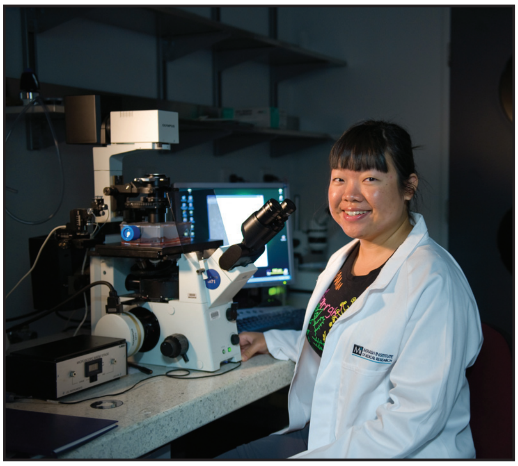
Centre for Reproduction & Development



Acting Centre Director: Associate Professor Mark Hedger

The Centre for Reproduction and Development (CRD) has a diverse and dynamic research focus including germ line and stem cell biology, reproductive biology and immunology, genetics and infertility. The biological systems used in our studies range from cultured cell lines, including human embryonic stem cells, through to laboratory rodents, domestic animals such as sheep and cows, and humans.

The Centre is built around four laboratories with a total of 25 staff and students, and offers a broad range of PhD and Honours projects. The research scientists within the CRD have a considerable track-record in the training of undergraduate and postgraduate students. Ours is a large, well resourced research-based Centre with expertise covering a broad range of techniques including proteomics, genomics, cloning, tissue culture and confocal and fluorescent microscopy and Super-Array technologies.

Projects on offer in the Centre explore testis development, testicular immunology and inflammation, potential therapeutic applications of human amnion stem cells, differentiation and re-programming of human embryonic stem cells, bovine cloning and nuclear transfer. The Centre has a strong focus on commercialisation of discoveries and the development of bench to bedside applications for improvement of human health.

Male Reproduction and Immunity

Project Leaders: Assoc Prof Mark Hedger and Dr Wendy Winnall
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The male reproductive tract and the immune system operate within a carefully balanced relationship that is essential for preserving reproductive ability, but also has much to tell us about the regulation of immunological responses as well. Our research is directed to understanding this interaction, how it is maintained, and why it sometimes goes wrong. Research projects will be developed in consultation with the student to enable the best fit between the interests of the student and the principal research aims of our laboratory team. The main project areas of interest to our laboratory are:

1. Studies on the response of the male reproductive tract to inflammation and how such events compromise androgen levels and fertility, through examination of the interactions between pro- and anti-inflammatory mediators (ie. cytokines, reactive oxygen species, steroids and prostanoids) in the testis in specific inflammatory disease models. These studies involve both in vivo and in vitro approaches, employing a range of morphological, immunological and molecular techniques.

Centre for Reproduction & Development

2. Investigation of novel regulators of leukocyte activity in the male reproductive tract. It is now firmly established that the somatic cells of the testis have a profound regulatory effect on immune cell function, thereby creating a unique immunological environment necessary to protect the developing sperm from immune attack. Elucidation of the specific molecules and detailed mechanisms involved may eventually lead to better treatment modalities for transplantation failure, autoimmune diseases and leukaemia and related cancers.

3. Mouse testicular macrophages are believed to have several unique functional properties associated with testicular immune privilege, but are still poorly characterised. We are using microarray analysis and real-time PCR to compare these cells to macrophages from other mouse tissues. This project will involve a broad range of computing, molecular and cellular techniques: the use of GeneSpring software to analyse genomic data, cell culture to isolate and purify macrophages from mice, real-time PCR, protein expression analysis and assays for specific cell functions. This project is a collaboration with the Centre for Innate Immunity and Infectious Disease.

4. Sertoli cells are epithelial cells in the testis which regulate spermatogenesis. These cells are capable of responding to inflammatory stimuli and appear to help protect the testis from damage due to infection. This project examines Sertoli cells responses to bacterial stimuli in terms of production of the cytokine IL-1alpha. We have recently shown that most of the IL-1alpha produced by Sertoli cells is not secreted, as expected, and predict that this protein is moving into the nucleus and acting as a transcription factor. This project will involve techniques such as Western blotting, immunohistochemistry and confocal microscopy to study this exciting new area of research within our laboratory.

Activin in inflammatory diseases

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Activin is a growth factor and cytokine found in many cells in the body. We have made an exciting discovery where activin can be released very rapidly as an 'alarm' cytokine in response to inflammatory signals. Work is currently focussed on how this system operates, and whether that knowledge could be used to develop new screening methods for patients or new classes of medical treatments. Potential projects could include analysing patient samples with important inflammatory diseases, using experimental models of key diseases, how particular cell types respond, or any of the above.

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Cell reprogramming

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Pluripotent embryonic stem cells (ESCs) could potentially generate specific cell types for treating serious diseases. A major problem limiting the clinical use of ESCs is the potential for tissues derived from these cells to be rejected by receiving patients. The most attractive solution to this problem comprises transplanting tissues derived from ESCs genetically matched to each patient. Somatic cell nuclear transfer (SCNT), where an adult somatic cell is returned to a pluripotent state (a process called reprogramming) following transplantation to an enucleated oocyte, can be used to provide such cells, however, ethical and practical limitations associated with both oocyte donation and human SCNT raise serious concerns about the suitability of this method.

Alternative approaches to reprogramming cells include 1) fusion of somatic cells with ESCs and 2) introduction of a few key pluripotent genes into the somatic cells, also know as induced pluripotent stem cells (iPSCs).

The following projects examine the potential to improve reprogramming of somatic cells.

1. Improving reprogramming efficiency of somatic cells by increasing viral delivery and expression of transcription factors.

2. Generation of iPSCs by using non-genetic Modifying strategies.

Hepatic tissue regeneration using human amnion stem cells

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Liver fibrosis and cirrhosis are common endpoints to liver diseases in humans independent of the cause. With advancing disease there is massive loss of hepatocytes that lead to reduced hepatic function and liver failure with transplant being the only curative therapy currently available. We have shown that epithelial cells isolated from human term delivered amnion (a membrane attached to the placenta) display properties of pluripotent / multipotent stem cells transdifferentiating into many cell lineages including hepatocytes, in vitro. Human amnion epithelial cells (hAEC) are extremely plentiful and possibly immune privileged offering exciting possibilities for potential allogeneic stem cell based therapies.

In this project the ability of hAEC to differentiate into hepatocytes and regenerate the damaged liver will be assessed. hAEC will be transplanted into immunocompetent mice that have undergone a partial hepatectomy. The molecular and biochemical processes regulating stem cell engraftment, survival and functional differentiation into hepatocytes and liver regeneration will be assessed.

These studies will be carried out in collaboration with the Dept. of Medicine. Techniques such as stem cell isolation, xenotransplantation, FACS, multikine ELISAs, immunohistochemical and molecular biological methods and electron microscopy will be used.

This project –forms a part of a pre-clinical assessment of the efficacy of hAEC in the treatment of liver cirrhosis.

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Human amnion epithelial cells for the treatment of lung diseases

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Chronic lung diseases, characterized by loss of gas exchanging alveolar epithelial cells, persistent inflammation and fibrosis, represent a major global health burden. Investigating if human amnion epithelial stem cells (hAEC) isolated from human term delivered placenta could be a potential cellular therapy for the treatment of chronic lung diseases, we found that hAEC transdifferentiate into alveolar epithelial cells, reduce inflammation and fibrosis regenerating and repairing the damaged lung in a mouse model of lung fibrosis.

In this project we would xenotransplant hAEC into mice with chronic lung injury and study the molecular mechanisms between the host and exogenous stem cells that lead to a reduction in inflammation and fibrosis.

In addition the safety profile of hAEC therapy will also be examined. Techniques such as stem cell isolation, xenotransplantation, FACS, multikine ELISAs, immunohistochemical and molecular biological methods and electron microscopy will be used.

This project will form part of a pre-clinical assessment of the efficacy of hAEC in the treatment of chronic lung diseases.

Immunogenicity of human amnion stem cells

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Our work using mouse models that mimic chronic lung disease and liver cirrhosis in humans have shown that transplantation of human amnion epithelial stem cells (hAEC) derived from term placenta, leads to tissue regeneration, stimulates repair and remodels the damaged organs. While these findings suggest that hAEC could have wide applications as a cellular therapy for a number of inflammatory and fibrotic diseases, it would be important to determine the immunogenicity of the hAEC to assess their suitability for allogeneic stem cell transplantation.

Through in vitro studies and in vivo tests using immunocompetent mice the effects of hAEC on innate and adaptive immune cells will be investigated. HLA Class I and II antigen expression by native and transdifferentiated stem cells, host immune responses elicited by these cells, alterations in chemokine and cytokine expression will be studied. Techniques used will include stem cell isolation, xenotransplantation, FACS and Luminex / multikine assays.