long-term survival of subcutaneous teratomas in major histocompatibility complex-mismatched recipients.

This project will focus on characterising the interaction between immune-cloaked mESCs and innate and adaptive immune cells using in vitro assays and a pre-clinical mouse model of multiple sclerosis.

ZENKER GROUP

Microtubules are highly dynamic cytoskeletal filaments regulating fundamental processes including cell division, migration and differentiation. The Zenker group seeks to understand how a cell’s structure and function is regulated by the continuous re-organization of the microtubule network. Live imaging is used to discover the spatio-temporal accuracy of the microtubule dynamics in animal models of developmental and stem cell biology.

Research Theme
• Unravelling microtubule dynamics at the single cell level using live imaging.
BOURNE GROUP

The Bourne group have garnered an international reputation for being at the forefront of visual neuroscience with a particular emphasis on development, plasticity and repair following injury.

The cerebral cortex of an adult is an intricate system of interconnected areas. How these areas emerge seamlessly and establish connections with other parts of the brain has yet to be determined.

The main focus of the group is to study the development and maturation of the cerebral cortex in primates and other mammals.

The group explore, at a cellular and system level, how the brain processes the environment, which is rich with visual information.

This approach provides the team with insights into how the primate visual cortex has evolved to possess multiple functionally unique areas, each with clearly defined boundaries.

Further understanding of visual system neurobiology will result in not only understanding how visual function works in a normal brain, but also in the repair and functional recovery of adult brains following an injury like stroke.

Research Themes:

- The development and maturation of the cerebral cortex of primates and other mammals, with a focus towards the visual cortex, which is responsible for visual perception and visual guidance of behaviour
- Clarifying the functional bases of disturbances of visual perception that emerge as a consequence of perinatal lesions
- How the mechanism of neuroplasticity could aid in brain injury rehabilitation
- Using cultures of cells and organ tissues in situ hybridisation and RNA expression profiling.

Project Description:

**Investigating the role of the pulvinar in schizophrenia**

The cognitive and behavioural symptoms associated with the neurodevelopmental disorder schizophrenia (SZ) suggest that a deficiency in processing and interpreting the sensory information, triggering maladaptive response. To date, most of the research has focused on analysing the structure and cell composition of the areas in the neocortex responsible for integrating and computing the flow of information. However, there is little knowledge regarding the structures in the thalamus relaying the information from one area to the other. The medial pulvinar (PM) is densely connected with sensory neocortical areas and cognitive regions located in the prefrontal cortex, playing a pivotal role in the processing streams affected in SZ. MRI and anatomical studies have in particular demonstrated a significant reduction of the volume and total neurone population in PM. In addition, research from our laboratory demonstrates that the pulvinar modulates the development and maturation of the neocortical areas it is connected with. Therefore, abnormal development of PM could result impair the formation of the neocortical regions traditionally implicated in SZ. Using our primate model, as both the pulvinar and dorsolateral prefrontal cortex are absent in rodents, we will use a combination of tracer injection, MRI and specific lesions to characterise the temporal sequence in which the PM connectivity is established and the consequences of abnormal PM development on the target neocortical areas, from a behavioural and anatomical perspective. This project will contribute to demonstrate the role of the pulvinar in SZ and elucidate the prolonged time course of SZ and the late onset of the symptoms.
The Kaslin group is interested in cellular plasticity. This refers to the ability of cells to take on characteristics of other cells in the body. But rather than study the process throughout the entire body, the group are focused in understanding the molecular and cellular mechanisms that control this process in the intact or injured vertebrate brain.

In the past, neural stem cells and brain regeneration has mostly been studied in vertebrates (such as rodents). The problem with this is that these vertebrates have very limited regenerated potential.

Enter the zebrafish. This fish is able to regenerate parts of their central nervous system, even in adults. Using the zebrafish model is therefore much more advantageous to research as it can answer questions that previously could not be answered.

Understanding the process of cellular plasticity is essential to the development of successful therapies to promote neural regeneration.

Research Themes:

- Understanding the molecular and cellular mechanisms that control cellular plasticity in the intact and injured vertebrate brain
- How neuronal stem cell niches arise and are being maintained, using high-resolution in vivo imaging, novel genetic tools and cellular reprogramming
- Using high-throughput methods to get a comprehensive understanding of the genetic networks that regulate cellular plasticity during homeostasis and regeneration.

Project Descriptions:

Developmental origin and role of adult stem cells in neural regeneration in the zebrafish brain

Stem cells are the basic building blocks of all organisms. Organ development and growth relies directly on stem cells to create a final functional structure, while stem cells in adulthood are needed for tissue maintenance and as a possible source of repair. In the last 25 years, the discovery that adult neural stem cells persist in the vertebrate brain has opened up new areas of research aimed at understanding their cellular and molecular signatures, and function under homeostasis and repair. A fundamental question that remains however is, what is the developmental origin of adult neural stem cells and their accompanying cellular and molecular properties. To address this question, we will make use of the zebrafish model, well known for its heterogeneous populations of brain stem cells throughout life and unique regenerative properties. Our lab has played a key role in identifying a number of adult neural stem cell phenotypes throughout neurogenic compartments of the adult zebrafish brain, however we hypothesize that these cells may originate from different early developmental time points and/or cell populations. Therefore, to uncover the origin, lineage, and role of adult neural stem cells we will use genetic lineage tracing, live in vivo confocal imaging, confocal imaging of sectioned juvenile and adult brain tissue, cell-cycle label retention assays, immunohistochemistry, in situ hybridization, and advanced image analysis and quantification.

Defining pro-regenerative factors that drive spinal cord regeneration

Immune cells acutely provide critical inflammatory signals that are required to restrict damage and initiate recovery after tissue injury. However, over-activation and/or the sustained presence of these signals produces the opposite effect, resulting in secondary cell death, chronic inflammation and scarring. Carefully balancing the inflammatory response is therefore essential and a critical part of successful regeneration. We have established that induced inflammation improves neural regeneration and that immune suppression blocks neural regeneration in the zebrafish spinal cord. Furthermore, leukocytes are the source for the pro-regenerative signals and leukocyte resolution overlaps with the completion of the regenerative process. RNA-seq gene expression analysis identified a number of key candidate pathways that promote neural regeneration. We hypothesize that immune cells secrete factors that orchestrate neural regeneration by acutely initiating the pro-regenerative programme and later resolving inflammation. To molecularly and celluly define the role and function of pro-regenerative signalling factors involved in spinal cord regeneration we will use transgenic reporter lines (neutrophils, macrophages/microglia, neurons and glia), CRISPR/Cas9 technology, in vivo imaging and pharmacological antagonist and agonists.
MERSON GROUP

The Merson Group investigates the life cycle of myelinating glial cells in the nervous system, in particular how they are generated during development, how they are regenerated after injury and their role in supporting the function of axons. A key long-term goal of our research is to develop novel therapies for the effective treatment of patients with multiple sclerosis and other demyelinating conditions. Dr Merson is offering several Honours projects in 2019.

Project 1: Assessing the evidence for an oligodendrocyte stem cell population in the adult brain

Oligodendrocyte progenitor cells (OPCs) are an abundant proliferative cell population in the vertebrate central nervous system (CNS). These cells are required not only for the generation of myelin-forming oligodendrocytes during early postnatal development but are also retained in the adult brain where they play key role in both de novo myelination and myelin regeneration following demyelinating injury. Experiments involving long-term administration of thymidine analogues to label dividing cells in adult mice have suggested that most, if not all OPCs exhibit proliferative capacity under normal physiological conditions. However, it remains unclear whether OPCs are homogeneous with respect to their proliferative capacity, or alternatively, whether they exist as a heterogeneous population comprised of cells with diverse proliferative activities akin to most other somatic stem and progenitor cell populations. In this project, the student will utilise a range of sophisticated in vivo genetic labelling techniques to test the hypothesis that OPCs arise from a restricted number of unipotent oligodendroglial-committed stem cells.

HYPOTHESIS: OL stem cells generate OPCs that function as rapidly-dividing transit amplifying cells that exhibit the capacity to self-renew and to differentiate into myelinating OLs.

AIMS:
1. Perform genetic fate-mapping of adult OPCs in a Brainbow reporter mouse to define the number and size of stable OPC clones
2. Perform long-term in vivo EdU labelling to determine the phenotype and localisation of non-EdU incorporating PdgfRa+ OPCs
3. Perform in vivo genetic labelling to identify long-term label-retaining PdgfRa+ cells within the CNS and define their phenotype and localisation

TECHNIQUES: Drug administration to mice, perfusion/fixation of mice, immunohistochemistry (intact brain whole mount and slide-mounted sections), confocal and light sheet microscopy.
Project 2: Examining myelin sheath turnover in mature oligodendrocytes

The generation of myelin, the fatty insulating membrane that ensheaths the axons of neurons in the central nervous system, is critical for rapid electrical conduction and optimal function of neural networks in vertebrate species. Emerging evidence suggests that myelin is constantly remodelled throughout life and that this remodelling forms an important mechanism of neural plasticity. A study in mice revealed that 29% of myelin-forming oligodendrocytes in the mouse corpus callosum were generated from postnatal day (P) 45 to 255 (Rivers et al., 2008) and in another study 30% of the oligodendrocytes in the mouse corpus callosum were generated between P60 and P120 (Zhu et al., 2011). Blocking the ability of mice to generate new oligodendrocytes has been demonstrated to impair their ability to learn complex motor task. Thus, at least in rodents, the production of new oligodendrocytes appears to be an important mechanism by which myelin is remodelled. In humans however, it is believed that the mechanism by which myelin is remodelled could be somewhat different. MRI studies indicate that individuals learning complex motor or cognitive tasks such as juggling or piano playing exhibit progressive increases in measures of fractional anisotropy within the white matter tracts associated with these tasks. Whilst there is evidence for the production of new myelin over time in the adult human brain, the degree of de novo oligodendrocyte production does not appear to be sufficient to account for these changes.

HYPOTHESIS: The production of new myelin internodes from existing mature oligodendrocytes is an alternate mechanism by which new myelin can be generated in the mature CNS.

AIMS:
1. Develop a novel genetic labelling approach to measure the birth date of individual myelinated segments of oligodendrocytes in mice. Adeno-associated virus encoding the myelin reporter will be administered to adult mice to map pre-existing and newly-generated myelin internodes that are produced during normal adult life.
2. Examined myelin remodelling in mice tasked with performing specific learning tasks to establish whether de novo myelin internode formation is activity-dependent and responsive to physiological demands.

TECHNIQUES: Molecular cloning, cell culture, mouse experiments, immunohistochemistry (intact brain whole mount and slide-mounted sections), confocal and light sheet microscopy.
RESEARCH GROUPS
ORGAN ENGINEERING AND SYNTHETIC BIOLOGY

JANOVJAK GROUP

The Janovjak group pioneers research in the emerging field of synthetic physiology, which lies at the interface of synthetic biology and mammalian physiology. The group has established new methods to ‘remote control’ essential cellular functions, such as cell growth and differentiation, with unprecedented precision, e.g. down to single cells or single stages during animal development and disease. These methods repurpose light, e.g. in optogenetics, as a synthetic ‘switch’ to understand and restore tissues affected by degeneration with a focus on Type I diabetes and Parkinson’s disease. The group’s research is interdisciplinary as it combines genetic and protein engineering with disease models in the mouse and the fruit fly. For more information about their research, please also visit the Janovjak Group website: www.janovjak-lab.com.

Research Themes:
• Engineering new genes and proteins for synthetic biology
• Deciphering the function and physiology of orphan receptors
• Controlling cell proliferation and survival in models of degenerative disorders

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RESEARCH GROUPS
ORGAN ENGINEERING AND SYNTHETIC BIOLOGY

Project Descriptions:

A first photochromic regulator of stem cell differentiation
Stem cells are pluripotent cells that can be differentiated into many different cell types and that harbour enormous technological and medical potential. The overall goal of this project is to establish a new approach to regulate stem cell differentiation using light as a synthetic signal. The group has recently developed a chemical molecule that acts as a potent differentiating agent of human stem cells but that, unlike any other known agent, can be reversibly (in-)activated by light. The specific aims of this project are to characterize this first photochromic regulator of stem cell differentiation and to apply it towards novel cell state and cell fate experiments.

Key techniques: Optogenetics, spectroscopy, cell culture, imaging, chemical biology

Pioneering synthetic neurobiology at the pre-synapse
The synapse is one of the most intricate biological structures and essential for nervous system function. Recent work in synthetic neurobiology has focused on manipulating synaptic signal transmission, e.g. using ‘designer receptors’ that were always targeted to the post-synaptic side. The overall goal of this project is to manipulate synaptic communication by modulating pre-synaptic terminals and synaptic vesicles. The group has recently identified a set of genes that are candidates to alter the neurotransmitter contents of synaptic vesicles by introducing ‘false’ neurotransmitters. The specific aims of this project are to characterize these genes in neuronal cell models and evaluate their potential as novel tools for manipulating synaptic communication and animal behaviour.

Key techniques: Cell culture, virus production, protein engineering, neurotransmitter assays

Embedded E. coli systems activated by light and sound
Synthetic biology research has in recent years focused on creating ‘designer’ cells that respond to artificial light and sound signals. These systems are promising for a range of technological and medical applications that would require ‘packing’ them into deliverable formats (e.g. in hydrogels or matrices). The overall goal of this project is to functionally embed prototypical light- and sound-activated cells in two-dimensional and three-dimensional artificial environments. The specific aims of this project are to engineer light- and sound-responsive model cells and to test their functionality in gel matrices.

Key techniques: Cell culture, imaging, protein engineering, electrical engineering
The Roselló-Díez group studies the signals that operate within the bones and between them and other tissues/organs during development and regeneration. At the local level, they study phenomena such as compensatory proliferation in response to biochemical and mechanical changes in the cell vicinity. At the systemic level, they are exploring the role of the vascular and nervous systems in the bidirectional communication between the bones and the rest of the body.

### Research Themes

**Characterising the local cell-autonomous and nonautonomous responses to an injury, including the production and role of alarm signal(s) and the response of stem/progenitor cells**

**Dissecting the inter-organ communication mechanisms that lead to systemic growth effects upon local injury, with a focus on the role of the vascular and nervous systems**

**Exploring the impact of the discovered injury response pathways on the buffering of developmental noise (random perturbations during normal development)**

**Exploiting the discovered injury response pathways for the treatment of animal models of dwarfism and fracture repair**

### Project Descriptions

#### Project 1: Cell-cell interactions during arrest-induced adaptive growth of the long bones

**Rosello-Diez lab – Project 1**

http://www.armi.org.au/research-leadership/rosello-diez-group

The compensation of developmental perturbations is paramount to achieve correct body proportions. In the Rosello-Diez lab we have developed mouse genetic models with which we can alter growth of the long bones in the embryonic limb and study the potential compensatory response. Using this strategy, we recently showed that misexpressing the cell cycle suppressor p21 in half of the chondrocytes that compose the growth plate (the cartilage region that drives bone growth) does not lead to a major growth defect, due to compensatory proliferation by the spared neighbour chondrocytes. We will test two potential scenarios: 1) The compensatory response is mediated by short-range interactions/diffusible signals and thus is only triggered in the **proximity** of the cells being insulted; 2) The response is a **community** effect that happens at the level of the whole growth plate, and is due to a travelling wave that self-propagates from the insulted cells. The student will culture mesenchymal limb cells from our genetic models in chondrogenic conditions, and live-image them using a fluorescent cell cycle reporter to assess proliferation in real time. Two main experiments will be performed: 1) Cells from control and experimental limbs will be combined in different proportions to determine ratio of mutant:WT cells that triggers compensatory proliferation; 2) p21 will be locally induced in regions of variable size, and proliferation assessed at short and long distances from p21 domains.

**Key techniques:** cell culture, live imaging, embryo dissection

#### Project 2: Characterising catch-up growth after signalling imbalance in the developing bones

http://www.armi.org.au/research-leadership/rosello-diez-group

The extracellular matrix-associated Connective Tissue Growth Factor (CTGF) is considered a double-edged sword during organ development and repair, as it can promote organ fibrosis and scarring but also wound healing. The developing bones produce CTGF, but its role during normal development and repair is not completely understood. In the Rosello-Diez lab we have developed mouse genetic models with which we can misexpress the gene of interest in the left -limb skeletal elements, such that the right limb remains as an internal control. Using this strategy, we have observed that misexpression of Ctgf in one third of the cells that compose the cartilage (chondrocytes) leads to a very severe bone shortening, with almost complete disappearance of one of the regions of the growing cartilage. Interestingly, the phenotype is transient, such that the cartilage eventually recovers its normal architecture and growth resumes. In this project, the student will perform histological analysis (immunohistochemistry, in situ hybridization, etc), skeletal preparations and dynamic histomorphometry to characterise the catch-up growth response at different time points. We will also express Ctgf from different tissues to distinguish between bone-intrinsic and -extrinsic effect of Ctgf. The elucidation of the complex roles of this growth factor, and the mechanisms underlying catch-up growth could have far-reaching implications in regenerative medicine.

**Key techniques:** mouse handling, embryo dissection, histology, (section and staining)
Further information

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