NEUROSCIENCE PROGRAM

Adult Stem Cell Group
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Recent demonstrations isolating stem cells from the central nervous system, and the ability of nervous tissues to regenerate have given hope for the treatment of neurodegenerative diseases. The capacity of olfactory receptor neurons to regenerate from a pool of multipotent stem cells signalled this region of the nervous system as an important source of adult neural stem cells. While the regenerative capacity of the olfactory neuroepithelium has been well studied less is know about the molecular events controlling adult olfactory stem cell activity. Therefore, the aim of the research in the adult stem cell group is to isolate and characterise adult olfactory stem cells and examine the molecular mechanisms involved in olfactory stem cell proliferation and differentiation.

Project 1: Isolation, identification and characterisation of olfactory stem cells
To isolate adult olfactory stem cells from the olfactory neuroepithelium to investigate the potential of these cells to proliferate and differentiate in culture. A major part of the project is to utilise our expertise in olfactory biology to isolate olfactory stem cells using flow cytometry. The identity of the olfactory stem cell is still unknown. We have developed culture methodology that has allowed us to isolate olfactory neurospheres from mice and demonstrate their proliferative and clonal capacity. With the use of extracellular markers to different populations of cells within the olfactory neuroepithelium, we will isolate homogeneous populations and study their capacity for proliferation and differentiation.

Project 2: Differentiation of olfactory stem cells into neural cell types
Characterisation of the ability of olfactory stem cells to proliferate and differentiate. BrdU incorporation experiments will be used to assess proliferation. Immunocytochemistry will be performed to determine the differentiation of the adult olfactory stem cells. A bank of antibody markers will be used to elucidate different neural cell types. For example, antibody markers of dopaminergic (dopamine β hydroxylase (DBH); tyrosine hydroxylase (TH)) and cholingergic (choline acetyltransferase (ChAT)) neurons will be employed to determine the type of neurons differentiating from the neurospheres. There is a substantial amount of evidence suggesting that there are certain stem cell genes: Wnt-3a, Pax6 and Musashi-1 that are involved in cell fate determination. Gene profiles will be examined by using RT-PCR to determine if these genes are involved in cell fate determination of the adult olfactory stem cells.

Hearing Research Group
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Project 1: Using adult stem cells to repair Hearing Loss
Ever wondered if your music player is too loud? Studies have shown that listening to loud music for extended periods can cause long-term hearing loss. The hearing loss results from damage to the sensory receptors for hearing, the hair cells in the inner ear. This project will explore whether adult stem cells can replace the damaged hearing cells. Mouse sensory stem cells from the nose, tongue and balance organ will be transplanted into the inner ear of deaf mice. Hearing levels will be tested before and after cell transplantation. All techniques are well established and currently functioning in our laboratory. Future studies with human stem cells offer a clinically relevant progression from animal studies.

Project 2: Brain pathways for locating sound in space
Can't hear in a noisy pub or restaurant? Hearing loss affects one in five Australians, many of whom experience difficulty in understanding speech in noisy spaces. The pathways in the brain that help us locate sounds and recognise speech are not fully understood. This research project will study the brain pathways and nerve cells involved in hearing using electrical recordings in brain slices. The goal is to improve treatment strategies for individuals with hearing loss, users of hearing aids, and deaf persons with cochlear implants.

A wide range of skills are available to students, including stem cell biology, immunohistochemistry, molecular biology, cell culture, electrophysiology, fluorescent confocal microscopy, and hearing testing. Laptop and conference travel guaranteed.

Try before you buy: Honours projects (1 year) are available before commencing a PhD project (3 years). Both Honours and PhD projects are carefully designed to achieve positive outcomes in the allotted time.

Neurodegenerative Disorders Group
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PhD Studies in Dr Bryce Vissel's group allow you the opportunity to learn and develop cutting edge technologies and approaches that will contribute to a deeper understanding and treatment of Parkinson's disease, Alzheimer's disease or spinal cord disorders. The group uses sophisticated approaches to understand how synaptic dysfunction leads to neurodegeneration and to identify potential approaches to reverse the disease process. In addition to studying mechanisms of neurodegeneration, the group studies stem cells and the mechanisms underlying regeneration in the nervous system. The goal of this work is to identify approaches that could drive recovery in the brain in diseases such as Parkinson's and Alzheimer's disease. All our projects will train you in a wide range of cutting edge approaches, including anatomy, physiology, animal behavior, cell culture, high-end microscopy, surgery and so on. Our group is helpful, friendly and highly motivated. These are kinds of studies you could undertake:

Project 1: Neural regeneration research and studies of stem cells
Students will have the opportunity to study neural regeneration in our group. Adult neurogenesis is the process by which the brain generates new nerve cells in the adult central nervous system (CNS) from stem cells that naturally exist in the brain. Stimulating neurogenesis may potentially offer a therapeutic approach for neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and spinal disorders. In our group, we are working to identify mechanisms that regulate adult neurogenesis (neural repair mechanisms) in the normal and diseased brain, to determine if manipulating these mechanisms may offer therapeutic potential. The students who are interested in research projects in this area will learn advanced techniques in the study of neurogenesis and neural stem cells. Techniques learned will include: (1) Stereotaxic survival surgery and gene therapy approaches, (2) Immunohistochemistry combined with advanced confocal microscopy and stereology for analysis of regeneration. (3) Use of in vitro cell systems, including neural stem cells, for studying neurogenesis. (4) Behavioural testing to determine the capacity for functional recovery in animal models (5) molecular biology. Research into mechanisms and role of neural regeneration is a cutting edge area of research worldwide and the research has significant potential to lead to important discoveries.

Project 2: Neurodegeneration research and studies of synapses
When neurons in the brain that secrete dopamine die, this causes Parkinson's disease, which leads to a profound loss of motor function and eventually death. The biology of dopamine neurons, which is absolutely critical to a range of diseases such as Parkinson's disease, is poorly understood. We are researching dopamine neuron synapses to develop a greater understanding of the role that dopamine synaptic function in normal behavior and in disease and we have several cutting edge projects available for students. The student will learn advanced techniques in studying dopamine synaptic function, including: (1) Culture of primary cells from mouse neural tissue, including glial cells, dopamine neurons and hippocampal neurons (2) Immunocytochemistry combined with advanced confocal live imaging microscopy (3) Advanced methods in microscopy for analysing active synapses formed by live neurons. (4) New concepts and techniques that few labs worldwide are able to achieve. The available research projects have significant potential to lead to important discoveries.

Eating Disorder Group
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Project 1: Neuropeptide Y family peptides and its receptors in cancer biology, diagnosis and therapeutic treatment

Neuropeptide Y (NPY) and NPY family peptides comprising peptide YY (PYY) and pancreatic peptide (PP) are 36-amino acid peptides acting on G-protein coupled receptors called Y1, Y2, Y4, Y5 and y6. Via Y receptors, NPY family peptides exert a wide range of physiological functions. Recently, NPY has emerged as a growth and angiogenic factor and been implicated in the control of tumour growth. Furthermore, the expression quantity and pattern of Y receptors changes in many tissues during neoplastic transformation. This project will look into the role of NPY family peptides and each Y receptor subtype in tumour biology; and investigate Y receptor expression quantity and pattern in different types of cancer models. Knockout mouse models and highly specific Y receptor subtype ligands will be used in this project to study above aspects. Potentials using Y receptor radio-ligands for in vivo tumour imaging will be explored.

Project 2: Neuropeptide Y family peptides and Y receptors in cancer anorexia

Neuropeptide Y (NPY) and two other NPY family peptides, PYY and PP, are the key regulators of appetite and satiety. Changes in their expression and secretion lead to altered eating behaviour. In many forms of cancer, loss of appetite (anorexia) occurs, indicating a dysfunction in the control of hunger and/or satiety mechanisms. This study will investigate the role of NPY system in the control of appetite in the pathological condition, cancer anorexia. NPY, PYY and PP levels in the circulation, NPY and Y receptor expression in different regions of the brain and their functional interactions will also be examined in anorexic cancer models. Ligands and Y receptor knockout models will be used to investigate role of each peptide and Y receptor subtype in cancer anorexia.

Cooper Group (ER Stress)
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Project 1: Elucidating the underlying molecular mechanism for the neurodegenerative disease ALS / Motor Neuron Disease

ALS is a devastating neurodegenerative disorder that attacks motor neurons leading to paralysis and death within 2-5 years after the onset of the disease and for which there are no effective therapies. ALS pathological and clinical features including abnormal proteinaceous accumulations (aggregates/inclusions) of misfolded mutant superoxide dismutase (SOD1) that mark degenerating motor neurons. No effective treatment exists for ALS so determining the underlying cellular molecular mechanism(s) is critical as a basis for developing a treatment or cure.

To identify the pathological mechanism of ALS we have developed a model system expressing lethal levels of mutant aggregating SOD1. We are currently screening 5000 genes for those whose overexpression suppress or enhance SOD1 toxicity. The identification of these genes will indicate both the dysfunctional molecular process responsible *and* identify genes whose modulation of expression may have therapeutic value. The project will first involve bioinformatic analysis to identify common pathways amongst the genes identified and then confirming the role of these pathways in our model system before expanding the analysis into cell culture, mouse and human models of ALS.

Our discoveries will have far reaching outcomes in terms of identifying the underlying disease molecular mechanisms and indicate avenues best suited for therapeutic intervention.

Project 2: **Identification of genetic risk factors for Parkinson's Disease (PD)**

PD is a neurodegenerative disease affecting >50,000 Australians who have already lost ~ 40% of dopamine producing neurons at time of diagnosis. Earlier diagnoses and new treatments are needed as current therapies are only partially effective.

αSynuclein is a natively non-toxic protein of unknown function that associates with synaptic vesicles. αSynuclein is also the central component in PD as its aggregated form is the main component of Lewy bodies, the primary pathological hallmarks of PD. Although the underlying cause of PD is unknown in >90% of cases the propensity of αSynuclein to become cytotoxic likely results from a complex interaction of unknown predisposing genes (risk factors). Identifying inherited risk factors will enhance our understanding of how Parkinson's disease develops and is an important step towards preventing the disease or to develop therapeutic agents that may inhibit the degeneration of neurons.

Using a new model system expressing nontoxic levels of αSynuclein, we screened for αSynuclein dependent toxicity upon loss of function of 5000 genes. We have identified the critical role of mitochondrial dysfunction as well as major signalling pathways. This project will investigate a group of these genes to identify the underlying molecular mechanism and then test in human brain samples.