

Monash Immunology and Stem Cell Laboratories

Honours and Postgraduate Projects for 2008

You will find below an outline of some of the projects that are currently being undertaken by MISCL in collaboration with colleagues in the University, nationally and internationally. The list is by no means exhaustive and is continually changing as new projects and collaborations come on line in this active and dynamic research department. You are advised to contact Group leaders directly in project areas that you may have an interest in if you wish to discuss their research interests further.

Immune-Reconstitution Laboratory

Rebuilding Immunity for Better Health

Group Leader: [Dr Richard Boyd](#)

Phone: 99050630; **Mobile:** 0419 317 533

Co-supervisor: [Dr Ann Chidgey](#)

Phone: 9905 0628

Laboratory website: [Immunology - stem cells - tolerance and thymic function](#)

The development and maintenance of the central cells of the immune system – T and B lymphocytes is critically dependent on the structural integrity of the thymus and bone marrow respectively. Failures in these processes are highly predictive of the development of a wide range of life threatening diseases including immunodeficiency, cancer and autoimmunity. The ability to manipulate the cellular contents and genetic make-up through gene therapy of stem cells of these organs, particularly the thymus, also provides a powerful means of approaching the clinical management of conditions such as bone marrow transplantation (haematopoietic stem cells; HSC) and organ transplantation, allergies, asthma, and severe infections including AIDS. In addition, the identification of epithelial stem cells which give rise to the specific stromal cells forming the microenvironment of the thymus, in which the haematopoietic stem cells undergo precisely programmed development into T cells, would provide a means of overcoming disease states in which the thymus fails to develop or in which the regulatory factors are of the incorrect type or proportion. The ability to regenerate the thymus represents one of the major challenges of modern medicine.

This laboratory has focused for many years on the cellular and molecular basis to thymus development and function and hence the production of T lymphocytes and their incorporation into the peripheral T cell pool. Recently we have identified a population of thymic epithelial cell progenitor cells which, when transferred into an athymic host, can form into a complete thymus organ. We have also shown that the thymus degeneration that occurs with age can be profoundly reversed by blocking the normally suppressive influence of sex steroids. Clinically, this can be achieved using a common hormone therapy to temporarily block production of testosterone or oestrogen. We currently have clinical trials in leukaemia /lymphoma patients in Melbourne who have undergone chemotherapy and bone marrow transplantation (HSC transplantation). These will be extended to major clinics in the US and UK . We are also undertaking vaccination trials in cancer patients in the US with trials in AIDS patients planned for Switzerland – all designed to rebuild the immune system. The next horizons will be other cancer patients receiving chemotherapy, tolerance to transplantation, and treatment of autoimmune

disease. Importantly, all of these new trials require thorough pre-clinical investigation as part of the laboratory research program.

In our research, we utilise an extensive range of the most recent materials and technologies and have an impressive national and international collaborative network. The laboratory has a long history of excellent Honours, MSc and PhD students and is very well funded including strong commercial links supporting not only the basic research but also several clinical trials on thymic regeneration in immunodeficiency states. We will also be active participants in National Institutes of Health (USA) research and clinical trial programs. We form the Immunology Core Program of the recently announced Australian Federal Government Biotechnology Centre for Excellence – the National Stem Cell Centre, centred on the Monash Clayton Campus. While retaining strong links with the Department of Immunology we will be an integral part of the newly formed Monash Immunology and Stem Cell Laboratories (MISCL) (Director Alan Trounson, Deputy Director Richard Boyd) which draws together the leading Monash research groups working in the exciting frontiers of stem cell research.

One or more research projects will be offered in the area of the rejuvenation of the immune system (thymus and bone marrow), through stem cells and/or by inhibition of sex steroids, and its manipulation through exogenous haematopoietic stem cells. In conjunction with gene manipulation of haematopoietic stem cell therapy as appropriate we are able to address the following:

1. Reversal of immunosuppression states such as post-chemotherapy/radiation therapy; aging
2. Restoration of a specific anti-tumour immune response. Restoration of a specific antimicrobial immunity eg. Herpes, papilloma virus, fungi (candidiasis), parasites (eg. pneumocystis carinii) and possibly hepatitis. Development of central tolerance in transplantation through manipulation of the regeneration thymus.
3. Increasing the efficacy of vaccination programs in general and post-exposure.
4. Normalisation of T cell immunodysregulation states eg. autoimmunity (multiple sclerosis, lupus rheumatoid arthritis), allergy, dermatitis/psoriasis.
5. Development of thymic-based (ie permanent and not requiring immunosuppressive drugs) tolerance to organ, tissue and cell transplantation, including new stem-cell derived therapies.
6. Management of HIV/AIDS including production of HIV-resistant T cells and dendritic cells.
7. Development of thymus epithelium from embryonic and adult stem cells.
8. The identification of the differential gene usage and hence molecular basis to the functionally distinct compartments of the thymus and bone marrow and their rejuvenation in the above states.

Embryonic Stem Cell Differentiation Laboratory

Group Leaders: Associate Professor Andrew Elefanty and Dr Ed Stanley

Phone: 9905 0650

Overview of PhD and Honours Projects

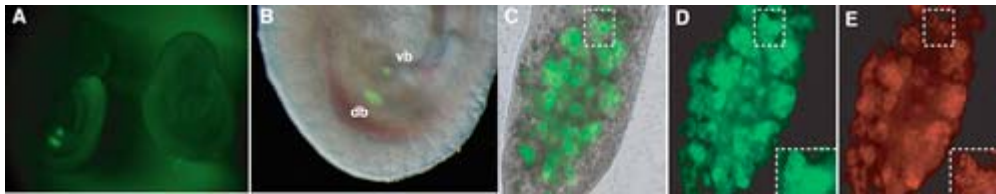
The directed differentiation of embryonic stem cells (ESCs) has been put forward as an avenue for the generation of mature functional cell types that could potentially find clinical application in the treatment of conditions where specific cell types are missing or diseased. For example, HESC derived insulin producing beta cells could potentially replace scarce cadaveric islets currently being used as a treatment for type 1 diabetes. Similarly, the possibility of generating large volumes of red blood cells by a manufacturing process could alleviate the growing shortage of donor derived blood for transfusions now being experienced worldwide. However, hampering progress toward these outcomes is an inability to efficiently direct the differentiation of ESCs to any desired outcome. The Embryonic Stem Cell Differentiation Laboratory has a number of areas of interest including the generation of therapeutically important cell types from ESCs. The projects listed below are a sample of those available for honours, PhD or post doctoral research.

Eligibility: Students applying for honours should have an aggregate second and third year average of approximately 75% and should be interested in pursuing a career in science. Students interested in PhD positions should have the same plus an honours score above 80% (H1 or equivalent) and therefore be eligible for either an APA or Monash University scholarship. Exceptions will be considered on a case-by-case basis. If you are unsure about your suitability please forward a copy of your CV to either Ed Stanley (ed.stanley@med.monash.edu.au) or Andrew Elefanty (andrew.elefanty@med.monash.edu.au) along with your expression of interest. Direct enquiries to either Andrew (+61 03 9905 0650) or Ed (+61 03 9905 0651) are also welcome.

1. Transcriptional Profiling of Pancreatic Progenitors

Supervisors: Sue Micallef, Andrew Holland, Ed Stanley, Andrew Elefanty

Background: Pancreatic b cells generated from differentiated embryonic stem cells (ESCs) represent a potential alternative to cadaver-derived islets for the treatment of type 1 diabetes. We have previously developed an embryonic stem cell line in which cells expressing a gene critical to the early development and function of the pancreas can be identified by the co-expression of a fluorescent marker ([Micallef et al, 2005 \(pdf\)](#)). Using this cell-line we are able to direct the differentiation of embryonic stem cells toward an endodermal and pancreatic fate. We have also generated a mouse line from these cells allowing a direct comparison between the cells made in the laboratory and those formed during embryogenesis ([Holland et al, 2006 \(pdf\)](#)). We have previously employed gene-profiling experiments to map the course of ESC differentiation and find new genes important to the differentiation process ([Hirst et al, 2006 \(pdf\)](#)). We now wish to apply similar strategies to dissect the process of pancreatic differentiation from ESCs.



Developmental expression of GFP in Pdx1^{GFP/w} mice mirrors that reported for Pdx1.

1. Fluorescent images of E9.5 Pdx1GFP/W and wild-type littermates demonstrated expression of GFP in the emerging dorsal (db) and ventral (vb) pancreatic buds.
2. Overlay of bright field and fluorescent images (Merge) of the Pdx1^{GFP/W} embryo shown in A.
3. Overlay of bright field and fluorescent images of an explant culture of E12.5 pancreas. D,E. GFP and Pdx1 (detected with an anti-Pdx1 antibody) expression in the same explant. The insets in the lower panels show the discrete nuclear localisation of Pdx1 in comparison with pan-cellular GFP.

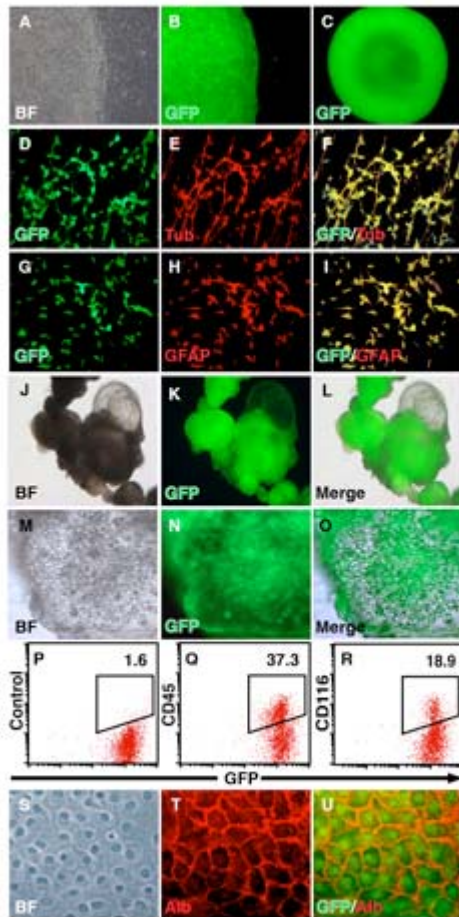
This project will involve the molecular phenotyping of different populations derived from Pdx1GFP/w ESCs and Pdx1GFP/w mice in order to match the developmental stage of cells from *in vivo* and *in vitro* sources. This analysis will also be used to identify novel markers of ESC differentiation.

Techniques to be employed will potentially include fluorescence activated cell sorting (FACS), RNA isolation, ESC differentiation, whole genome microarray analysis and *in silico* interrogation of gene expression (microarray analysis), tissue culture and microdissection.

2. Gene targeting vectors for genetic modification of Human Embryonic Stem Cells

Supervisors: Ed Stanley, Andrew Elefanty

Background: The ability to genetically modify human embryonic stem cells is critical to utilising these cells to study their commitment to specific cell lineages. We have previously used gene targeting in mouse ESC cells tag genes whose expression marks specific stages of embryogenesis ([Micallef et al 2005 \(pdf\)](#), [Ng et al 2005 \(pdf\)](#)). We have recently begun applying this same technology to generate HESC lines with genes encoding fluorescent proteins inserted into specific loci whose expression marks a variety of interesting cell types ([Costa et al, 2005 \(pdf\)](#)).



This picture is taken from Costa et al (2005) and shows that the HESC line, *Envy*, expresses green fluorescent protein in all kinds of differentiated cell types. Panels A to I show neural cell types expressing GFP, J to K shows GFP⁺ embryoid bodies, M to O demonstrates that GFP expression is maintained in blood cells and S to U shows GFP expressing liver like cells. *Envy* cells will be very useful for tracking HESCs and their derivatives following transplantation and in cultures containing mixtures of different cell types.

This project will involve the design and building of gene targeting vectors using a variety of different cloning techniques. Students will be instructed in aspects of vector design and assembly. Preliminary experiments will involve testing of vectors in appropriate cell lines.

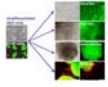
Techniques will potentially include polymerase chain reaction (PCR), Real time PCR, restriction digestion and ligation, HESC culture, Flow cytometry, Vector design, Southern Blot analysis, Cell electroporation and transfection.

3. Lineage specification during ES differentiation

Supervisors: Ed Stanley, Andrew Elefanty

Background: The specification of particular cell lineages during ESC differentiation is dependent on the growth factor milieu and media composition the ESCs are exposed to. In order to efficiently produce cell types with therapeutic value it will be necessary to guide ESC differentiation along specific pathways. Our laboratory has established protocols for the directed differentiation of mouse and human ESCs to a variety of

different cell types including heart, blood, endothelium, endoderm and neurons using a serum free media ([Ng et al 2005a](#), [Ng et al 2005b \(pdf\)](#), [Micallef et al 2005 \(pdf\)](#), [Costa et al 2005 \(pdf\)](#))(see below picture).



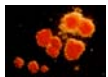
This project will involve further analysis of the culture conditions promoting the formation and patterning of ectoderm, mesoderm and endoderm from human embryonic stem cells.

Techniques will potentially include HESC culture and differentiation, Flow cytometry, Real time PCR, cell transplantation into immunodeficient mice, Statistical data analysis

4. Red Blood cell development from Human embryonic stem cells

Supervisors: Ed Stanley, Andrew Elefanty

Background: The eligibility criteria for safe blood donation are continually being restricted in an attempt to limit the transmission of pathogens (both known and unknown) to the recipients of blood products (<http://www.arcbs.redcross.org.au/>). Human embryonic stem cell derived Red Blood Cells (RBCs) represent a potential alternative to donor-derived blood, provided methods for the production of this cell type can be optimised. During development, red blood cell formation (erythropoiesis) occurs at a number of embryonic sites and transits through a series of sequential developmental switches culminating in the generation of mature enucleated erythrocytes (adult RBCs). A key focus of the Embryonic Stem Cell Differentiation Laboratory is to understand and control the formation of red blood cells from HESCs in an efficient and scalable manner.



This picture shows a multi-focal colony of human red blood cells differentiated from human embryonic stem cells in a serum free medium. The colonies form in methylcellulose (a semi-solid media) and each colony, which contains hundreds of cells, is derived from a single red blood cell progenitor. Red cells made in this way could eventually replace blood collected from donors and provide a safe and reliable source of blood cells for use in blood transfusions. See Ng et al 2005b

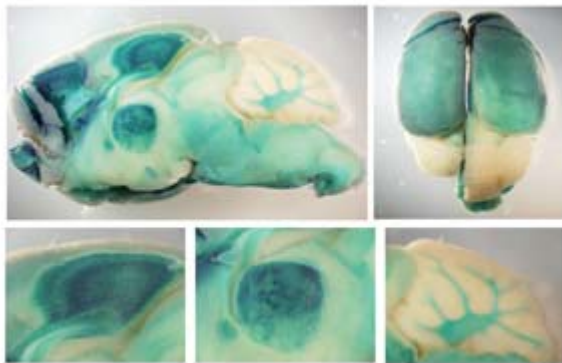
This project will involve dissection of the developmental stages of erythropoiesis using genetically tagged HESCs as tool to track and identify each stage.

Techniques will potentially include HESC culture and differentiation, Flow cytometry, Real time PCR, cell transplantation into immunodeficient mice, gene targeting, Southern blot analysis.

5. Analysis of the function of Slain, a novel stem cell gene

Supervisors: Claire Hirst, Ed Stanley, Andrew Elefanty

Background: We have previously used gene-profiling experiments to identify a new family of stem cell genes expressed in mouse and human embryonic stem cells ([Hirst et al, 2006 \(pdf\)](#)). Slain1, the founding member of this family, is highly conserved throughout vertebrate species yet shares no sequence similarity with any previously identified proteins or protein subdomains. We have generated a mouse line in which the bacterial beta galactosidase gene has been inserted into the slain locus and are using this line to track expression of Slain1 in the mouse. Other experiments aimed at placing Slain into the context of existing biochemical or signalling pathways are also underway. Understanding the function of Slain1 is likely to provide a novel insight into factors regulating the growth and differentiation of embryonic stem cells.



This figure shows expression of the Slain1 gene in the brain of an adult mouse in which the Slain1 locus has been tagged with the bacterial beta galactosidase gene.

This project will involve analysis of Slain1 function using in vivo and in vitro models, including Slain1 knockout mice, ESC differentiation and protein-protein interaction studies

Techniques **will potentially include ESC culture and differentiation, Flow cytometry, Real time PCR, mouse genotype and phenotype analysis, histological analysis, immunohistochemistry, gene targeting, southern blot analysis, fluorescence microscopy**

Fetal Development, Stem Cells and Differentiation Group

(Incorporating Stem Cells and Differentiation Group of Founding Director Professor Alan Trounson)

Group Leader: [Professor Graham Jenkin](#)

Phone: 9905 0700

Fetal Well-being Overview

Our current research interests focus on the control of ovarian function during the cycle and in early pregnancy, the maintenance of early pregnancy, development and well-being of the embryo and fetus and the initiation of normal and premature parturition.

Our recent studies on the presence and source of inhibin, activin and related proteins in fetal tissues and fluids indicate that they may be important in prevention of early embryonic loss, in fetal growth and development and, particularly, in fetal compromise in late gestation. This work may lead to novel approaches for the prevention of brain damage during development of at risk fetuses and of clinical monitoring of fetal well being during late gestation.

Fetal Well-being Projects

1. Does antioxidant treatment during late-pregnancy improve neonatal outcome in an ovine model of intrauterine growth restriction (IUGR)?

Supervisors: [Dr Suzie Miller](#), [Dr Veena Supramaniam](#), [Prof Graham Jenkin](#), in collaboration with Prof Euan Wallace, Obstetrics and Gynaecology and Dr Marianne Tare and Assoc Prof David Walker, Physiology

Phone: 9905 2542

Email: suzie.miller@med.monash.edu.au

Intrauterine growth restriction (IUGR) affects up to 10% of the population and is associated with an increased risk of perinatal mortality and increased risks of short and long-term morbidity. It has been shown in human IUGR that markers of oxidative stress are significantly upregulated in the placenta and fetus. Oxidative stress, and elevated levels of reactive oxygen species, may have detrimental effects on the developing fetus, and may be responsible for some of the poor outcomes which are observed in IUGR infants. We hypothesise that treatment with the antioxidant melatonin will reduce oxidative stress and improve fetal and neonatal wellbeing. In this project we will induce IUGR in fetal sheep; half of the ewes will be treated with melatonin and half with placebo. We will then let the ewes deliver and monitor a range of outcome measures in the lamb to assess whether melatonin improves outcome.

This project will combine whole animal physiology, surgical techniques and postnatal animal monitoring with studies of cardiac structure and function and brain histology and immunohistochemistry. This project may impact on the treatment options available to obstetricians treating human IUGR.

2. The effects of steroid administration on the cardiovascular system of IUGR fetuses.

Supervisors: [Dr Suzie Miller](#), [Dr Veena Supramaniam](#), [Assoc Prof Helena Parkington](#) and [Dr Kelly Crossley](#), in collaboration with Prof Graham Jenkin, MISCL and Prof Euan Wallace, Obstetrics and Gynaecology.

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Glucocorticoids are routinely administered to pregnant women at risk of preterm delivery in an effort to mature the fetal lungs for birth. There is no question that this treatment saves the lives of many newborns. However, glucocorticoids are powerful regulators of vascular function and as such glucocorticoid treatment may place the growth restricted (IUGR) fetus at risk, since they already demonstrate cardiovascular impairment. Using our ovine model of intrauterine growth restriction (IUGR) we have shown that blood flow responses to betamethasone (a synthetic glucocorticoid) are quite different in IUGR fetuses when compared to normally grown fetuses which may have consequences that persist into adulthood. The effects of these changes in blood flow and subsequent impact on development of specific organs remains entirely unexplored and therefore in this project we will look closely at the brain, heart and lungs to examine possible differences between IUGR and normal fetuses administered betamethasone.

This project will combine whole animal physiology, surgical techniques and animal monitoring and experimentation with studies of cardiac and lung structure and function. We hope that this project will provide an important insight into the mechanisms occurring, and possible management strategies, in human IUGR pregnancies.

3. Effects of activin and potential new tissue growth factors on the structure and function of the developing chick brain

Supervisor: [Dr Suzie Miller](#), [Dr Sharon Ricardo](#) and [Professor Graham Jenkin](#)

Phone: 9905 0775

Infection or deficiencies in supply of nutrients and/or oxygen during prenatal development are significant factors contributing to brain injury and have major sequelae for subsequent neurodevelopmental outcome. We have shown in sheep that activin A levels are increased during fetal stress and others have shown that activin A assists the survival of neurons. Clinical evidence also implicates activin A as a novel marker of fetal compromise and might therefore be used to predict poor pregnancy and developmental outcome. In this project, using the developing chick model, we combine the expertise of a number of departments to examine whether activin A is upregulated during infection, hypoxia or malnutrition. Furthermore, whether administration or inhibition of activin A or novel new growth factors affect the structure of the brain and subsequent cognitive function of the hatched chick.

Other fetal well-being project areas

- The effect of fetal hypoxia on fetal well-being in late gestation and in the newborn in the sheep and in the human; in collaboration with Prof Euan Wallace, Dept. Obstetrics and Gynaecology.
- The role of in activin in fetal hypoxia, a possible diagnosis tool in monitoring fetal well-being. Potential studies in sheep and small animals including activin knock out mice.
- Premature labour and its inhibition. Indices of monitoring and diagnosis of premature labour. Molecular characteristics of differentially expressed cells and genes in the uterus associated with induction of labour; in collaboration with Associate Professor Helena Parkington, Dept. of Physiology.

Stem Cells and Differentiation Overview

Embryonic stem cells and embryonic germ cells provide a potentially indefinite renewable source of cells and tissue for research and transplantation. Therapeutic products based on stem cell research provide a means for changing paradigms of medical treatment. Activating stem cells that already exist in a patient's own body or delivering therapies containing adult-sourced or embryo-sourced stem cells creates opportunities for regenerating the human body in ways only recently thought impossible. The research undertaken by this group includes studies on the basic biology of stem cells and germ cells, the potential to turn these cells into other cells and their interaction with the biological control systems in the human body. Initially the group will establish methods of precisely identifying stem cells, establish methods to expand stem cell numbers without their losing their pluripotential state and define methods of predictably and reproducibly directing the differentiation of stem cells to produce definable cells able to regenerate the tissues and organs of the human body. The group also has a major research program in the control of germ cell growth and differentiation.

Stem Cells and Differentiation Projects

1. Stem Cells Models for Studying in vivo Engraftment and Differentiation

Supervisors: [Dr Hayley Dickinson](#), [Professor Graham Jenkin](#), [Dr Ursula Manuelpillai](#), [Dr Suzanne Miller](#), in collaboration with Richard Boyd, Andrew Elefanty and Ed Stanley (MISCL), David Walker (Physiology) and Euan Wallace (Obstetrics & Gynaecology)
Phone: 9905 0775

Stem cell therapy is emerging with great promise in the areas of tissue regeneration and cell-based transplantation procedures. We are using pre-immune fetal sheep, and Spiny Mice as models to demonstrate that human stem cells; including HSCs, MSCs, Cord and Cord Blood Stem Cells, Embryonic Stem Cells and Amnion Stem Cells, can be incorporated into blood and tissue to form differentiated, functional cells. If this is proved to be possible, there may be an opportunity to use these cells or other types of stem and stem related cells for a variety of treatments and therapies where organs or tissues have become damaged in the adult or even for treatment of unborn children suffering from degenerative diseases. These studies will also provide insights into the development of the immune system in the fetus and neonate and may provide novel "immune tolerant" animals for the study of stem cell engraftment and repair in diseased or damaged tissues.

2. Stem Cells and Tissue Scaffolds

Supervisors: [Professor Graham Jenkin](#) and [Dr Tony Goldschlager](#)
Phone: 9905 0775

In this study, we aim to investigate the suitability of novel new biomimetic matrices to form tissue structures. Our initial aims are to develop suitable matrices from which to develop a trachea/bronchus for the therapeutic alleviation of Chronic Obstructive Pulmonary Disease (COPD) and to produce biomimetic spinal discs for repair of discs damaged by trauma or degenerative processes. The use of stem cells in the repair of

the respiratory tract in neonatal and adult respiratory diseases is a major focus. ([See Stem Cells and Differentiation Group](#))

The advent of tissue engineering in the last few decades, together with stem cell developments, has given researchers the potential ability to suitably engineer cellular constructs for replacement of damaged tissues. We will study the characteristics of biomatrices both *in vitro* and *in vivo* in collaboration with commercial companies. We will determine the appropriateness of our cellular scaffolds for the production of engineered tissues. We will determine the most appropriate polymer compositions and stem cell combinations that can be developed into the most viable scaffold for therapeutic use.

3. Amnion Derived Stem Cells and Respiratory Repair

Supervisors: [Ursula Manuelpillai](#), [Dr Hayley Dickinson](#), [Professor Graham Jenkin](#) in collaboration with Richard Boyd and Euan Wallace (Obstetrics & Gynaecology)
Phone: 9905 0775

Of particular interest to our group are human amnion derived epithelial stem cells which have many of the characteristics of embryonic stem cells, but which can be obtained without the ethical issues associated with the derivation of embryonic derived stem cells. Our group is studying the properties of these cells *in vitro* and *in vivo*, their derivation, characteristics including plasticity and their potential therapeutic use in repair of respiratory epithelium and in spinal disk repair.

4. Embryonic Stem Cells and Differentiation into Lung Tissue

Supervisors: [Dr Antonietta Giudice](#), [Dr Anna Michalska](#)
Phone: 9905 0700

The directed differentiation of mouse and human embryonic stem cells into respiratory epithelium of the upper airways and alveolar compartments of lung tissue is being examined *in vitro* and *in vivo* in animal models of lung disease. Markers for early differentiation events are being identified from tissue microarrays and it is intended that reporter genes be inserted into promoter sequences to enable purification of the cells differentiating into pulmonary progenitors.

5. Differentiation of Mesenchymal Stem Cells from Bone Marrow, Umbilical Human Cords and Placental Amnion for Lung Repair in respiratory diseases (Pulmonary Fibrosis, Emphysema – COPD, Cystic Fibrosis)

Supervisors: [Dr Ursula.Manuelpillai](#), [Prof Euan Wallace](#), [Prof Graham Jenkin](#), [Dr Rebecca Lim](#)
Phone: 9905 0700

The use of mature (adult) mesenchymal stem cells (MSCs) and placental amniocytes for repair of COPD and CF is being examined in several animal models and the human. MSCs can be obtained from bone marrow stroma and other sources, and by using molecular and cell transplantation techniques in animals with COPD and CF, the colonisation, pulmonary differentiation and lung function are being determined. Projects are integrated in this research program.

6. Embryonic Stem Cells, Gene Markers in Embryonic Stem Cells, and Differentiation Pathways

Supervisors: [Dr Antonietta Giudice](#), [Dr Anna Michalska](#), [Dr David Cram](#), [Dr Rebecca Lim](#), [Dr Jitong Guo](#)

New human embryonic stem cells (ESCs) are being made, expanded and differentiated. ESCs are also being studied in mouse and horse using conventional and nuclear transfer methods (cloning). The human ESCs are made from excess and donated human IVF embryos and the scientists are using gene targeting (homologous recombination) to insert fluorescent marker genes into the genes of interest for differentiation in mouse and human ESCs. These pathways include the respiratory, liver and thymic lineages. The group is also studying disease specific embryonic stem cells as a model for exploring the cause of complex diseases and diseases caused by gene mutation (eg. Cystic Fibrosis and Huntington's Disease). The expression of the disease pathology in vitro could make these ESCs amenable to molecular screening for new candidate drugs which may be useful in modifying the disease pathologies in vivo.

7. Identifying the Developmentally Competent Human Eggs and Embryos

Supervisor: [Dr Gayle Jones](#), [Dr David Cram](#)

Phone: 99050778

The research program is determining the gene expression profile of the normal, viable human oocyte and how this is perturbed by pathologies such as diabetes, polycystic ovarian disease, conditions such as advanced maternal age and obesity. The program is also examining the influence of cytoplasmic components including mitochondria on oocyte developmental competence. Where possible, proteomic analysis is used to define proteins influencing oocyte developmental competence.

The research group is also examining the gene expression profile and gene function in human blastocysts and correlating this to the capacity to develop to term.

Multiple human embryos are usually transferred to patients to achieve a satisfactory pregnancy rate. The research group has developed new methods for blastocyst biopsy, gene expression profiles of the trophoblast using microarrays and embryo identification by DNA/RNA fingerprinting. The developmental capacity of embryos is correlated to their expression of developmental genes and those associated with implantation. The group is developing these methods to demonstrate that single embryos can be chosen for successful IVF pregnancy.

These projects have a direct influence on embryological techniques, patient treatment and expected outcomes of IVF/ART in cases of infertility and inherited genetic diseases

8. Embryonic Stem cells and Prostate Tissue and Cancer Stem Cells

Supervisors: [Dr. Renea Taylor](#)

Phone: 9905 0623

A recently published method to directed the differentiation of human embryonic stem cells into prostate tissue in vivo has been developed in this laboratory. We are aiming to adapt the tissue recombination model to understand the role of stem cells, epithelial cells and stromal components in prostate cancer. We are targeting genes known be involved in prostate cancer initiation and progression and silencing them in the hESCs by shRNA technology.

9. Spectroscopic Imaging of Differentiating Cells and their Secretory Products

Supervisors: [Dr Phillip Heraud](#), [Dr David Cram](#)

Phone: 9905 0765

The project uses state of the art Infra Red and Raman spectroscopic imaging technologies and light from the Australian Synchrotron to achieve the biochemical measurements in human reproductive cells, culture media, to assess the products of viable cells. These technologies are being developed as diagnostic screens to separate viable and unviable embryos in IVF. The studies also include examination of the earliest signs of disease in differentiating embryonic stem cells that have mutations for Cystic Fibrosis and Huntingtons Disease

No undergraduate knowledge of chemistry is assumed

10. Stem Cell – Germ Cell Gamete Formation

Supervisors: [Dr Orly Lacham-Kaplan](#)

Phone: 9905 0781

The ability of oocytes to fertilize and result in a normal embryo is strongly associated with the oocyte maturation stage. Immature oocytes at the GV stage are unable to induce sperm decondensation, and therefore, are unable to be fertilized. Once reached the MII stage in-vivo or in-vitro oocyte acquire the ability to be fertilized by sperm. The developmental competence of the oocytes after fertilization, however, is different with in-vivo matured MII oocytes being the most capable of developing into viable embryos. The aim of the study is to identify if oocytes at different stages of maturation are also different in somatic cell reprogramming following nuclear transfer. The study will involve tissue culture and chromosomal analyses.

Embryonic stem cells can also be induced to form germ stem cells and these germ cells can be directed into oocytes or sperm in vitro and in vivo. The research is identifying drivers of differentiation and optimizing these genetic pathways, and examining the normality of putative oocytes and sperm that are produced.

11. Reprogramming somatic cells for multipotentiality and pluripotentiality using nuclear transfer

Supervisors: [Dr Jitong Guo](#)

Phone: 9905 0700

Application of stem cells for cell therapies to treat degenerative disorders, tissue damage and disease requires compatibility of donor and recipient tissues to avoid graft versus host disease and immune rejection. Compatibility across normal histocompatibility barriers can be achieved by nuclear transfer of a patient's somatic cells into enucleated oocytes (nuclear transfer – NT). Researchers are studying the potential to use the oocytes of laboratory animals to reprogram somatic cells (of other species eg. horse) by NT and mitochondrial replacement. The reconstituted oocytes have no laboratory animal DNA and the NT embryos are being studied for their potential development into embryonic stem cells. Other studies involve the cell fusion of nuclear-free cytoplasts, nuclear containing karyoplasts and cell extracts of embryonic stem cells for reprogramming liver cells, pancreatic islet cells and cancer cells into progenitor cell types that may be useful for cell expansion and cell therapies, or for study of the cause of some diseases eg. cancers.

Renal Regeneration Laboratory

Group Leader: [Dr Sharon Ricardo](#)

Phone: 9905 0671

1. [Adult Stem Cells in Renal Regeneration and Repair](#)
2. [Polycystic Kidney Disease and Bone Marrow Stem Cells](#)

1. Stem Cells in Renal Regeneration and Repair

The development of new stem cell-based therapies in combination with newly discovered repair factors may offer alternatives for renal transplantation. This field of regenerative medicine is the focus of the Renal Regeneration Laboratory. Therapies may involve the administration of stem cells or potential regenerative growth factors to patients that will slow the development of kidney disease and/or regenerate damaged kidney tissue. Both embryonic and adult kidneys are being studied to provide insights to facilitate renal regeneration therapies.

Recent research has suggested that the plasticity of adult stem cells may be broader than initially thought. For example, in addition to organ-specific stem cells there has been considerable excitement over the diversity of bone marrow cells to repair a number of different adult organs including the kidney. Bone marrow cells are a class of adult stem cell that localise predominantly to the bone marrow and are responsible for production of mature blood cells. However, bone marrow cells may also form specialised cells of adult organs, including specialised kidney cells, in response to injury.

The Renal Regeneration laboratory is using experimental mouse models of renal disease to provide information on how kidneys can repair themselves. Adult and embryonic stem cells are being delivered to experimental models of diabetes, acute renal failure and genetic renal diseases. State-of-the-art imaging techniques are used to trace adult stem cells derived from green fluorescent transgenic mice or GFP-positive cell lines. This helps to define their potential to integrate and repair damaged kidney cells and reduce the process of scarring leading to improved kidney function.

Research projects are available in the following areas:

1. Bone marrow transplantation studies using GFP-transgenic mice to examine the role of adult stem cells in tissue remodeling and repair. We use a number of clinically relevant experimental mouse models with a focus on diabetic nephropathy, fibrosis and acute models of inflammatory injury and repair.
2. Molecular analysis of the pathways and factors controlling endogenous renal self repair.
3. The reparative role of the tissue macrophage during development and in adult disease.
4. The potential of human embryonic stem cells to form renal cells (co-supervised by Dr Andrew Laslett, Australian Stem Cell Centre).

2. Polycystic Kidney Disease and Bone Marrow Stem Cells

Supervisor: [Dr James Deane](#) and [Dr Sharon Ricardo](#)

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Polycystic kidney disease is a common genetic condition that causes fluid filled cysts in the kidney. We are using the Oak Ridge Polycystic Kidney (*orpk*) mouse model and bone marrow transplantation to investigate the biology and treatment of PKD. Mutations that cause PKD result in the inappropriate proliferation of cells in the epithelial layer of ducts and tubules in the kidney leading to cyst formation. It has recently been discovered that damage to this epithelial layer is repaired by the integration of cells derived from stem-cells in the bone marrow. The morphology and composition of these integrated cells suggests that they are becoming new epithelial cells.

This mechanism has also been demonstrated to operate for donor bone marrow following transplantation, meaning that cells derived from donor marrow can integrate into the renal epithelial layer of a host kidney. We will take advantage of this phenomenon by using bone marrow transplantation to introduce traceable, genetically dissimilar cells to the renal epithelium. Cells from PKD-afflicted *orpk* mice will be introduced to the renal epithelium of genetically normal mice to allow the cellular dynamics of cystogenesis to be studied. Genetically normal cells will also be introduced to the renal epithelium of PKD-afflicted *orpk* mice in an attempt to reduce cyst formation and test the feasibility of stem cell-based PKD treatments.

Neuroimmunology

Group Leader: Professor Claude Bernard DES (Sorbonne), Msc (Montr), DSc (Stras)

Multiple Sclerosis Research Group

Research interests

The major focus of the Neuroimmunology Laboratory is to study in human and experimental animals, facets of immunology, genetics, biochemistry, microbiology and behaviour pertaining to the causation of various acute, progressive and destructive neurological disorders such as Multiple Sclerosis (MS). The major objective of our research is to understand the basic underpinnings of MS and attempt to translate these findings to develop new therapeutic strategies for people with MS.

Specifically we are interested in

Development of therapeutics to a) suppress the auto-inflammatory response and b) to promote and enhance CNS regeneration.

Understanding factors contributing to susceptibility and the molecular and cellular mechanisms underlying the disease process.

Recently, we have discovered that targeting Nogo-A, a specific molecule responsible for preventing neurite outgrowth and consequently the failure of the central nervous system to regenerate, blunts clinical signs and pathology associated with the EAE model of MS. This suggests that blockade of this deleterious molecule may help maintain and/or restore the neuronal integrity of the CNS following immune insult in diseases like MS.