PROJECTS 2016

THE UNIVERSITY OF MELBOURNE AT THE ROYAL MELBOURNE HOSPITAL
(RMH Departments: Medicine, Radiology, Surgery, Psychiatry, Obstetrics & Gynaecology RWH and affiliated institutes)

Enrolling Department: Medicine RMH
Melbourne Medical School, The University of Melbourne

HONOURS

Bachelor of Biomedicine and Bachelor of Science (Degree with Honours)

COURSE CODES:
BH-BMED - Bachelor of Biomedicine (Honours)
For students who have successfully completed or are about to complete the Bachelor of Biomedicine at the University of Melbourne.

BH-SCI - Bachelor of Science (Honours)
For all other applicants who have successfully completed or are about to complete a Bachelor of Science or equivalent

and

Master of Biomedical Science

Affiliations: The Royal Women’s Hospital, Western Hospital (Footscray & Sunshine), Northern Hospital, The Peter MacCallum Cancer Centre, The Burnet Institute, Melbourne Brain Centre, Florey Neuroscience Institute, Melbourne Neuropsychiatry Centre, Mental Health Research Institute, Baker IDI Heart & Diabetes Institute.
# TABLE OF CONTENTS

## AGEING

1. Acquired epilepsy in Alzheimer’s disease - also offered as MBiomedSc
2. Characterisation of the Onset and Progression of Tauopathy in the Pontomedullary Brainstem Nuclei of mice undergoing Neurodegeneration
3. Lifestyle Factors for Healthy Ageing – also offered as MBiomedSc
4. Causes of Depressive Symptoms in Early Ageing – also offered as MBiomedSc
5. Alcohol use and effects on mood in elderly women – also offered as MBiomedSc
6. Early detection and prevention of age associated diseases using imaging - ONLY offered as MBiomedSc
7. Can statins protect against cognitive decline associated with dementia? - also offered as MBiomedSc
8. Nutrient intake and plasma beta-amyloid - also offered as MBiomedSc
9. Current definitions of sarcopenia: Associations with indicators of falls and fracture risk in older adults - also offered as MBiomedSc
10. The metabolic syndrome and musculoskeletal health in older adults - also offered as MBiomedSc

## ALCOHOL

11. Why do some people with hepatitis C continue to drink? - also offered as MBiomedSc

## ANAESTHESIA AND PERIOPERATIVE MEDICINE

12. The evaluation of anaesthetic drugs and techniques on the postoperative quality of recovery – also offered as MBiomedSc

## ARTHRITIS AND INFLAMMATION RESEARCH CENTRE

13. The role of urokinase plasminogen activator (u-PA) and its receptor (u-PAR) in arthritis and inflammation
14. The role of granulocyte macrophage colony stimulating factor (GM-CSF) in arthritis and inflammation
15. The role of Interferon Regulatory factors in Arthritis
16. The role of a novel macrophage inflammatory mediator in arthritis
17. Molecular signaling pathways controlling gene expression during chronic disease progression
18. Elucidating molecular signaling pathways controlled by anti-inflammatory steroids

## AUTISM

19. Investigating the mechanism of action of antipsychotic drugs in brain regions regulating aggression in a mouse model of Autism - also offered as MBiomedSc
20. Investigating the interaction between skeletal muscle and bone—also offered as MBiomedSc

21. Developing New Therapies for Musculoskeletal Disease—Investigating the Fundamental Mechanisms of Osteocyte Mechansensing—also offered as MBiomedSc

22. Bone health in children and young people with epilepsy treated with anti-epileptic drugs (AEDs)—also offered as MBiomedSc

23. Real world assessment of falls risk using novel mobile technology—also offered as MBiomedSc

24. Is hyponatremia linked with low bone density in patients with epilepsy?—offered as MBiomedSc and potentially Honours

25. Polycystic Ovarian Syndrome (PCOS) in a cohort of young women—characterization and associations—also offered as MBiomedSc

26. Measuring bone and muscle health in young women—also offered as MBiomedSc

27. A critical analysis of Sunsmart behaviour in young Australian women—also offered as MBiomedSc

28. Recruitment of young women into health research via social networking sites: the impact of advertising and study characteristics—also offered as MBiomedSc.

29. Air pollution may impair vitamin D status in young Victorian women—also offered as MBiomedSc

30. Factors associated with self-perception of body image in young women—also offered as MBiomedSc

31. Fear of needles: evaluation of BrightHearts: A biofeedback mediated relaxation/distract app

32. Investigation of genes associated with increased risk of endometriosis


35. Brain Computer Interface—Evaluating the anatomical suitability of sheep as a model for a brain computer interface using retrograde axonal transport..


37. Sex differences in social dysfunction of paediatric brain injury

38. Post-traumatic epilepsy after traumatic injury to the paediatric brain

39. Does a mild traumatic brain injury during brain development alter the consequences of subsequent injury in adulthood?

40. The role of Co in brain injury and disease.
41. Treatment with an interleukin 1 receptor antagonist in a novel model of multi-trauma 13
42. Biomarkers of brain concussin in Australian Rules Footballers 13

CANCER .................................................................................................................................................... 14
43. Glioma stem cells: biology and molecular targets 14
44. Twist as a Regulator of EMT in Gastric Cancer and its role in invasion 14
45. Validation of candidate genes involved in the progression of gastric cancer 14
46. Role of the Tumour Microenvironment in Gastric Cancer 15
47. Characterization of cross-talk between tumour and stromal cells in inducing metastasis and resistance to chemotherapy in ovarian cancer. ONLY available for MBiomedSc 15
48. Elucidating the role of mesenchymal stem cells in promoting metastasis of ovarian cancer cells 16
49. TGF- signalling and cancer development 16
50. Integrated Genomics of metastatic, lethal Prostate Cancer 17
51. Prostate Cancer – what can we learn from its mistakes? 17
52. Integrated Genomics of Bladder Cancer 18
53. STAT3-mediates Resistance to EGFR targeted therapy in Cancer 18
54. The Molecular Determinants of Brain Tumour Progression and Resistance to Therapy 18
55. Using animal and human patient models to interrogate transcriptional networks in glioma 19
56. Using animal and human patient models to unravel new pathways driving glioma 19
57. Defining the epidermal growth factor receptor signaling network in brain tumour stem cells 20
58. Role of oncogenic signaling pathways on brain cancer cell – tumour microenvironment interactions 20
59. New roles for nutrient sensing kinases in brain cancer 20
60. Regulation of invadopodium function and involvement in cancer cell invasion 21
61. Molecular biomarkers for Human Papillomavirus-related cancer progression 21
62. Human Papillomavirus (HPV) Genotype Surveillance 21
63. In vitro brain tumour model – studying epileptic seizure development and sensitivity to anti-cancer therapy. 22

CANCER – FERTILITY PRESERVATION .......................................................................................................... 22
64. Fertility issues in children and adolescents with cancer 22

CARDIOLOGY ............................................................................................................................................ 23
65. Cardiac benefits by delayed reperfusion after acute myocardial infarction in mice 23
66. High resolution ultrasound evaluation of cardiac abnormalities in a mutant strain of mice with rheumatoid arthritis
67. Feasibility and effects of inorganic sodium nitrate in decompensted heart failure
68. Prospective evaluation of non-invasive cardiac haemodynamic assessment for therapeutic guidance in acute and ambulatory heart failure
69. Novel ways of Detecting and Managing Chronic Diseases (Chronic Kidney Disease/Diabetes/Cardiovascular Disease) in Primary Care
70. Do the coronary small vessels respond less well to medication in patients with diabetes or renal failure – also offered as MBiomedSc
71. Natural History of Coronary Plaque Evolution Through Optical Coherence Tomography – ONLY offered as MBiomedSc
72. Evaluation of Coronary Stent Apposition and Intimal Healing Through Optical Coherence Tomography – ONLY offered as MBiomedSc
73. Unravelling the neural circuits that drive increases in sympathetic nerve activity in heart failure
74. Central cardiovascular control: uncovering the role of inflammatory cytokines in the area postrema

CARDIOLOGY - PAEDIATRICS

75. Body composition and cardiovascular risk in children: The Longitudinal Study of Australian Children’s Child Health Check Point – also offered as MBiomedSc
76. Which measures of growth and body composition best predict cardiovascular risk in adults? A study of the parent cohort from The Longitudinal Study of Australian Children’s Child Health Check Point – also offered as MBiomedSc

CLINICAL RESEARCH

77. Hospital acquired electrolyte disorders – also offered as MBiomedSc

CLINICAL RESEARCH – SURGICAL

78. The utility of colonoscopy in women of child bearing age
79. Opportunities to diagnose Colorectal Cancer – are we missing them?
80. A scoring system for the assessment of process in rectal cancer management
81. The presentation of colorectal cancer in the era of screening
82. In patients with a foot wound undergoing revascularization surgery, what is the time frame for improvement in ankle and toe systolic pressures? A pilot study

COLORECTAL MEDICINE AND GENETICS

83. Serrated Polyposis Syndrome - also offered as MBiomedSc
84. Prospective studies on penetrance for cancer in Lynch Syndrome – also offered as MBiomedSc
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.</td>
<td>CAPP3: a randomized controlled trial of aspirin dosage in Lynch Syndrome – also offered as MBiomedSc</td>
<td>31</td>
</tr>
<tr>
<td>86.</td>
<td>The Human Variome Project (HVP) and familial bowel cancer - also offered as MBiomedSc</td>
<td>31</td>
</tr>
<tr>
<td>87.</td>
<td>Biogrid and IBD data basing - also offered as MBiomedSc</td>
<td>31</td>
</tr>
<tr>
<td>88.</td>
<td>Locus Specific Databases in Hamartomatous polyposis syndromes:</td>
<td>31</td>
</tr>
<tr>
<td>89.</td>
<td>The Structure and Functions of an Inflammatory Bowel Disease Service:</td>
<td>31</td>
</tr>
<tr>
<td>90.</td>
<td>C-reactive protein (CRP) and Crohn’s disease – CRP as a potential phenotypic marker for disease</td>
<td>32</td>
</tr>
<tr>
<td>91.</td>
<td>ELECTROPHYSIOLOGY.......................................................................32</td>
<td></td>
</tr>
<tr>
<td>92.</td>
<td>How do Anti-Epileptic Drugs Work? - also offered as MBiomedSc</td>
<td>32</td>
</tr>
<tr>
<td>93.</td>
<td>How do Antipsychotic Drugs Trigger Seizures? - also offered as MBiomedSc</td>
<td>32</td>
</tr>
<tr>
<td>94.</td>
<td>Multi-Electrode Recording in the Rat Brain - also offered as MBiomedSc</td>
<td>33</td>
</tr>
<tr>
<td>95.</td>
<td>ENDOCRINOLOGY, DIABETES &amp; BONE DENSITY .......................................33</td>
<td></td>
</tr>
<tr>
<td>96.</td>
<td>Assessment of the effect of ankle arthrodesis on muscle and bone function using an integrated experimental and computational approach– also offered as MBiomedSc</td>
<td>33</td>
</tr>
<tr>
<td>97.</td>
<td>EPILEPSY AND NEUROPHARMACOLOGY..................................................33</td>
<td></td>
</tr>
<tr>
<td>98.</td>
<td>Reducing Epilepsy Deaths – Learning from the NCIS (National Coronial Information System)</td>
<td>33</td>
</tr>
<tr>
<td>99.</td>
<td>Keeping the Brain and the Heart in Sync – HERG channels in the CNS - also offered as MBiomedSc</td>
<td>34</td>
</tr>
<tr>
<td>100.</td>
<td>Modelling Epilepsy and Epilepsy Drug Effects–Computational Neuroscience Project</td>
<td>34</td>
</tr>
<tr>
<td>101.</td>
<td>Sodium Channels in Epilepsy - also offered as MBiomedSc</td>
<td>34</td>
</tr>
<tr>
<td>102.</td>
<td>Long-term outcome of newly diagnosed epilepsy - also offered as MBiomedSc</td>
<td>35</td>
</tr>
<tr>
<td>103.</td>
<td>Investigating the role of a Cav3.2 calcium channel mutation in contributing to the epileptic phenotype using congenic rat strains and a knock in mouse model - also offered as MBiomedSc</td>
<td>36</td>
</tr>
<tr>
<td>104.</td>
<td>Investigating molecular and physiological determinants of Sudden Unexplained Death in Epilepsy in acquired and genetic animal models of epilepsy - also offered as MBiomedSc</td>
<td>37</td>
</tr>
<tr>
<td>105.</td>
<td>Serotonin in epilepsy</td>
<td>38</td>
</tr>
<tr>
<td>106.</td>
<td>Projects in network analysis of genetic epilepsy</td>
<td>38</td>
</tr>
<tr>
<td>107.</td>
<td>Multi-site patch clamp recording of cortical micro networks</td>
<td>38</td>
</tr>
<tr>
<td>108.</td>
<td>High density multi-electrode array recording of in vitro networks in epilepsy</td>
<td>39</td>
</tr>
</tbody>
</table>
109. In vivo electrophysiological analysis in mouse models of genetic epilepsy
110. “CLARITY” based glass brain imaging in health and disease
111. MRI tractography in mouse models of genetic epilepsy: Creation of prognostic and diagnostic structural biomarkers
112. High content automated analysis of ion channels in epilepsy
113. Optogenetic modulation of the area tempestas – an epilepsy hot spot
114. Zinc and seizures
115. Will HCN channel antagonists be good antiepileptic drugs?
116. Inhibitory neuron subtypes in cortical circuits: an examination of their structure, function, and connectivity

GASTROENTEROLOGY

117. Barrett’s Oesophagus – also offered as MBiomedSc

GENOMICS

118. GAERS versus NEC: Genetics of epileptic and non-epileptic rat strains– also offered as MBiomedSc
119. When synonymous mutations aren’t silent – also offered as MBiomedSc
120. Neurocognitive complaints and epilepsy prognosis – also offered as MBiomedSc
121. Genomics of adverse response to antiepileptic drugs - also offered as MBiomedSc

IMAGING

122. Neuroimaging
123. Network Activity in Brain Tissue Recorded with Combined Calcium and Voltage-Sensitive Dye Imaging and Electrophysiology - also offered as MBiomedSc

INFECTIOUS DISEASES AND IMMIGRANT HEALTH

124. Monitoring the efficacy of a training program in gastroenterology in the Pacific - also offered as MBiomedSc

INJECTING DRUG USE

125. Investigating blood/blood product donation practices among Australian people who inject drugs (PWID)
126. Exploring the similarities and differences of hepatitis C treatment and opiate substitution treatment therapy in people who inject drugs to inform increasing access HCV treatment in this population
127. The outcomes of transitioning between prison and community for people with a history of injecting drug use
128. The persistence of risk among people who inject drugs - also offered as MBiomedSc
129. Mapping public injecting drug use in urban Melbourne - also offered as MBiomedSc
130. Understanding and reducing the barriers to community based point of care hepatitis C testing in people who inject drugs

**INNATE IMMUNITY AND HOST DEFENCE**

131. Immune Cell Signalling Regulation During Inflammation

**INNATE PHAGOCYTOSIS & NEURODEGENERATION**

132. Leukocyte surface and functional biomarkers for prognosis of age-related macular degeneration

133. Identification of serum glycoproteins inhibiting innate immunity - also offered as MBiomedSc

134. How does the brain remove the excess number of neurons during development and aging - also offered as MBiomedSc

135. Identify the transcriptional regulatory factors of the P2X7 receptor - also offered as MBiomedSc

**MALARIA**

136. Hiding out in the Placenta. Investigating how glycosaminoglycans can modulate the immune system during malaria and pregnancy.

137. Cross reactive antigens expressed in severe malaria

138. Are novel bromodomain proteins required for malaria parasite growth and gene regulation?

139. Gene regulation mechanisms in the transmissible stages of the malaria parasite - also offered as MBiomedSc

140. Characterizing new surface proteins of the malaria parasite - also offered as MBiomedSc

141. Investigating the effects of GM-CSF and M-CSF derived human macrophages on phagocytosing *P. falciparum* infected erythrocytes and cytokine production - also offered as MBiomedSc

142. A role for Adipose Tissue in Malaria? - also offered as MBiomedSc

143. Investigating the acquisition and maintenance of immunity to malaria in infants and pregnant women

144. Identifying antigen targets of the acquired immune response during severe malaria

145. Understanding the targets and mechanisms of human immunity to malaria

146. Developing new diagnostics and treatments for malaria

147. Vaccines against malaria

148. Identifying targets and mechanisms of the acquired immunity to severe malaria in children

149. Understanding mechanisms that mediate human immunity to malaria

150. Developing new diagnostics and treatments for malaria

151. Healthy Mothers, Healthy Babies in Papua New Guinea – The impact of Nutrition, Malaria and STIs on pregnant women and infants

152. Development of novel point-of-care diagnostics tests and surveillance tools

154. Host cell modification in malaria parasites. – *also offered as MBiomedSc* 

**MEDICATION SAFETY**

155. How do cognitive and functional impairment relate to the use of anticholinergic medications in patients aged 65 years and over in rehabilitation and geriatric evaluation and management settings? – *also offered as MBiomedSc*

156. Safe and appropriate medication prescribing of older patients with coronary heart disease in hospital - *also offered as MBiomedSc*

**MOTOR NEURON DISEASE**

157. Neurodegeneration – Stimulating autophagy to improve intracellular proteostasis in MND - *also offered as MBiomedSc*

158. Neurodegeneration – Transcriptomic profiling of motor neuron populations in development and MND - *ONLY offered as MBiomedSc*

**MULTIPLE SCLEROSIS/NEUROLOGY**

159. Defining cervical dysplasia incidence and management in immune-compromised patients with Multiple Sclerosis

160. Investigating the effects of vitamin D treatment on immune cells of people with Multiple Sclerosis - *also offered as MBiomedSc*

161. Management of radiologically active relapsing remitting multiple sclerosis - *also offered as MBiomedSc*

162. How does therapy change the course of multiple sclerosis relapses? - *also offered as MBiomedSc*

163. Does disease modifying therapy change the phenotype of multiple sclerosis relapses? - *also offered as MBiomedSc*

**NEPHROLOGY**

164. Finding genetic mutations in new types of inherited kidney disease: focal segmental glomerulosclerosis – *also offered as MBiomedSc*

**NEUROPSYCHIATRY AND STRESS BIOLOGY**

165. The relationship between dietary quality, nutrient biomarkers, and major depressive disorder – *also offered as MBiomedSc*

166. Integrative modelling of a microglial response to neuroinflammation and the role of mGluR5: Implications for neuronal homeostasis.

167. 3D Cortical Modelling Using Biomaterials

168. Towards a brain-based measure of human anxiety sensitivity (*offered as MSc only*) – *ONLY available as MBiomedSc*
<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Additional Notes</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>169</td>
<td>Predicting treatment response in young people with major depression using functional neuroimaging – ONLY available as MBiomedSc</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>170</td>
<td>Mapping the Human Schizophrenia Connectome – also offered as MBiomedSc</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>171</td>
<td>Human Connectome Bioinformatics – also offered as MBiomedSc</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>172</td>
<td>Neuroimaging in schizophrenia-spectrum disorders – also offered as MBiomedSc</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>173</td>
<td>Effects of oxytocin genetic variants on brain and behavior in schizophrenia</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>174</td>
<td>MRI volumetry and shape analysis in frontotemporal dementia and schizophrenia</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>175</td>
<td>Characterisation of physiological stress responses in patients with depression and epilepsy - also offered as MBiomedSc</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>176</td>
<td>Functional disconnections and the pathophysiology of psychosis - also offered as MBiomedSc</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>177</td>
<td>Antidepressants in epilepsy</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>178</td>
<td>Temporal lobe epilepsy, the HPA axis and depression - also offered as MBiomedSc</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>179</td>
<td>Does stress contribute to epilepsy? - also offered as MBiomedSc</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>180</td>
<td>High Frequency Brain Wave Patterns in a Rodent Model of Schizophrenia</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>181</td>
<td>Estrogen, antipsychotics and schizophrenia – also offered as MBiomedSc</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>182</td>
<td>Early life stress and memory development</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>183</td>
<td>Regulation of emotional memory across development</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>184</td>
<td>The role of dopamine receptor 1 vs 2 in adolescent vulnerability to anxiety.</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>185</td>
<td>Neural circuitry underlying extinction of fear across development.</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>186</td>
<td>Understanding the transcriptional effects of estrogen based therapies in the CNS.</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>187</td>
<td>Deciphering the receptor mediated pathways which regulate neural synchrony and cognitive ability</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>188</td>
<td>Towards preventative prenatal treatment strategies for schizophrenia</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>189</td>
<td>Understanding the genetic contribution to schizophrenia</td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

**NEUROVASCULAR**

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Additional Notes</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>190</td>
<td>Imaging predictors of neurological recovery post acute stroke intervention</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>191</td>
<td>Continuous monitoring of motor recovery post acute stroke rescue: development of a broadband-based portable motion detector (REWIRE system) - also offered as MBiomedSc</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>192</td>
<td>Acute stroke rescue: clot retrieval. Does imaging characteristics predict the histopathology of clot composition? - also offered as MBiomedSc</td>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

**NEWBORN RESEARCH**

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Additional Notes</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>Breathing support in extremely premature babies – reducing nasal trauma</td>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>
194. What are the genes affected in structural renal disease and renal complement diseases? – also offered as MBiomedSc

195. Small vessel disease causing stroke and dementia – also offered as MBiomedSc

196. The Contribution of Endothelial Progenitor Cells to Retinal Vascular Regeneration

197. Pharmacogenomics in IBD - also offered as MBiomedSc

198. Development of a low cost, point-of-care diagnostic test to prevent abacavir hypersensitivity

199. Express ambulatory point-of-care molecular diagnosis - also offered as MBiomedSc

200. A decision support system for implementation of pharmacogenomics in epilepsy treatment - also offered as MBiomedSc

201. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire - also offered as MBiomedSc

202. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effect - also offered as MBiomedSc

203. Pharmacogenetics: do mutations in CYP 2C19 alter the clinical effectiveness of clopidogrel in patients with cerebrovascular disease? - also offered as MBiomedSc

204. A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy - also offered as MBiomedSc

205. Life-long Lifestyle Factors for Healthy Ageing – also offered as MBiomedSc

206. Iron and Fatigue – also offered as MBiomedSc

207. Vitamin D deficiency and balance - also offered as MBiomedSc

208. An epidemiological exploration of the HIV cascade in Victoria

209. Sexting, porn, and Tinder. An investigation of education and health promotion needs and evidence

210. Sex, drugs and rock’n’roll: Young people and risk behaviours

211. Agents of YEAH Needs Assessment

212. Trends in STI testing and positivity in priority populations in Australia

213. Understanding risky single occasion drinking and links to harms in a cohort of young Melburnians – also offered as MBiomedSc

214. Modeling the syphilis epidemic in Victoria – also offered as MBiomedSc

215. Low income as a barrier to opioid substitution therapy - also offered as MBiomedSc
216. Understanding changes in haemostasis during pregnancy and pregnancy complications – also offered as MBiomedSc

217. Stem cells and their Potential to Treat Clinically Important Disorders of Pregnancy - also offered as MBiomedSc

218. Stem Cell Microvesicle Repair of the Damaged Endothelium in Preeclampsia. - also offered as MBiomedSc

219. How do hormones work: investigating new steroid receptors

220. Can dietary phytophenols prevent the development of diabetes in pregnancy? - also offered as MBiomedSc

221. Can dietary phytophenols stop preterm birth? - also offered as MBiomedSc

SPINAL CORD INJURY .................................................................76

222. Acute management of traumatic central cord syndrome

2015/16 KEY DATES ........................................................................77

HONOURS ENTRY REQUIREMENTS .............................................77

HONOURS COURSEWORK ..........................................................77

HOW TO APPLY - HONOURS .....................................................78

MASTER OF BIOMEDICAL SCIENCE - COURSEWORK .............80

HOW TO APPLY - MBIOMEDSC ................................................80

ENQUIRIES .................................................................................81

RMH DEPARTMENT LINKS: .......................................................81
### AGEING

1. **Acquired epilepsy in Alzheimer’s disease - also offered as MBiomedSc**
   - **Supervisors:** Professor Patrick Kwan, Dr Nigel Jones
   - **Project Sites:** Department of Medicine (RMH), Melbourne Brain Centre at Parkville
   - **Contact:** Professor Patrick Kwan, E: Patrick.kwan@unimelb.edu.au
     Dr Nigel Jones, E: ncjones@unimelb.edu.au
   - **Project description:** People with Alzheimer’s disease (AD) are 10 times more likely to develop epilepsy compared with age-matched controls. Recurrent seizures and their treatment with conventional antiepileptic drugs may exacerbate cognitive decline, yet the pathological basis for the increased risk of epilepsy is largely unknown, and there are no treatments that prevent epilepsy in AD patients. The relationships between the pathological processes of AD and neuronal hyperexcitability are poorly understood. Elucidating the pathomechanisms of epileptogenesis in AD is critical in identifying effective therapeutic strategies to prevent the development of epilepsy in this high risk and vulnerable population.

   The novelty of this project lies in its aims to directly address the mechanisms of epileptogenesis in AD through the study of relevant animal models of AD and acquired epilepsy. It will identify the mechanistic processes of epileptogenesis in AD under a coherent hypothesis. The aims will be achieved by subjecting transgenic AD models reflecting the pathological hallmarks to acquired epileptogenesis and treating them novel compounds. The phenotypic changes (epileptogenesis and cognitive/behavioural outcomes) will be correlated with the molecular and cellular changes in these pathways. The findings will identify novel therapeutic approaches to prevent the development of epilepsy in AD patients.

2. **Characterisation of the Onset and Progression of Tauopathy in the Pontomedullary Brainstem Nuclei of mice undergoing Neurodegeneration**
   - **Supervisors:** Dr Davor Stanic, Dr Tara Bautista and A/Prof Mathias Dutschmann
   - **Project Site:** Florey Institute of Neuroscience and Mental Health (Howard Florey Laboratories)
   - **Contact:** Dr Davor Stanic T: 83440182 E: davor.stanic@florey.edu.au
   - **Project description:** Swallowing disorders that increase the risk of aspiration and subsequent pneumonia are prevalent in the elderly and patients suffering neurological diseases, such as Alzheimer’s disease. Swallowing disorders are often attributed to weakening of the aging upper airway and digestive tract musculature; however, disturbed neural coordination of breathing and swallowing is increasingly evident in such diseases. Recent research in our laboratory identified three key brainstem areas that are critically involved in the coordination of swallowing and breathing: 1) **Nucleus of the solitary tract (NTS)**, which generates a phasic or rhythmic ‘command’ to produce sequential swallowing in response to sensory stimuli; 2) **Nucleus ambiguus (NA)**, which contains the laryngeal motoneurons innervating the vocal folds; and 3) **Kölliker-Fuse nucleus (KF)**, which provides tonic drive for the laryngeal adductors and completely seals the trachea during, and between, swallows.

   **PROJECT 1**
   This project examines the underlying brainstem pathology linking dementia and swallowing dysfunction in an established mouse model of neurodegeneration. The onset and progression of tauopathy and neurofibrillary tangle-related morphology will be characterised in the brainstem of mice undergoing neurodegeneration, with particular focus on the NTS, NA and KF. The project also aims to identify the neurochemical profile of neurons in these brainstem regions that are susceptible to tauopathy.

   **PROJECT 2**
   Using adult born stem cells to replace neurons lost as a consequence of disease has the potential to be of great benefit to sufferers of neurodegenerative disorders. However, despite the extensive research efforts that have gone into examining
the biology and therapeutic potential of adult stem cells, the precise cues that modulate the birth of neurons in the adult brain remain unknown.

This project examines whether: a) the rate of stem cell division; b) migration of newly born cells; and c) the positioning and phenotype of newly born cells in the olfactory bulb and dentate gyrus, are altered in an established model of neurodegeneration.

Techniques include: immunohistochemistry, and stereology

3. **Lifestyle Factors for Healthy Ageing – also offered as MBiomedSc**
   Supervisor: A/Professor Cassandra Szoeke
   Project Site: Dept of Medicine, UoM, Parkville, Vic 3052.
   Women’s Healthy Ageing Project (WHAP)
   Contact: A/Professor Cassandra Szoeke T: 61 3 8344 1835
   E: cszoeke@unimelb.edu.au
   **Project Description:** Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. For example smoking, alcohol consumption and a lack of physical activity have been linked to an increased rate of cognitive impairment and cardiovascular diseases. Studies investigating lifestyle factors have been limited by cohort sampling bias, cross sectional designs, short follow-ups and small sample sizes. Furthermore the frequency and intensity of lifestyle alteration is still not defined. In this project we examine a 20 year longitudinal dataset to determine the influence of lifestyle (i.e. alcohol consumption, smoking, diet and physical activity) on cognitive performance and health.

   This project will involve direct hands-on participant evaluation. You will also have the opportunity to work with a rich database with lifestyle data that spans over 20 years. As well as an opportunity for publication.

4. **Causes of Depressive Symptoms in Early Ageing – also offered as MBiomedSc**
   Supervisor: A/Professor Cassandra Szoeke
   Project Site: Dept of Medicine, UoM, Parkville, Vic 3052.
   Women’s Healthy Ageing Project (WHAP)
   Contact: A/Professor Cassandra Szoeke T: 61 3 8344 1835 E: cszoeke@unimelb.edu.au
   **Project Description:** It is predicted that by 2051, 26.1% of Australians will be older than 65 years and 9.4% will be 80 years or older (Australian Bureau of Statistics, 2001). With prevalence rates of depression in the elderly set to rise in accordance with the population surge identifying preventative measures and means of early detection in this population is especially important. The focus of this project will be to examine factors which affect the rating of depressive symptoms on three different standardised and widely used measures in a cross-section of women entering late-life. The Hospital Anxiety and Depression Scale (HADS), the Centre for Epidemiological Studies – Depression Scale (CES-D) and the Geriatric Depression Scale (GDS) will be administered to the cohort of the Women’s Healthy Ageing Project in 2012/2013. Analysis will be conducted examining the consistency of item rating between measures in order to identify correlations between scales. Psychological and social data will also be obtained from the cohort and will allow for the identification of any factors influencing the rating of measures.

   Major benefits from this study are:
   1. There is opportunity for publication within one year
   2. You will have access to a unique database with two decades of psychological and social data
   3. This study would be particularly suited to an individual wishing to gain experience in the areas of geriatric psychology and/or depression.

5. **Alcohol use and effects on mood in elderly women – also offered as MBiomedSc**
   Supervisors: A/Professor Cassandra Szoeke
   Project Site: Dept of Medicine, UoM, Parkville, Vic, 3052.
   Contact: A/Professor Cassandra Szoeke T:61 3 8344 1835 F: 61 3 9387 9384
   E: cszoeke@unimelb.edu.au
   **Project Description:** Alcohol consumption in women is becoming an increasing public health concern. Depression, the most prevalent and persistent mental disorder in women, has been shown to be related to alcohol consumption. This study examines the association between alcohol intake and depression in community-dwelling older women.

   The Women’s Healthy Ageing Project (WHAP) has prospective longitudinal, epidemiological data on alcohol consumption and mood of Australian women from age 45 over 25 years.
6. Early detection and prevention of age associated diseases using imaging - **ONLY offered as MBiomedSc**

**Supervisor:** Professor Patricia Desmond, A/Professor Cassandra Szoeke  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic 3052.  
Women’s Healthy Ageing Project (WHAP)  
**Contact:** A/Professor Cassandra Szoeke T: 61 3 8344 1835  
E: cszoeke@unimelb.edu.au / Cassandra.szoeke@mh.org.au

**Project Description:** Australia’s population is ageing at a dramatic rate with about two million people aged over 70 years at present. As populations age, the disabilities of the oldest age groups become increasingly important. Studies have identified cardiovascular diseases to be the most prevalent chronic disease in the elderly, followed by cognitive impairment. Identifying the at-risk population for these illnesses is an important step towards developing treatment and prevention strategies. An aim of this study is to examine emerging measures for identifying early at-risk populations in an epidemiologically sampled cohort of women. These measures include the use of Magnetic Resonance Imaging (MRI) neuroimaging quantifying the accrual of white matter hyperintensities (WMH) as a measure of cerebrovascular disease (CVD). It has been found that white matter hyperintensity volume could predict 1-year cognitive decline, and therefore should be considered as a variable of interest in AD trials.

Major benefits from this study are:-
- The study has data over 20 years already collected
- There is opportunity for a publication
- This project will suit a candidate with an interest in neuroimaging

7. Can statins protect against cognitive decline associated with dementia? - **also offered as MBiomedSc**

**Supervisors:** A/Professor Cassandra Szoeke  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic, 3052. Women’s Healthy Ageing Project (WHAP).  
**Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F: 61 3 9387 9384  
E: cszoeke@unimelb.edu.au

**Project Description:** Cognitive impairment is becoming an increasingly researched field in ageing, particularly with dementia being in the top five leading causes of burden in Australia. Despite these already high and increasing prevalence rates, there is no curative treatment for AD. Therefore the identification of individuals who are at increased risk of AD and the implementation of preventive interventions is necessary until a treatment is found. Cardiovascular risk factors, including cholesterol, are typically thought to be associated with an increased risk of dementia. However the use of statins (cholesterol lowering medication) and its effect on cognitive performance has not been thoroughly investigated, particularly assessing duration of use. This research will help us identify the short term and long term effects of cholesterol-lowering medication on cognition, and whether statins can be used as prevention against dementia.

Major benefits from this study are:-
- A unique opportunity to work on an Australian dataset with midlife and late-life data collected (data over 20 years).
- There is opportunity for publication within one year.
- This project will suit a candidate with interest in commercialisation and ageing.

8. Nutrient intake and plasma beta-amyloid - **also offered as MBiomedSc**

**Supervisors:** A/Professor Cassandra Szoeke  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic, 3052. Women’s Healthy Ageing Project (WHAP).  
**Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F: 61 3 9387 9384  
E: cszoeke@unimelb.edu.au

**Project Description:** There is increasing evidence to suggest that diet may play an important role in preventing or delaying the on-set of Alzheimer’s disease (AD). Research has reported that a Mediterranean-type diet is associated with a lower risk of prevalent AD. One important pathological hallmark of AD is beta-amyloid (Aβ) peptide deposition in the brain, resulting in formation of plaques. However little is known about the possible association between nutrient intake and Aβ plasma. In this study, we will examine whether dietary intake of nutrients (data already collected from a food frequency questionnaire) is associated with plasma Aβ levels in a cross-sectional analysis of women aged 65 years and over. Aβ levels will be examined using Positron Emission Tomography (PET) scans (data already collected) in collaboration with imaging experts.

Major benefits from this study are:-
- The nutritional data set has already been collected
- The project will suit a candidate with interest in dietary factors and health
- There is opportunity for publication within one year
- This project will suit a candidate with an interest in media or commercialisation and is keen for industry interaction

You will gain invaluable experience and networking opportunities in ground breaking research
9. **Current definitions of sarcopenia: Associations with indicators of falls and fracture risk in older adults** - *also offered as MBiomedSc*

   *Supervisors: Dr David Scott, A/Professor Kerrie Sanders*
   *Project Site: Melbourne Medical School, Sunshine Hospital, St Albans*
   *Contact: Dr David Scott T: 8395 8108 E: d.scott@unimelb.edu.au*

   **Project description:** Sarcopenia describes the age-related decline in skeletal muscle mass and function which leads to disability in older adults. Sarcopenia does not receive adequate attention in clinical settings in part due to a number of conflicting definitions and assessment techniques. This study will investigate whether sarcopenia defined by current definitions is associated with indicators of falls (including balance and walking ability) and fracture (including bone quality measurements using dual-energy X-ray absorptiometry and peripheral quantitative computed tomography) risk in community-dwelling older adults.

10. **The metabolic syndrome and musculoskeletal health in older adults** - *also offered as MBiomedSc*

    *Supervisors: Dr David Scott, A/Professor Kerrie Sanders*
    *Project Site: Melbourne Medical School, Sunshine Hospital, St Albans*
    *Contact: Dr David Scott T: 8395 8108 E: d.scott@unimelb.edu.au*

    **Project description:** The metabolic syndrome is a constellation of cardiometabolic disorders including visceral obesity, dyslipidaemia, hyperglycaemia and hypertension. The metabolic syndrome is highly prevalent in older adult populations. In addition to increased risk for cardiovascular disease and type II diabetes, it is likely that the metabolic syndrome contributes to declines in muscle (sarcopenia) and bone (osteoporosis) quality with age. This study will investigate whether older adults with the metabolic syndrome demonstrate poorer muscle and bone quality, determined by advanced imaging techniques, compared to healthy older adults.

**ALCOHOL**

11. **Why do some people with hepatitis C continue to drink?** - *also offered as MBiomedSc*

    *Supervisor: Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute*
    *Project Site: Burnet Institute*
    *Contact: E: Hellard@burnet.edu.au*

    **Project Description:** Acquiring hepatitis C (HCV) in the developed world, once infected with HCV, alcohol use is the strongest known modifiable determinant of HCV disease progression. Alcohol consumption has been found to raise the viral load and accelerate hepatic fibrosis in the context of HCV infection, and heavy alcohol consumption is a risk factor for premature death from HCV. Moreover, as well as impacting on liver disease progression, heavy alcohol use may influence the likelihood of successful HCV treatment.

    The proposed project involves in-depth interviews with up to 25 consenting participants living with HCV from the Melbourne Injecting Cohort Study (MIX). Interviews will address alcohol use and other related exposures and outcomes, including participants’ alcohol consumption prior to and after HCV diagnosis, any medical advice regarding alcohol consumption they may have received, advice from peers with HCV regarding alcohol consumption, perception of alcohol consumption practices amongst peers with HCV, participants’ understanding of the relationship between alcohol-related and injecting drug use-related behaviours, clinical symptoms and other effects of HCV on relationships and self-perception, current self-management strategies for living with HCV.

**ANAESTHESIA AND PERIOPERATIVE MEDICINE**

12. **The evaluation of anaesthetic drugs and techniques on the postoperative quality of recovery** – *also offered as MBiomedSc*

    *Supervisors: Prof Colin Royse*
    *Project Site: The Royal Melbourne and Epworth Hospital campuses*
    *Contact: Prof Colin Royse colin.royse@unimelb.edu.au*

    **Project description:** Improving postoperative quality of recovery is a major initiative in anaesthesia and perioperative medicine. Different anaesthetic drugs and different techniques will be evaluated in clinical trials using the Postoperative Quality of Recovery Scale (PostopQRS) as the measurement tool. This tool measures recovery from the patient’s perspective in physiological, emotive, nociceptive, functional and cognitive domains. Projects are already established, ethics in place and commenced.
ARTHRITIS AND INFLAMMATION RESEARCH CENTRE

The Arthritis and Inflammation Centre is headed by Professor John Hamilton who leads a team of scientists that focuses on inflammation-associated diseases, including arthritis, host pathogen interaction and cancer. The pathology of most diseases involve some degree of inflammation with macrophages often being the major cell type; as a result the Centre focuses primarily on macrophage biology and the effects of macrophage-associated inflammation on other cell types such as stem cells.

We employ a variety of techniques and strategies including gene-based strategies (for example, micro-array technology) to understand disease causation, protein-based strategies (including proteomics, immunoprecipitation, cell transfection) to study the cellular signal transduction pathways associated with disease, and mouse models and clinical material to analyse disease in vivo.

Key components of the biology involve an analysis of how macrophage lineage cells are altered during inflammatory disease, how at a molecular level these cells survive, proliferate, differentiate or are activated, and how to down-regulate the cellular functions aberrant in disease. There is some emphasis on growth factor biology/biochemistry and on signal transduction pathways implicated strongly in human arthritis, cancer and stem cell biology.

13. The role of urokinase plasminogen activator (u-PA) and its receptor (u-PAR) in arthritis and inflammation

**Supervisor:** Dr Andrew Cook  
**Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr Andrew Cook T: 8344 3290 E: adcook@unimelb.edu.au

**Project Description:** Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the population. Fibrin deposition, cell migration, and tissue destruction and remodeling are key components in the pathology of RA joints. The plasminogen activators (PAs), urokinase (u-PA) and tissue-type (t-PA), which converts plasminogen to plasmin, are implicated in these processes; however their precise roles in such processes, particularly for u-PA and its receptor (u-PAR), have yet to be defined. In this project you will study the role of u-PA and the u-PAR, in inflammation and arthritis using mice genetically altered mice such that u-PA or u-PAR have been rendered inactive. In particular, the effect of u-PA on cell migration to an inflammatory site, on tissue destruction and remodeling, and in activating/suppressing other key cytokines/proteases (eg metalloproteinases (MMPs)) involved in these processes will be studied.

**Skill acquisition:** experience with animal models of human disease, measurement of inflammatory mediator mRNAs by real time-PCR and their concentrations by ELISA, and the use of FACS and immunohistochemistry to study cell populations.

14. The role of granulocyte macrophage colony stimulating factor (GM-CSF) in arthritis and inflammation

**Supervisor:** Dr Andrew Cook  
**Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr Andrew Cook T: 8344 3290 E: adcook@unimelb.edu.au

**Project Description:** Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the population. We have shown that GM-CSF is important for the development of several models of inflammation and arthritis. Furthermore, blockade of GM-CSF is effective at reducing arthritis severity. Phase 1 clinical trials are now underway in human rheumatoid arthritis. However, we still do not completely understand how GM-CSF is acting during inflammation and arthritis. In this project you will study the role of GM-CSF in inflammation and arthritis, and in particular, its role in monocyte/macrophage survival and activation.

**Skill acquisition:** experience with animal models of human disease, measurement of inflammatory mediator mRNAs by real time-PCR and their concentrations by ELISA, and the use of FACS and immunohistochemistry to study cell populations.

15. The role of Interferon Regulatory factors in Arthritis

**Supervisors:** Dr Andrew Cook and Prof John Hamilton  
**Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr Andrew Cook T: 8344 3290 E: adcook@unimelb.edu.au

**Project Description:** Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. In this project you will investigate how the transcription factors, called interferon regulatory factors (IRFs), control gene
expression in macrophages during inflammatory models of arthritis. You will also determine if targeting IRFs would be a beneficial treatment for arthritis.

You will be cutting tissue sections and measuring the expression of these novel proteins. You will be inducing murine models of arthritis, measuring a number of clinical parameters, collecting and processing tissue, and measuring gene/protein expression by histology, real-time PCR, Western blotting and FACS analysis. You will also be using siRNA, and nanoparticles to deliver therapeutic drugs in the arthritis models.

**Skill acquisition:** a variety of molecular and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting

### 16. The role of a novel macrophage inflammatory mediator in arthritis

**Supervisors:** Dr Andrew Cook and Prof John Hamilton  
**Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr Andrew Cook T: 8344 3290 E: adcook@unimelb.edu.au

**Project Description:** Through a microarray screen of inflammatory macrophages we have identified a novel potential therapeutic target for the treatment of arthritis. Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. In this project you will investigate the expression of this potential therapeutic target in patients’ tissue samples and in an inflammatory model of arthritis, and determine if targeting this protein would be a beneficial treatment. In this project you will be cutting tissue sections and measuring the expression of this novel protein. You will be inducing a murine model of arthritis and measuring a number of clinical parameters, collecting and processing tissue, and measuring gene/protein expression by histology, real-time PCR, Western blotting and FACS analysis. You will also be using siRNA, and nanoparticles to deliver therapeutic drugs in the arthritis model.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting

### 17. Molecular signaling pathways controlling gene expression during chronic disease progression

**Supervisors:** Dr. Adrian Achuthan and Prof. John Hamilton  
**Project Site:** Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr. Adrian Achuthan T: 8344 3298 E: aaa@unimelb.edu.au

**Project Description:** Inflammation is now known to be associated with many chronic diseases such as cancer, Alzheimer’s disease, obesity/type II diabetes and heart disease. This project aims to understand molecular signalling pathways controlling the expression of genes critical for the progression of such diseases. In this project you will explore in molecular terms how a particular inflammatory cell type (macrophage/dendritic cell) can adapt to provide a pro-inflammatory environment with consequences for persistence or otherwise of these significant diseases. More specifically, you will investigate how transcription factors control the expression of pro-inflammatory and anti-inflammatory cytokines. Elucidation of these molecular pathways may lead to the development of novel therapies.

**Techniques:** You will acquire a wide-range of skills in cell biology (primary human monocytes/macrophage culture, ELISA assays, confocal microscopy and flow cytometry), and biochemistry and molecular biology (Western blotting, Real-Time PCR and siRNA-mediated gene knock-down).

### 18. Elucidating molecular signaling pathways controlled by anti-inflammatory steroids

**Supervisors:** Dr. Adrian Achuthan and Prof. John Hamilton  
**Project Site:** Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr. Adrian Achuthan T: 8344 3298 E: aaa@unimelb.edu.au

**Project Description:** Steroids (glucocorticoids) are widely used to treat the chronic inflammation and pain associated with many diseases such as rheumatoid arthritis and osteoarthritis. Unfortunately, there are side effects associated with usage of glucocorticoids in such diseases. In this project you will use genome-wide approaches such as microarray to indentify the genes that are regulated by glucocorticoids. More specifically, you will investigate molecular signalling pathways that lead to activation of transcription factors that lead to differential expression of glucocorticoid-controlled genes in inflammatory conditions. Enhancing our understanding of molecular signalling pathways that are governed by glucocorticoids may lead to improved clinical therapies with minimal side effects.

**Techniques:** You will acquire a wide-range of skills in cell biology (primary human monocyte/macrophage culture, ELISA assays, confocal microscopy and flow cytometry), and biochemistry and molecular biology (Western blotting, Real-Time PCR and siRNA-mediated gene knock-down).
AUTISM

In this project, the aim is to elicit and characterise sniffing and other upper airway behaviours in the *in situ* preparation of rodents, a premier tool for studying central respiratory control. Techniques involved will include electrophysiology (nerve recordings) and immunohistochemistry.

19. **Investigating the mechanism of action of antipsychotic drugs in brain regions regulating aggression in a mouse model of Autism** - also offered as MBiomedSc

*Supervisors:* Dr Elisa Hill, Professor Anthony Hannan & Professor Terence O’Brien
*Project Site:* Department of Medicine (RMH), University of Melbourne
*Contact:* Elisa Hill E: elhill@unimelb.edu.au; Prof Anthony Hannan E: anthony.hannan@unimelb.edu.au; Prof Terence O’Brien E: obrientj@unimelb.edu.au

**Aim of Project:** Studying neuronal activity in brain regions regulating aggression in the NL3 mouse model of Autism. Specifically, the project will investigate:

i. Changes in excitatory/inhibitory activity, and
ii. effects of antipsychotic drugs on network activity in brain slices.

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder characterised by impairments in social interactions, communication, and repetitive behaviour. Aggressive behaviour is reported in 49-68% of ASD patients. Atypical antipsychotics such as risperidone are prescribed for children with ASD demonstrating aggressive behaviours. However, side effects are common and treatments are not effective for all patients. The mechanisms of action of risperidone are not well characterised.

NL3 mice express a mutation in the Neuroligin-3 gene identified in two brothers with autism. These mice show a robust aggressive phenotype which is reversed with risperidone treatment. To determine how risperidone affects neuronal activity, this project will examine the neurophysiology of specific brain regions involved in the neurobiology of aggression: i) the prefrontal cortex, ii) ventromedial hypothalamus (VMH), iii) basolateral amygdala, and iv) the periaqueductal gray (PAG)).

**Skills:** Characterisation of neuronal subtypes and network activity using patch clamp electrophysiology in brain slices, fluorescence immunohistochemistry in fixed slices for cellular morphology.

BONE AND MINERAL RESEARCH

20. **Investigating the interaction between skeletal muscle and bone** – also offered as MBiomedSc

*Supervisors:* Dr Jonathan Gooi
*Project Site:* Department of Medicine RMH, University of Melbourne
*Contact:* Dr Jonathan Gooi, Tel: 9288 2598; email: jgooi@unimelb.edu.au

**Project Description:** Skeletal muscle has a close functional relationship with bone. Both show major changes during aging and in the same way, sarcopenia and osteoporosis both contribute to frailty. Throughout life, the tissue mass of bone and muscle are intimately connected. Increases in muscle and bone mass result from weight-bearing exercise, while disuse results in the loss of both. For example muscular dystrophies are associated with relatively low bone density and an increased incidence of fractures. Conversely, significant increases in muscle mass, resulting from myostatin deficiency is associated with increases in bone mineral density. Despite these observations pointing to a coupling of bone and muscle mass, the precise mechanisms responsible for synchronizing bone and skeletal mass remains unclear.

A variety of clinical observations have provided support for the hypothesis that skeletal muscle plays an integral role in normal bone formation. It has previously been observed that covering bone fractures with muscle flaps improves fracture healing in cases of traumatic orthopaedic injury, whereas damage to muscle surrounding a bone fracture can delay fracture healing. These observations suggest that skeletal muscle has the capability to act as a local paracrine or endocrine source of osteogenic factors. This has important implications for the field of bone biology as it provides novel therapeutic opportunities for targeting muscle in order to restore the osteoporotic skeleton.

While the ability of skeletal muscle to secrete growth factors and cytokines is well established, the impact of the skeletal muscle secretome on bone is less well understood, with a large number of unanswered questions. For example, how do muscle and bone cells communicate and regulate each other’s functions? Do skeletal muscle secreted products have specific effects on osteoblastic bone formation, osteoclastic bone resorption or osteocytic mechanosensing? Does the skeletal muscle secretome differ based on the type of muscle activity such as concentric and eccentric contraction, disuse or damage? Are these signals dependent on mechanical stimulation and what effects do loading/unloading have? Finally, do bone-derived signals influence skeletal muscle function? These unanswered questions demonstrate the need to
critically address the cellular interactions between skeletal muscle and bone. Therefore the aim of this project is to investigate cellular communication between muscle and bone cells.

21. **Developing New Therapies for Musculoskeletal Disease – Investigating the Fundamental Mechanisms of Osteocyte Mechanosensing**— *also offered as MBiomedSc*

   **Supervisors:** Dr Jonathan Gooi  
   **Project Site:** Department of Medicine RMH, University of Melbourne  
   **Contact:** Dr Jonathan Gooi, Tel: 9288 2598; email: jgooi@unimelb.edu.au

The human skeleton performs a variety of essential roles for our daily health and wellbeing, including protection of vital organs, movement, blood cell production and a reservoir for mineral storage. Throughout our lives our skeleton undergoes continual remodelling to successfully fulfill these roles. However, an imbalance of remodelling can result in severe musculoskeletal diseases, including osteoporosis, which affects millions of people worldwide. Currently, treatments of osteoporosis prevent further bone loss, however are not capable of forming new bone. Thus, there is an urgent need for treatments that can rebuild fragile bones. This project aims to address the fundamental causes of musculoskeletal disease, specifically osteoporosis.

This project will capitalise on my recent development of a novel three dimensional (3D) osteocyte cell culture model which will enable, for the first time, an in depth investigation of osteocyte differentiation and mechanosensing in an in vivo like setting. Therefore, the broad aim of this work is to characterize the fundamental mechanisms by which osteocytes differentiate, contribute to the sensing of mechanical load and to understand their role in the control of osteoclast and osteoblast function and the maintenance of bone strength throughout life. This knowledge will be readily translated into new interventions strategies to improve osteoporosis outcomes and aid in the treatment of musculoskeletal disease.

The specific aims are to:
1) Investigate the mechanisms of osteocyte differentiation  
2) Determine how osteocytes perceive mechanical signals  
3) Understand the osteocyte response to mechanical stimulation

22. **Bone health in children and young people with epilepsy treated with anti-epileptic drugs (AEDs)**— *also offered as MBiomedSc*

   **Supervisors:** Professor John Wark, Dr Peter Simm, Professor George Werther, Dr Sandra Petty  
   **Project Site:** Department of Medicine (RMH)  
   **Contact:** Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

**Project Description:** Epilepsy and the use of anti-epileptic drugs (AEDs) are known to be associated with low bone mass and the risk of bone disease. In most patients, AED therapy once initiated is taken for many years if not for life. Moreover, it is well-established that AED therapy is a major cause of bone fractures in our community. However, there are still limited data concerning bone problems in children and adolescents taking these medications. We propose a novel study to explore their bone health looking at a number of measures, including analysing bone geometry and bone strength, which have not been described previously in this cohort. We will also follow these patients' growth and development as well as their bone mass accrual and the number of fractures and other injuries that they sustain. These data will give great insight into the effects of epilepsy and its treatment on bone health and lead to improved management of bone health issues in young patients taking AEDs. The findings also will help us to establish a clinical model for the management of bone health in these patients.

Students undertaking this project will gain substantial experience in clinical study design, data collection and management, data analysis and interpretation, as well as translational aspects of biomedical research.

23. **Real world assessment of falls risk using novel mobile technology**— *also offered as MBiomedSc*

   **Supervisor:** Prof John Wark, Dr Tharshan Vaithianathan, Dr Frances Batchelor  
   **Project Site:** Department of Medicine (RMH), National Ageing Research Institute, Parkville.  
   **Contact:** Professor John Wark E: jdwark@unimelb.edu.au

**Project description:** Comprehensive testing regimens for balance and falls risk require sophisticated, expensive laboratory resources and highly-trained staff. The test procedures also do not truly simulate daily living conditions where most falls occur. This project will comprise clinical testing of a novel approach to falls risk assessment using simulated daily living conditions and mobile sway detection technology incorporating low cost inertial sensors (accelerometers, gyroscopes and magnetometers) developed by National ICT Australia (NICTA). The ability to detect age-related differences in performance and impairments, particularly in postural sway, associated with a history of falls will be evaluated and compared with conventional testing procedures. Students will gain first-hand experience in a wide range of functional motor testing, the use of novel motion-sensing technology including signal processing, and in the quantitative analysis of movement data.
24. Is hyponatraemia linked with low bone density in patients with epilepsy? – **offered as MBiomedSc and potentially Honours**

**Supervisors:** Prof John Wark  
**Project Site:** Medicine (RMH)  
**Contact:** Prof Wark (jdwark@unimelb.edu.au)

**Project description:** Project aim: To determine whether hyponatraemia, which is common in epilepsy patients, contributes to their osteoporosis risk.

Epilepsy patients treated long term with antiepileptic medications (AEDs) have an increased risk of osteoporosis and low-trauma fractures, but the mechanism underlying these risks remains uncertain. Chronic hyponatraemia also is common in these patients and hyponatraemia has been linked with an increased osteoporosis risk in other patient groups. However, whether hyponatraemia contributes to the risk of bone loss and fractures in epilepsy patients appears not to have been examined. Therefore, we will identify epilepsy patients with a history of bone density testing from our clinical and research patient populations and seek any relationship between bone density, reported fracture history and serum sodium levels. Data will be adjusted for relevant covariates including age, sex and known osteoporosis risk factors. This clinically-based study is highly feasible and has the potential to lead to a major improvement in understanding of the pathogenesis of fracture risk in one of the most important causes of low-trauma fractures.

**BIOLOGY —WOMEN’S HEALTH**

25. Polycystic Ovarian Syndrome (PCOS) in a cohort of young women – characterization and associations – **also offered as MBiomedSc**

**Supervisors:** Prof John Wark, Dr Yasmin Jayasinghe, Ms Alexandra Gorelik, Prof Suzanne Garland  
**Project Site:** RMH city campus  
**Contact:** Prof John Wark e: jdwark@unimelb.edu.au  
Dr Yasmin Jayasinghe E: yasmin.jayasinghe@unimelb.edu.au

**Project description:** The Young Female Health Initiative (YFHI) and Safe-D studies are projects comprehensively investigating the health of young Victorian women. Assessments include lifestyle and health questionnaires and an extensive site visit with comprehensive health testing. PCOS is currently regarded as a common significant health problem in young women and these studies provide an ideal opportunity to improve understanding of this condition and its associations in young women.

26. Measuring bone and muscle health in young women - **also offered as MBiomedSc**

**Supervisors:** Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik, Ms Stefanie Hartley,  
**Project Site:** Department of Medicine, (RMH) Parkville Campus  
**Contact:** E: jdwark@unimelb.edu.au

**Project description:** The Leonardo mechanograph is an instrument which measures muscle strength and power, and balance. The device has not been previously used in young women. Likewise, peripheral quantitative computed tomography (pQCT), which provides highly-resolved measures of bone density and bone strength, is a method not commonly used in young adults. What are the normative data ranges for Leonardo mechanography and pQCT for young women and how are these measures of muscle and bone health related? This project will focus on establishing the normative data range for these instruments in this population of young women. Subsequently, the relationship between these important measures of muscle and bone health and their determinants can be explored.

27. A critical analysis of Sunsmart behaviour in young Australian women - **also offered as MBiomedSc**

**Supervisors:** Prof John Wark, Dr George Varigos, Ms Stefanie Hartley, Prof Suzanne Garland.  
**Project Site:** Department of Medicine, (RMH) Parkville Campus  
**Contact:** E: jdwark@unimelb.edu.au

**Project description:** Recommendations re sun-smart behaviour can be complex and confusing. What do young women understand about sun-smart behaviour and how do they perceive their own sun-smart behaviour? Young women’s understanding of recommended sun-smart behaviours and their perception of their own sun-smart behaviours will be the focus of this research project. Self-reported data will be compared to objectively measured sun exposure using personal UV dosimeters.
28. Recruitment of young women into health research via social networking sites: the impact of advertising and study characteristics – also offered as MBiomedSc.

Supervisors: Prof John Wark, Dr Shanton Chang, Prof Suzanne Garland, Ms Stefanie Hartley
Project site: Department of Medicine (RMH), Parkville campus
Contact: jdwark@unimelb.edu.au

Project description: The Young Female Health Initiative (YFHI) has successfully recruited young Victorian women aged 16 – 25 years into a range of health-related research projects via Facebook advertising and information conveyed from linked secure study-specific websites. Preliminary analysis suggests differences in the characteristics of participants recruited into these studies. What are the determinants and consequences of these different recruitment patterns? Do such differences impact on the outcomes of these studies? These important questions will be addressed by comparing study populations recruited into several YFHI projects.

29. Air pollution may impair vitamin D status in young Victorian women - also offered as MBiomedSc

Supervisors: Prof John Wark, Ms Alexandra Gorelik, Ms Stefanie Hartley,
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: E: jdwark@unimelb.edu.au

Project description: Recent European research has identified a potentially worrying relationship between vitamin D status and local measures of air quality. Is there an association between air quality and vitamin D levels in young women living in Victoria? This project will explore a possible association between air quality in postcode of residence and serum vitamin D levels in young women. Validated models of air quality based on monitored levels of air pollution will be applied to study these relationships.

30. Factors associated with self-perception of body image in young women - also offered as MBiomedSc

Supervisors: Prof John Wark, Dr Yasmin Jayasinghe, Dr Nicola Reavley, Ms Stefanie Hartley, Prof Suzanne Garland
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: E: jdwark@unimelb.edu.au

Project description: Disturbances of body image perception are becoming increasingly common in young women and may lead to major health problems. How does young women’s body image perception correlate with objective measures of body mass and composition and what factors are associated with disturbed body image? The student will examine questionnaire data from young women covering body image, and compare this with clinical measurements including BMI, hip and waist measures, and body composition measured using DXA scans. There is scope to examine associations between body image and nutrition, disordered eating, measures of mood and lifestyle behaviours.

31. Fear of needles: evaluation of BrightHearts: A biofeedback mediated relaxation/ distraction app

Supervisors: Professor John D Wark, Professor Suzanne M Garland, A/Professor Rachel Skinner, Ms Stefanie Hartley
Project Site: Department of Medicine, RMH, Parkville Campus
Contact: suzanne.garland@thewomens.org.au; 8345 3670
jdwark@unimelb.edu.au; 9342 7109
stefanie.hartley@mcri.edu.au; 8345 3692
rachel.skinner@health.nsw.gov.au

Project description: Some young people experience considerable anxiety associated with receiving injections and needles, such as in blood collection and immunisation. BrightHearts (BHS) is a novel biofeedback mediated interactive digital artwork app, developed to reduce anxiety and perception of pain during painful medical procedures. BHS uses an iPad to display a colourful geometric artwork and musical sounds, which respond to changes in heart rate transmitted by a wireless wristband heart rate monitor. Users learn to reduce their heart rate through slower breathing and are rewarded with more interesting and intense visual display and sounds.

Aim: to reduce self-reported anxiety and perception of pain, prior to and during venepuncture.

Setting: Participants will be young women aged 16-25 years attending a health assessment visit for the research project SAFE-D.

Design: A randomized controlled trial. 120 women will be recruited to the study and 60 randomly assigned to use BHS before and during venepuncture and 60 to standard practice during venepuncture. Post intervention, all participants will complete an 8-10 minute questionnaire via iPad, assessing pain, fear and anxiety. The primary outcome is self-reported anxiety. We compare anxiety scores between groups.
If BHs is found to be successful, it has the potential to be used to reduce anxiety in young people having medical procedures such as venepuncture and immunisation. Given fear of needles has the potential to result in young people avoiding these important procedures, BHs could make a difference in uptake of procedures and improve the procedural experience for young people.

32. **Investigation of genes associated with increased risk of endometriosis**  
Supervisors: Prof Peter Rogers, Dr Sarah Holdsworth-Carson, Dr Jane Girling  
Project Site: Department of Obstetrics and Gynaecology, Royal Women’s Hospital  
Contact: Prof Peter Rogers (parogers@unimelb.edu.au), Dr Jane Girling E: jgirling@unimelb.edu.au  
**Project description:** Endometriosis is a disease where endometrial tissue grows outside of the uterus, most commonly on the organs and tissues of the peritoneal cavity. It can cause severe pain, and is associated with peritoneal inflammation, fibrosis and adhesions. It has been estimated that 8-10% of women in their reproductive years suffer from endometriosis. Endometriosis is a complex disease with a genetic basis. Recent genome wide association studies have identified several candidate genes linked to the risk of endometriosis. In this project, we will develop studies to examine the function of these genes in uterine tissues with the aim of determining how candidate genes and gene pathways may contribute to endometriosis pathophysiology.

**BRAIN BIONICS**

33. **Brain Machine Interface – MRI Compatibility and Electrochemical Safety of a novel Brain Machine Interface.**  
Supervisors: Nicholas Opie, Sam John, Thomas Oxley  
Project Site: Department of Medicine, Royal Melbourne Hospital  
Contact: Nicholas Opie – 0438 089 306; E: Nicholas.opie@unimelb.edu.au  
**Project description:** Our team has developed a stent-based brain machine interface that is capable of recording neural information without requiring invasive open brain surgery. We aim to implant in a first-in-human trial in 2018 and demonstrate the capability of our device to enable direct brain control of an exoskeleton by a person with paralysis. This project will develop and conduct experiments to evaluate whether it is safe for patients implanted with our device to undergo MRI scans. Further, this project will evaluate electrochemical properties of the device, identifying and quantifying any degradation products caused through chronic implantation and material dissolution.

34. **Brain Machine Interface – Biological Evaluation of a novel Brain Machine interface.**  
Supervisors: Nicholas Opie, Sam John, Thomas Oxley  
Project Site: Department of Medicine, Royal Melbourne Hospital  
Contact: Nicholas Opie – 0438 089 306; E: Nicholas.opie@unimelb.edu.au  
**Project description:** Our team has developed a stent-based brain machine interface that is capable of recording neural information without requiring invasive open brain surgery. We aim to implant in a first-in-human trial in 2018 and demonstrate the capability of our device to enable direct brain control of an exoskeleton by a person with paralysis. This project will design and evaluate hemodynamic responses to implanted devices and will assist in optimization of fabrication materials and methodologies.

35. **Brain Computer Interface – Evaluating the anatomical suitability of sheep as a model for a brain computer interface using retrograde axonal transport.**  
Supervisors: Sam John, Thomas Oxley, Nicholas Opie  
Project Site: Howard Florey Institute of Mental Health and Neuroscience  
Contact: Sam John- 0433030540, E: sam.john@unimelb.edu.au  
**Project Description:** Recent studies have demonstrated that sheep are capable of executing a range of cognitive tasks and have generated interest in using sheep as a model of neurological conditions. However, comparatively little is known about the neuroanatomy and cortical projections or variability of the cortex of sheep. The goal of the present neuroanatomical study in sheep is to verify the topography and density of connections of the forelimb representations in the M1 of sheep.

Supervisors: Sam John, Thomas Oxley, Nicholas Opie
Project Site: Department of Medicine Royal Melbourne Hospital
Contact: Sam John- 0433030540, E: sam.john@unimelb.edu.au

Project description: The aim of this study is to histopathologically evaluate the safety of chronically implanted neurovascular interface compared to subdural and epidural devices. Histopathological assessment will evaluate device encapsulation, foreign body response including inflammation as well as bacterial or fungal infections.

37. Sex differences in social dysfunction of paediatric brain injury

Supervisors: Dr. Bridgette Semple, Prof. Terence O’Brien
Project Site: Dept. Medicine (Royal Melbourne Hospital), Melbourne Brain Centre, Parkville
Contact: Dr Bridgette Semple E: Bridgette.Semple@unimelb.edu.au

Project description: There is increasing awareness that social dysfunction can have a significant impact on long-term quality of life for survivors of paediatric traumatic brain injuries (TBI). In a rodent model of TBI at postnatal day 21, approximating a TBI during early childhood, male mice exhibit reduced social and sexual behaviours by adulthood. However, the underlying mechanisms which result in these deficits remain undefined. Further, most work to date has been focused on males, and it is unknown whether females show a similar vulnerability. This project aims to: (a) identify changes in endocrine function across a time course after early life injury, which may contribute to the observed social problems; and (b) determine whether social and sexual deficits after injury are dependent upon sex. Techniques involved: small animal handling and surgery; brain perfusion and fixation; brain dissection; molecular analyses (Western blot, ELISA); MRI analysis; behavioural assessments to evaluate recovery.

38. Post-traumatic epilepsy after traumatic injury to the paediatric brain

Supervisors: Dr. Bridgette Semple, Prof. Terence O’Brien
Project Site: Dept. Medicine (Royal Melbourne Hospital), Melbourne Brain Centre, Parkville
Contact: Dr Bridgette Semple E: Bridgette.Semple@unimelb.edu.au

Project description: Epilepsy is a common consequence of traumatic brain injury (TBI) in children, and is associated with long-term behavioural consequences. Existing anti-epileptic drugs show poor efficacy at alleviating late-onset post-traumatic seizures. Several inflammatory mediators including interleukin-1 (IL-1) and high-mobility group box protein-1 (HMGB-1) have been implicated in both neurodegeneration after TBI and epilepsy. This project aims to elucidate the potential contribution of these inflammatory pathways to the development of post-traumatic epilepsy. Results from this study will pave the way for novel therapeutic targeting of inflammatory mediators to improve quality of life for brain-injured children. Using a mouse model of paediatric TBI, the acute inflammatory response will be manipulated using pharmacological agents, and long-term outcomes (behavioural assessments, video-EEG and MR imaging) will be evaluated. Techniques involved: small animal handling and surgery; brain perfusion and fixation; MRI analysis; behavioural assessments to evaluate long-term recovery; electrode implantation, video-EEG recording and analysis.

39. Does a mild traumatic brain injury during brain development alter the consequences of subsequent injury in adulthood?

Supervisors: Dr. Bridgette Semple, Dr. Sandy Shultz, Prof. Terence O’Brien
Project Site: Dept. Medicine (Royal Melbourne Hospital), Melbourne Brain Centre, Parkville
Contact: Dr Bridgette Semple E: Bridgette.Semple@unimelb.edu.au

Project description: Mild traumatic brain injuries (mTBI) account for the majority of TBI cases and are common in individuals of all ages. While a single mTBI typically results in transient neurological disturbances, there is evidence that repeated mTBI can induce chronic neurological impairments and neurodegenerative disease. Recent studies have characterised repeated mTBI to the adult rodent brain, as often occurs in the sporting arena; however, the potential consequences of repeated injuries while the brain is still maturing has been neglected to date. Further, athletes may receive their first mTBI during childhood or adolescence, and there is initial associative evidence suggesting that individuals who have exposure to mild brain insults during childhood and adolescence experience worsened outcomes after a mTBI in adulthood. This project therefore aims to investigate whether a mTBI to the developing brain (during early life or adolescence) affects the consequences of a subsequent mTBI in adulthood, using a mouse model of mTBI. Techniques involved: small animal handling and surgery; brain perfusion and fixation; immunohistochemistry and microscopy to identify pathological markers of injury; behavioural assessments to evaluate sub-acute and long-term recovery.
40. **The role of Co in brain injury and disease.**

**Supervisors:** Dr. Blaine R. Roberts, Dr. Dominic Hare  
**Project Site:** Florey Inst. Neuroscience and Mental Health-Melbourne Brain Centre  
**Contact:** Dr. Blaine R. Roberts blaine.roberts@florey.edu.au

**Project description:** Cobalt is an essential micronutrient that acts as a cofactor in a number of neurologically important metalloproteins and small molecules. We have recently found that there is a perturbation in the levels of cobalt and other biometals following traumatic brain injury (TBI) in humans and a number of acute brain injury animal models. This project will use a metalloproteomic approach to determine the precise cobalt-binding species that is responsible for this alteration in brain cobalt levels following TBI. Specifically, this project will use multidimensional chromatography and a range of mass spectrometry approaches to isolate, characterise and quantify the protein or proteins associated with cobalt dyshomeostasis, and to determine if this effect is due to either disrupted cobalt brining or altered protein expression. Additionally, this project will examine if this perturbation in cobalt levels is reflected in the periphery, and if so, the possibility of a rapid field-test for TBI via cobalt assay.

41. **Treatment with an interleukin 1 receptor antagonist in a novel model of multi-trauma**

**Supervisors:** Dr. Sandy Shultz, Prof. Terence O’Brien, Dr. Bridgette Semple, Dr. Stuart McDonald  
**Project Site:** Melbourne Brain Centre and Royal Melbourne Hospital, University of Melbourne  
**Contact:** Dr. Sandy Shultz, E: sshultz@unimelb.edu.au

**Project description:** Traumatic brain injury (TBI) is a leading cause of death and morbidity, and there is no treatment to improve TBI outcomes. Although many TBI patients suffer concurrent bone fractures, pre-clinical TBI research utilises ‘single-hit’ models not featuring the pathophysiological complexities induced by multi-trauma, which may account for failures in translating pre-clinical findings to the clinical setting.

To address this, Dr. Shultz and his team recently developed an internationally unique mouse model of multi-trauma and identified the pro-inflammatory cytokine interleukin-1β (IL-1β) as an important factor in the neuropathogenesis of these devastating injuries. This project will now employ this novel mouse model to assess the therapeutic benefits of an IL-1 receptor antagonist (IL-1ra) in multi-trauma. This project will involve advanced neuroimaging, behavioral, cellular, and molecular methods.

42. **Biomarkers of brain concussion in Australian Rules Footballers**

**Supervisors:** Dr. Sandy Shultz, Prof. Terence O’Brien, Prof. Andrew Kaye  
**Project Site:** Melbourne Brain Centre and Royal Melbourne Hospital, University of Melbourne  
**Contact:** Dr. Sandy Shultz, E: sshultz@unimelb.edu.au

**Project description:** Brain concussion, a common form of mild traumatic brain injury (TBI), is a serious medical and societal issue. Of particular concern are individuals who are at high risk of suffering multiple concussions — such as athletes playing collision sports — because repeated concussions may contribute to chronic neurological impairments and neurodegenerative disease. There is evidence that the long-term adverse effects of repeated concussion are due to the recurring insults occurring before the brain has recovered from the initial concussion and is still in a period of increased vulnerability. Currently there are no reliable markers that indicate when the brain is no longer in this state of increased vulnerability, but the identification of such biomarkers would allow them to be used to guide medical decisions, so as to reduce the effects of repeated concussion.

There are a number of promising concussion biomarker platforms. Physical, psychological, and cognitive symptoms are common after concussion, and symptom scales and neuropsychological testing are currently used in concussion management. Magnetic resonance imaging (MRI) is a non-invasive tool that may identify changes in the brain after a concussion, and monitor the recovery of these changes. Blood samples can be used to measure markers that may provide information about the pathophysiology, progression, and recovery of concussion.

In this project we will use advanced and multimodal MRI, proteomic, behavioural, cellular and molecular methods, to assess the pathophysiology of concussion, and identify MRI, blood, and behavioural biomarkers that can detect these changes and estimate recovery. This will be done in Melbourne University Football club athletes (i.e. amateur Australian Rules Football).
CANCER

43. Glioma stem cells: biology and molecular targets
Supervisor: Dr Andrew Morokoff
Co-Supervisors: A/Prof Kate Drummond, Prof Andrew Kaye.
Location: Department of Surgery, Royal Melbourne Hospital
Contact: Dr Andrew Morokoff (morokoff@unimelb.edu.au) T: 9035 8586
Project Description: Gliomas are common malignant brain tumours with an extremely poor survival because of their highly invasive nature and high recurrence rate. Recently a subpopulation of cells with stem-cell like properties has been identified in gliomas and these cells are thought to be related to recurrence and treatment resistance. Furthermore, certain molecular pathways that lead to invasion, apoptosis and drug resistance effects may be ‘switched on’ specifically in glioma stem cells. This project involves establishing stem cell cultures directly from surgical brain tumour samples and isolating cancer stem cells in neurosphere cultures in vitro. These cell lines will be assessed for alterations of molecular signalling pathways including new techniques such as next-generation whole genome and transcriptome sequencing. These cell lines and mouse xenograft models utilising bioluminescence will be used to test novel compounds targeting these pathways.

44. Twist as a Regulator of EMT in Gastric Cancer and its role in invasion
Supervisors: A/Professor Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne
Contact: A/Professor Alex Boussioutas T: +61 03 9656 1287 E: alexb@unimelb.edu.au or alex.boussioutas@petermac.org; Dr Rita Busuttil T: +61 03 9656 1287 E: Rita.Busuttil@petermac.org

Gastric cancer (GC) is often diagnosed at advanced stages, giving patients a 5-year survival of less than 20%. Advanced stage GC is directly correlated with increased local invasion of the cancer through the gastric wall and, at more advanced stages into adjacent structures.

Epithelial Mesenchymal Transition (EMT) is one mechanism which has been proposed as a modulator of invasion in GC as well as other cancer types. This project seeks to expand on previous work in our laboratory exploring the role of TWIST, a master regulator of EMT, in gastric cancer. We have previously shown that TWIST is more highly expressed at the invasive front of the tumor compared to its core indicating that EMT is occurring in this area. It is conceivable that reducing TWIST expression could be used as a means to decrease the invasive capacity of a cancer.

This project will aim to further explore the role of TWIST in the invasion of GC and its potential utility as a therapeutic target. A broad range of techniques including bioinformatics, cell culture, shRNA lentivirus mediated gene knockdown, and molecular biology will be applied.

We are looking for motivated students (both Honours and PhD students) to strengthen our group.

45. Validation of candidate genes involved in the progression of gastric cancer
Supervisors: A/Professor Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne
Contact: A/Professor Alex Boussioutas T: +61 03 9656 1287 E: alexb@unimelb.edu.au; Dr Rita Busuttil T: +61 03 9656 1287 E: Rita.Busuttil@petermac.org
Project Description: Gastric cancer (GC) is the fourth most common cancer globally and in many western countries is usually only diagnosed at advanced stage giving patients a 5-year survival rate of less than 20%. GC has distinct premalignant stages that have significant propensity to progress. The premalignant cascade consists of easily identifiable histological stages from chronic atrophic gastritis (ChG), intestinal metaplasia (IM) and dysplasia. The progression through these stages, particularly IM, takes years, offering a large window of opportunity to intervene. However not all patients with IM will progress and selection of patients for high-risk surveillance would reduce the burden of unnecessary screening, patient anxiety and improve outcomes due to early detection of disease.

Relatively little is known about the key genetic events leading to IM. Our laboratory is currently in the process of completing the first comprehensive analysis of IM in the world and seeks to identify candidate genes involved in the progression of IM to GC that can be used to reliably predict the progression to GC in humans by using a genomics based approach. Identification of such genes offers an opportunity to study the molecular mechanisms involved and pinpoint targets for prevention and therapy. The aim of this project is validate these candidate genes using an independent data set and then characterizing these genes using functional assays and animal models.
We are looking for motivated students (both Honours and PhD students) to strengthen our group. The project will use broad range techniques including bioinformatics, cell culture, animal models and molecular biology.

46. Role of the Tumour Microenvironment in Gastric Cancer

Supervisors: A/Professor Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne
Contact: A/Professor Alex Boussioutas T: +61 03 9656 1287 E: alexb@unimelb.edu.au
Dr Rita Busuttil T: +61 03 9656 1287 E: Rita.Busuttil@petermac.org

Project Description: Gastric cancer (GC) is the fourth most common cancer globally and 7th in incidence in Australia. It has a poor survival rate which can be attributed to the advanced stage at diagnosis in most patients. The molecular and cellular mechanisms underlying the development of GC are not well described.

Traditionally cancer research involved studying the cancer cell itself. More recently, there has been growing interest in studying the normal cells and molecules which surround the cancer cell. This tumour microenvironment consists of a variety of stromal cell types including cells such as fibroblasts. It is believed that the dynamic communication between tumour cells and the surrounding cell types may play a major role in cancer initiation, progression and establishment of metastatic disease. The aim of this project is to investigate tumour-stromal interactions in gastric cancer utilizing established and primary cell lines. Once the molecular pathways by which a tumour cell progresses has been elucidated it is possible that these processes could be exploited in the development of novel therapeutics.

This project will use a broad range of techniques such as live cell microscopy, cell culture techniques and siRNA to interrogate the function of gene products that influence tumour-stroma communication.

Our previous genomic experiments has provided us with a number of exciting candidate genes that may be involved in this interaction. This is novel research that may have a major benefit to our understanding of cancer and improve patient outcomes.

47. Characterization of cross-talk between tumour and stromal cells in inducing metastasis and resistance to chemotherapy in ovarian cancer. ONLY available for MBiomedSc

Supervisors: Dr Nuzhat Ahmed, Prof Jock Findlay (Women’s Cancer Research Centre, Royal Women’s Hospital & Department of Obstetrics & Gynaecology, University of Melbourne)

Project Site: Work will be conducted at the laboratories of the Royal Women’s Hospitals
Contact: Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. T: 8345 3734 E: Nuzhat.Ahmed@thewomens.org.au

Aims/Hypothesis: Hypotheses
- Peritoneal dissemination of ovarian cancer is dictated by the extent of invasiveness in the tumour cells of ascites that survive as peritoneal tumour aggregates (PTCs), and is largely dependent on the biological changes induced by the surrounding stroma. We further hypothesize that identification of cross talk between tumour PTCs and stroma will successfully identify potential molecules involved in the predisposition of the tumour cells to metastasise locally as well as respond to chemotherapy.

Specific aims
- (i) To determine whether cancer associated fibroblasts (CAFs isolated fresh from ascites) can alter the spheroid forming and invasive ability of ovarian cancer cell lines in vitro; & (ii) to determine if CAFs can alter the response of ovarian cancer cell lines to chemotherapy.

Background/Rationale: About 75% of ovarian cancer patients are diagnosed at an advanced-stage as symptoms are non specific and diagnosis delayed until the tumour has metastasized to the surrounding abdominal peritoneum and omentum. This type of peritoneal dissemination is almost unique to ovarian cancer and occurs due to the exfoliation of transformed ovarian surface epithelial cells. In the peritoneal cavity transformed cells disseminate as single cells or PTCs influenced by the flow of peritoneal tumour fluid or ascites. The unique biology of tumour cell exfoliation from the surface of the ovary, survival as single cells or as PTCs in the peritoneum, predisposition to peritoneal organs and innate resistance to chemotherapy suggests that ovarian cancer PTCs possess distinct traits which enables them to self renew and adapt to the changing local environment. In animal models of cancer, normal epithelial cells have been shown to become malignant when surrounded by tumour-derived fibroblasts but not normal fibroblasts. These results signal the need to study the biological alterations induced by stroma on ascites tumours cells of ovarian cancer.

Outcomes/Benefits: This proposal represents a novel model of ovarian cancer progression where the inherent traits in ascites PTCs will be compared in the presence and absence of associated stroma. PTCs and stromal cells will be isolated from the ascites of ovarian cancer patients and evaluation of the biological alterations induced by the associated stroma that result in enhancing the metastasising capacity of ascites PTCs will be assessed by biological methods such as Western
48. **Elucidating the role of mesenchymal stem cells in promoting metastasis of ovarian cancer cells**

**Supervisors:** Dr Bill Kalionis (Pregnancy Research Centre, RWH), Dr Nuzhat Ahmed (The Fiona Elsey Cancer Research Institute, Ballarat).

**Project Site:** Work will be conducted at the laboratories of the Royal Women’s Hospital

**Contact:** Dr Bill Kalionis, Pregnancy Research Centre, RWH. T: 8345 3748 E: bill.kalionis@thewomens.org.au

**Hypothesis** - Mesenchymal stem cells (MSC) residing in ovarian stroma or in non-ovarian tissues can promote ovarian cancer metastasis.

**Specific aims** - (i) To determine whether MSC derived from ascites of ovarian cancer patients or those derived from human placenta can alter the growth, invasive and ovcaspHERE forming abilities of ovarian cancer cell lines in vitro; & (ii) to determine if MSC can alter the response of ovarian cancer cell lines to chemotherapy.

**Background/Rationale:** MSC within tumour stroma are derived from the resident tissue or from the circulation or recruited from tissues not related to the tumour. Few recent reports have shown MSC to promote cancer metastasis by initiating paracrine signalling or through enriching the population of ‘tumour initiating cells’ commonly known as ‘cancer stem cells’. About 75% of ovarian cancer patients diagnosed at an advanced-stage have peritoneal dissemination in the form of ascites containing single cells and tumour cellular aggregates. Recent data in our laboratory suggests that MSC forms an important component of ascites of ovarian cancer patients. This warrants the need to study the biological alterations (phenotype) induced by MSC on the growth, invasiveness and response to chemotherapy in ovarian cancer cell lines in vitro.

**Outcomes/Benefits:** This proposal will compare the inherent traits and chemotherapy response of ovarian cancer cells in the presence and absence of MSC. MSC will be isolated from the ascites of ovarian cancer patients as well as from the placenta of women undergoing caesarean section. Differences in the biological phenotype of ovarian cancer cells in the presence and absence of MSC will be assessed by methods such as Western blot, quantitative PCR, immunofluorescence, flow cytometry, MTT and ³H-thymidine uptake assays. The identification of these changes/molecules may lead to the development of novel therapeutic targets either independently or by inhibiting the effects of MSC on ovarian cancer cells. Human ethics application (HEC#09/09) has been approved by the Royal Women’s Hospital Human Ethics Committee.

49. **TGF-β signalling and cancer development**

**Supervisors:** Dr. Hong-Jian Zhu (and Dr. Rodney Luwor, Bo Wang, Catherine Winbanks)

**Project Site:** Cancer Signalling Laboratory, Department of Surgery (5th Floor, Clinical Sciences Building, The Royal Melbourne Hospital)

**Contact** Dr Hong-Jian Zhu T: 8344 3025 E: hongjian@unimelb.edu.au; Dr Rodney Luwor T: 8344 3027 E: rluwor@unimelb.edu.au

**Project description:** Traditionally, key-lock or on-off models dominate the molecular understanding of cellular signalling and disease development, with most studies focusing on linear molecular signalling cascades. With the advent of large scale molecular techniques such as proteomics and microarrays, cross-talk between signalling networks has been implicated to play critical roles in cancer development. It challenges the physiological validity of the switch on-off model. Our lab, using molecular, cellular and gene targeted animal models as well as human patient samples, has established that the moderation of signalling sensitivity by other pathways, rather than a black-white switch on-off, specifically of the TGF (Transforming Growth Factor-) signalling pathways determines cancer progression. These findings have been published in top-ranking biomedical journals including *Nature Medicine* (11:845-52, 2005). Given the medical significance, current works in our lab are supported by 4 NHMRC and 1 Cancer Council grants totalling more than $2 million.

This lab aims to understand the molecular fundamentals of TGF signalling mis-regulation and its causation effect on early tumor development and late tumor invasion and metastasis. In particular, we focus on the few major oncogenic molecular pathways’ cross-talk with TGF signalling in various stages and types of cancer development. Concurrently, we are also devising strategies utilizing our unique molecular insights to convert tumor-causing signalling to directly tumor-killing.

The following projects are designed for students to participate in forefront cancer research and to achieve excellent novel results in a relative short time frame (9-10 months).

- **Project A:** Converting oncogene signalling to tumor killing in brain cancer
Project B: Stat3 mediated impairment of TGF - signalling in head&neck and breast cancer

Project C: Targeting TGF - signalling expansion in brain tumor invasion

Project D: Regulation of TGF - signaling by Wnt pathway in the development of colon cancer

Techniques to be used: Cell culture, reporter assays (gene expression), adenoviral work, molecular biology, Western and Northern blotting (protein and mRNA respectively), thymidine assays (cell proliferation), real-time PCR, immunofluorescence and immunohistochemistry, siRNA (gene silencing), animal imaging.

Preferred background and quality of student: biochemistry, pathology, medical sciences; good nature as a person, passionate and dedication in research, perseverance in problem solving.

50. Integrated Genomics of metastatic, lethal Prostate Cancer

Supervisors: A/Prof Chris Hovens and Dr Niall Corcoran
Project Site: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building and Prostate Cancer
Eapworth Hospital, Richmond
Contact: A/Prof Chris Hovens T: 9342 7703/4 E: chovens@unimelb.edu.au

Project description: With over 20,000 diagnoses per year, Australian men have the highest rate of prostate cancer in the world. Currently our research team are addressing some of the most important clinical questions today in prostate cancer management using genomics and proteomics experimental designs. We have access to human tissue samples taken from men undergoing surgery together with the clinical informatics that indicate their outcomes, therefore this project will have high clinical relevance and impact.

The aim of the project is to delve deeper into our analyses of the genomics of prostate cancers from patients who have either died or who have metastatic disease. We have identified a number of candidate regions and changes that may be key to driving prostate cancer metastasis and subsequent lethality. Projects will focus on validating these findings in independent cohorts of patients and starting to examine experimentally the biology behind the observed changes and how they impact on tumor behaviour. Research students will work within a team of experienced scientists and have access to scientific expertise and equipment through our department, associated institutions and existing collaborations with leading urologists. Our commitment to academic excellence and links with the Australasian Prostate Cancer Conference, one of the largest urology meetings in the region, ensure additional exposure to publication and presentation opportunities for the motivated researcher.

Benefits to student: Molecular and clinical research in the one, multi-collaborative project encompassing basic research and clinical interaction.

Requirements for students: Dedicated, passionate and committed. Must have done very well academically.

51. Prostate Cancer – what can we learn from its mistakes?

Supervisors: A/Prof Chris Hovens, Dr Michael Clarkson
Project Site: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building
Contact: Dr Michael Clarkson E: michael.clarkson@epworth.org.au

Background/Rationale: “So many roads. So many detours. So many choices. So many mistakes.” Although Sarah Jessica Parker was almost certainly not thinking about cancer when she said this, it none the less applies. One of the first identifiable “mistakes” that occur in Prostate cancer are genomic rearrangements, some of these contribute directly to cancer initiation and progression. There are also rare cases where the cancer genome has become hypermutated. We and others have found that hypermutator forms of prostate cancer have mutation or deletion in genes that are required for DNA mismatch repair, MSH2 or MSH6. In order to better understand the mechanism by which MSH2 becomes mutated and the consequences of this gene inactivation we have obtained prostate cancer samples from patients heterozygous for germline MSH2 and MSH6 defects (Lynch syndrome). These individuals have a 10 fold higher chance of developing Prostate cancer than the general population and a 10 year earlier onset. Since androgen has been shown to direct genomic rearrangements we hypothesise that, in Lynch syndrome, the second copy of the MSH2 gene is inactivated by an androgen dependent mechanism. Interestingly, in the five known examples of the hypermutator phenotype, none appear to exhibit the most common genomic rearrangements seen in Prostate cancer. From this, we hypothesise that MSH2 is required for androgen dependent genomic rearrangements.

Project Description: We will conduct complementary experiments to address our two hypotheses at the same time. Lynch syndrome patient material will be characterised in order to define both the type of mutation in MSH2 and whether it contains other androgen dependent genomic rearrangements that are commonly seen in prostate cancer. We will also examine whether androgen dependent genomic rearrangements are able to disrupt the MSH2 gene and if MSH2 is required for androgen dependent rearrangements.
52. Integrated Genomics of Bladder Cancer
   Supervisors: A/Prof Chris Hovens and Dr Niall Corcoran
   Project Site: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building and Prostate Cancer Epworth Hospital, Richmond
   Contact: A/Prof Chris Hovens T: 9342 7703/4 E: chovens@unimelb.edu.au
   Project description: With over 2000 patients diagnosed with Bladder Cancer (BC) each year and a significant amount of them having recurrent and progressive disease despite optimum therapy, BC is a very serious cancer. Currently our research team is investigating how bladder cancer progresses at a molecular level using genomic approaches. We have access to human tissue, plasma and urine samples taken from men undergoing surgery together with the clinical informatics that indicate their outcomes, therefore this project will have high clinical relevance and impact.

   The aim of the project is to probe deeper into our analyses of the genomics of bladder cancers. We have identified a number of candidate markers that are altered across various stages of bladder cancer. Projects will focus on validating these findings in independent cohorts of patients and starting to examine experimentally the biology behind the observed changes and how they impact on tumour behaviour. Research students will work within a team of experienced scientists and have access to scientific expertise and equipment through our department, associated institutions and existing collaborations with leading urologists. Our commitment to academic excellence and an excellent track record of publications, ensure additional exposure to publication and presentation opportunities for the motivated researcher.

   Benefits to student: Molecular and clinical research in the one, multi-collaborative project encompassing basic research and clinical interaction.

   Requirements for students: Dedicated, passionate and committed. Must have done very well academically.

53. STAT3-mediates Resistance to EGFR targeted therapy in Cancer
   Supervisors: Dr Rodney Luwor
   Project Site: Dept of Surgery, Royal Melbourne Hospital
   Contact: T: 8344 3027, E: rluwor@unimelb.edu.au
   Project description: During physiological processes the intracellular protein Signal Transducer and Activator of Transcription 3 (STAT3) is activated by many growth factors and cytokines (e.g. EGF, IL-6, IL-11...etc) resulting in transcription of many genes involved in a multitude of cellular processes. However, uncontrolled or un-attenuated STAT3 phosphorylation and activation results in cancer initiation, progression and metastasis of many tumour types. Therefore, understanding how STAT3 is regulated or controlled within the cell is pivotal for cancer biology and may allow greater scope for therapeutic intervention into STAT3-driven tumourigenesis. Recently, we have shown that many colon cancer cell lines are resistant to a clinically approved anti-EGFR monoclonal antibody, Cetuximab. However, blocking STAT3 activation could re-sensitize these tumour cells to the growth inhibitory effects of cetuximab. Therefore we hypothesise that activation of STAT3 provides an alternative mechanism for resistance to EGFR targeted therapy and targeting IL-6, IL-11 or STAT3 can overcome this resistance. Our Honours/Masters program offers students a choice of projects within our STAT3 signalling research. This project seeks to evaluating novel regulators of STAT3 and determining whether these regulators have a role in driving STAT3-mediated resistance to anti-EGFR therapy. Furthermore, this project has the scope to evolve into a PhD project starting in 2017/18 pending the ability of the incumbent student.

   Skills acquisition: Cell biology techniques including Cell transfections, western blotting, immunofluorescence staining and confocal microscopy, luciferase reporter assays, RT-PCR and potentially animal handling and injecting.

54. The Molecular Determinants of Brain Tumour Progression and Resistance to Therapy
   Supervisors: Dr Rodney Luwor, Dr Leonie Quinn and Dr Theo Mantamadiotis
   Project Site: Dept of Surgery, Level 5, Clinical Sciences Building, Royal Melbourne Hospital (also Dept of Anatomy & Neurosciences and Dept of Pathology, University of Melbourne)
   Contact: Dr Rodney Luwor; T: 8344 3027, E: rluwor@unimelb.edu.au
   Project Description: Glioblastoma Multiforme (GBM) is the most devastating and aggressive tumour of the central nervous system accounting for approximately 50% of all primary brain tumours. Surgery, followed by irradiation and concomitant and adjuvant temozolomide is now considered the standard of care for GBM patients. However, the overall prognosis remains abysmal for GBM patients with a median survival of only 15 months. The presence of pre-existing intrinsic resistance and the ability of GBM tumours to develop or acquire resistance represents a major challenge to successful treatment. Resistance to temozolomide is common; however the exact mechanisms and key molecules that mediate resistance are not clearly elucidated.

   Our Honours/Masters program offers students a choice of projects within two major themes based on our GBM-orientated research. Firstly, projects will be designed to explore novel molecular mediators of GBM proliferation,
migration and invasion and potentially evaluate treatment strategies to overcome GBM progression. Alternatively, students will perform projects that seek to explore potential molecular candidates in mediating resistance to current therapy. Both these project directions will utilise a large set of brain tumour cell lines and human brain tumour tissue and serum archived within our department. Furthermore, this project has the scope to evolve into a PhD project starting in 2017/18 pending the ability of the incumbent student.

**Skills/Techniques acquired:** Cell biology techniques including Cell transfections, western blotting, immunohistochemistry, confocal microscopy, luciferase reporter assays, RT-PCR, migration and invasion assays and potentially animal handling and injecting

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**55. Using animal and human patient models to interrogate transcriptional networks in glioma**

**Supervisors:** Dr Leonie Quinn, Dr Rodney Luwor and Dr. Theo Mantamadiotis

**Project Site:** Dept of Anatomy and Neuroscience, Dept of Surgery (RMH) and Dept of Pathology, University of Melbourne.

**Contact:** Dr Leonie Quinn l.quinn@unimelb.edu.au Dr Rodney Luwor: rluwor@unimelb.edu.au and Dr. Theo Mantamadiotis: theom@unimelb.edu.au

**Project description:** With no effective drug treatments for malignant glioma these tumours are invariably lethal. One key discovery in glioma biology is that tumour progression correlates with activation of the PI3K signaling pathway. Indeed, preclinical trials are underway for therapeutics targeting PI3K/AKT in malignant glioma. Unfortunately, these studies have already revealed rapid acquisition of tumour resistance and relapse, which highlights the importance of understanding the activity of downstream targets. The transcription factor and oncogene MYC is upregulated in 70% of all human cancers. Elevated levels of MYC correlate with poor patient survival, which suggests MYC might also be a driver of glioma malignancy. Most MYC-driven cancer is due to upregulation of expression, but the networks controlling MYC transcription in malignancy are largely unknown. This project builds on our exciting observation that a key transcription factor linked with glioma, CREB, is a critical downstream target of PI3K-driven glioma in mouse genetic models. Preliminary data also suggests that CREB can regulate expression of MYC and a second oncogene, Cyclin D. Thus this project will aim to use Drosophila, mouse and human glioma models to investigate whether CREB drives brain tumour growth by regulating transcription of MYC and/or CycD.

Skills and techniques - This research will use a combination of in vivo genetic models (Drosophila and mouse) and ex vivo human cancer models. Techniques used to unravel the mechanisms of glioma progression will include molecular biological (eg. Real time PCR, Chromatin Immunoprecipitation, western blotting) and cell biological techniques (cell culture, cell transfection, immunohistochemistry, confocal microscopy, migration and invasion assays).

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**56. Using animal and human patient models to unravel new pathways driving glioma**

**Supervisors:** Dr Leonie Quinn, Dr Rodney Luwor and Dr. Theo Mantamadiotis

**Project Site:** Dept of Anatomy and Neuroscience, Dept of Surgery (RMH) and Dept of Pathology, University of Melbourne.

**Contact:** Dr Leonie Quinn l.quinn@unimelb.edu.au Dr Rodney Luwor: rluwor@unimelb.edu.au and Dr. Theo Mantamadiotis: theom@unimelb.edu.au

**Project description:** With no effective drug treatments for malignant glioma these tumours are invariably lethal. One key discovery in glioma biology is that the EGFR/RAS/PI3K axis is activated in most gliomas. Indeed, preclinical trials are underway for therapeutics targeting PI3K/AKT and RAS/RAF in malignant glioma. Unfortunately, these studies have already revealed rapid acquisition of tumour resistance and relapse, which highlights the importance of understanding the activity of downstream targets. The transcription factor and oncogene MYC is upregulated in 70% of all human cancers. As therapeutically targeting MYC itself has proved unfeasible, we need to find new ways to indirectly target MYC in cancer. Most MYC-driven cancer is due to upregulation of expression, but the networks controlling MYC transcription in malignancy are largely unknown. The single stranded DNA binding protein FBP is essential for transcription of the MYC oncogene, and dysregulation of FBP is linked with a wide variety of cancers, eg. kidney, breast, liver, lung, bladder, prostate, gastrointestinal and brain. Elevated levels of FBP and MYC correlate with poor patient survival, which suggests FBP and MYC abundance/activity might also be drivers of glioma malignancy. This project builds on our exciting observation that FBP is a critical downstream target of EGFR/RAS/PI3K. We aim to use Drosophila, mouse and human glioma models to determine how the FBP-MYC axis drives MYC expression and brain tumour growth.
Skills and techniques - This research will use a combination of **in vivo** genetic models (*Drosophila* and mouse) and **ex vivo** human cancer models. Techniques used to unravel the mechanisms of glioma progression will include molecular biological (eg. Real time PCR, Chromatin Immunoprecipitation, western blotting) and cell biological techniques (cell culture, cell transfection, immunohistochemistry, confocal microscopy, migration and invasion assays).

57. **Defining the epidermal growth factor receptor signaling network in brain tumour stem cells**  
**Supervisors:** Dr. Theo Mantamadiotis, Dr Leonie Quinn and Dr Rodney Luwor  
**Project Site:** Dept of Pathology, Dept of Anatomy and Neuroscience and Dept of Surgery (RMH), University of Melbourne.  
**Contact:** Dr. Theo Mantamadiotis: theom@unimelb.edu.au; Dr Leonie Quinn l.quinn@unimelb.edu.au; Dr Rodney Luwor: rluwor@unimelb.edu.au  
**Project description:** Aberrant cell signalling underlies the loss of growth control, enhanced survival, inappropriate migration and drug resistance in tumour cells. In malignant brain tumours such as Glioblastoma Multiforme (GBM), a number of key components of signaling pathways are known to be inappropriately activated due to mutations. The epidermal growth factor receptor (EGFR) is mutated in about 30% of GBM patients. The downstream effects of the EGFRVIII mutation in brain tumour cells leads to a spectrum of cell signaling events which promote the transcription of many genes which orchestrate pro-tumorigenic cell characteristics. A key transcription factor which lies downstream of the EGFR pathway is CREB, which has recently been shown to have a role in regulating cell human brain tumour cell growth. In this project, the activation of CREB, in a variety of human tumour cell lines, including cancer stem cells which express wild-type EGFR and EGFRVIII, will be examined using cell and molecular techniques. The CREB-dependent transcriptome will also be investigated to understand whether there is a distinct set of EGFRVIII CREB-dependent target genes compared to wild-type EGFR.

58. **Role of oncogenic signaling pathways on brain cancer cell – tumour microenvironment interactions**  
**Supervisors:** Dr. Theo Mantamadiotis, Dr Leonie Quinn and Dr Rodney Luwor  
**Project Site:** Dept of Pathology, Dept of Anatomy and Neuroscience and Dept of Surgery (RMH, University of Melbourne.  
**Contact:** Dr. Theo Mantamadiotis: theom@unimelb.edu.au; Dr Leonie Quinn l.quinn@unimelb.edu.au; Dr Rodney Luwor: rluwor@unimelb.edu.au  
**Project description:** Brain cancer comprises a group of cancers exhibiting complex cellular and genetic heterogeneity. This complexity accounts for the gaps in knowledge of biological processes underlying brain tumour pathology, the availability of only limited effective therapies and poor prognosis for patients. This project will focus on understanding the mechanisms involved in brain tumour stem cell (BTSC) growth and the influence glial cells have on BTSCs, focussing on the PI3K and CREB pathways by using cells derived from mouse brains with mutations in PI3K and CREB. The influence of chemotherapy on these cells will also be investigated.

Students are expected to delve into recent accessible literature, developing an appreciation of the PI3K and CREB pathways in brain cancer biology. Techniques to be used include immunohistochemistry, stem cell culture and various molecular biology techniques.

59. **New roles for nutrient sensing kinases in brain cancer**  
**Supervisors:** Dr Linda Parsons, Dr Leonie Quinn, Dr Rodney Luwor and Dr. Theo Mantamadiotis  
**Project Site:** Dept of Anatomy and Neuroscience, Dept of Pathology, and Dept of Surgery (RMH) University of Melbourne.  
**Contact:** Dr Linda Parsons: l.parsons@unimelb.edu.au; Dr Leonie Quinn l.quinn@unimelb.edu.au; Dr Rodney Luwor: rluwor@unimelb.edu.au; Dr. Theo Mantamadiotis: theom@unimelb.edu.au;  
**Project description:** The project will suit those who are interested in using developmental models to dissect the mechanism of cancer initiation and progression. Our lab uses the vinegar fly developmental model, *Drosophila*, to interrogate cancer biology. An emerging theme of cancer biology is that availability of nutrients and energy (metabolism) in cancer cells is intricately linked to tumourigenesis. Exciting work from our lab has revealed that “nutrient sensing kinases” SIK2 and SIK3 are key regulators of cell growth in *Drosophila*. In mice and *Drosophila* there is evidence that SIK2&3 act as a ‘fuel gauges’ monitoring cellular levels of ATP, glucose and lipids. How nutrient sensing kinases coordinate regulate metabolism and cell growth is currently unknown.

This proposal exploits the fact that the signalling pathways that regulate the potent oncogene MYC, which are upregulated in most cancers, are highly evolutionary conserved between flies, mice and humans. This project will use sophisticated *Drosophila* genetic models for stem cell behavior in glioma to explore our hypothesis that SIK2 and SIK3
regulate MYC expression and activity to control metabolism and cell growth underlying cancer progression. Ultimately the outcomes of this study will be translated into mouse and human brain cancer models.

Skills and techniques - This project will encompass a wide range of cell biology (immunofluorescence analysis of whole mount tissues, microdissection, confocal microscopy), genetics and molecular biology techniques (qRT-PCR, Chromatin Immunoprecipitation, Co-IP and western analysis).

60. Regulation of invadopodium function and involvement in cancer cell invasion
Supervisors: Dr Stanley Stylli
Project Site: Dept of Surgery, Level 5, Clinical Sciences Building, The Royal Melbourne Hospital
Contact: Dr Stanley Stylli; T: 9035 5236, E: sstylli@unimelb.edu.au

Project description: The cause of death for up to 90% of cancer patients is the metastatic spread of cancer cells from the primary tumour and the subsequent development of a secondary tumour or tumours at a distant site. Many patients normally present with symptoms relating to the localized primary disease which can be managed with a number of therapies including surgery, radiation and chemotherapy. But numerous patients return post-therapy with a developed metastatic lesion at a secondary site. The dissemination of metastatic cells involving the migration and infiltration of these invasive cells is commonly thought to require two events. This includes increased cellular motility, accompanied with the proteolytic processing of the extracellular matrix (ECM) and subsequent penetration through the surrounding tissues.

A property shared by several types of tumour cells with high invasive or metastatic potential is an ability to form structures known as invadopodia. They are dynamic actin-rich protrusions which adhere to and proteolytically degrade ECM substrates via the activities of secreted extracellular proteases. Functional (matrix-degrading) invadopodia have been observed in tumour cell lines and primary tumour cells derived from ex vivo tumour specimens from a number of cancers, primarily head and neck squamous cell carcinoma and breast cancer specimens. This suggests that there is a possible role for invadopodia in tumour cell invasion of many cancers.

Invadopodia formation and function are dependent on multiple proteins and signaling pathways. Therefore understanding how invadopodia are regulated and controlled within a tumour cell is essential and strategies aimed at disrupting invadopodia could form the basis of novel anti-invasive therapies for treating cancer patients in the future. This honours project will involve studies that explore the role of a number of invadopodia proteins in cancer cells, how they contribute to their invasive/metastatic phenotype and ultimately influence response to treatment protocols.

Skills/Techniques acquired: Cell Biology techniques including cell culture and cell transfections (overexpression and siRNA gene silencing), western blotting, zymography, immunofluorescence and immunohistochemistry, confocal microscopy, migration/invasion assays, reporter assays.

61. Molecular biomarkers for Human Papillomavirus-related cancer progression
Supervisors: A/Professor Sepehr Tabrizi, Dr Alyssa Cornall, Professor Suzanne Garland
Project Site: Women’s Centre for Infectious Diseases (RWH), Bio21 Institute
Contact: A/Prof Sepehr Tabrizi: sepehr.tabrizi@thewomens.org.au; Dr Alyssa Cornall: alyssa.cornall@mcri.edu.au

Project description: The majority of cancers of the cervix (>99%) and the anal canal (>80%) are associated with Human Papillomavirus (HPV) infection, yet not all HPV infections lead to cancer. Cancer development is preceded by certain molecular changes; these include epigenetic modifications such as methylation of viral gene promoters, and changes to the expression of viral and cellular gene products. Using techniques such as laser capture microdissection (LCM), HPV genotype sequencing, quantitative PCR, sequencing of methylation patterns and analysis of p16 expression, this project will involve the characterization of pre-cancerous lesions based on molecular changes to viral gene regulation, in order to identify molecular markers that can more accurately predict progression to cancer.

62. Human Papillomavirus (HPV) Genotype Surveillance
Supervisors: Dr Alyssa Cornall, A/Professor Sepehr Tabrizi, A/Professor Jane Hocking, Professor Suzanne Garland, Dr Dorothy Michalek
Project Site: Department of Microbiology and Infectious Diseases, RWH, Parkville Campus
Contact: Dr Alyssa Cornall: alyssa.cornall@mcri.edu.au
A/Prof Sepehr Tabrizi: sepehr.tabrizi@thewomens.org.au
Dr Dorothy Machalek: Dorothy.machalek@mcri.edu.au
**Project description:** Human Papillomavirus (HPV) is the causative agent for cervical and a proportion of other anogenital cancers, and of genital warts. In 2007, Australia became the first country to introduce a fully government-funded National HPV Vaccination Program and is now vaccinating boys and girls against HPV genotypes 6, 11, 16 and 18. Following the introduction of the vaccination program, surveillance of HPV genotypes in the population is required to determine vaccine effectiveness, i.e. measuring the impact in a real world situation. This project will involve genotype testing of clinical surveillance samples. Self-collected genital samples of participants recruited from general practice clinics, including both men and women aged between 18 and 35 years old, will be tested for HPV genotypes. Data from women will help evaluate the direct effect of the vaccine on vaccinated populations, while data from men (most of whom will not have been vaccinated) will provide valuable baseline data of HPV prevalence in men. This project will involve sample logging and processing, DNA extraction, quality control testing, PCR and genotyping, data management and epidemiological data analysis.

63. **In vitro brain tumour model – studying epileptic seizure development and sensitivity to anti-cancer therapy.**

**Supervisors:** Dr Chris French, Dr Andrew Morokoff, Dr Rodney Luwor
Professor Terence O’Brien

**Project Site:** Department of Surgery, Department of Medicine RMH, Melbourne Brain Centre

**Contact:** Dr Chris French - frenchc@unimelb.edu.au

**Project description:** Malignant brain tumours are notoriously difficult to treat and are often complicated by severe epileptic seizures. Research into therapies has been hampered by a limited range of model systems to explore pathogenesis and treatment of these tumours. We have developed an *in vitro* model of aggressive brain tumours using a rat brain culture technique. This uses several well-characterised human tumour cell lines as well as tumour “stem-cells” available in our laboratories. These are seeded into a section of brain maintained in tissue culture. The project has two aims – to examine the effects of conventional and novel treatments on the tumours as well as the development of epileptic seizure activity in the system. Seizure development will be assayed by electrophysiological recordings.

This novel technique in this project has the potential to provide important insights into the pathophysiology and treatment of brain tumours and tumour-related epilepsy.

**CANCER – FERTILITY PRESERVATION**

64. **Fertility issues in children and adolescents with cancer**

**Supervisors:** Dr Yasmin Jayasinghe, Dr Lisa Orme, Dr Leanne Super

**Project site:** The Royal Children’s Hospital and The Royal Women’s Hospital, Melbourne

**Contact:** E: yasmin.jayasinghe@unimelb.edu.au

**Project description:** Fertility loss is one of the side effects of cancer treatment. Advances in reproductive technologies may one day offer children and adolescents with cancer, the possibility of future fertility through ovarian or oocyte tissue retrieval and storage prior to commencement of cancer therapy. However such treatments are regarded as investigational in children due to immaturity of gonadal tissue, and also pose unique clinical and ethical dilemmas with respect to informed consent and beneficence for the young person. It is now recommended that where cancer treatment poses a fertility risk, fertility preservation should be discussed with all patients, and with parents or guardians. Long-term survivors report dissatisfaction with the quality of such discussions, or have no memory of them. Over 95% of paediatric oncologists surveyed in Australia and New Zealand believe that centre-specific clinical protocols are necessary to establish standards of care. However such guidelines rarely exist. Furthermore there is little information on recovery of gonadal function post chemotherapy in children and adolescents, to further guide discussions regarding fertility options after chemotherapy.

Several sub-studies are available which may assist with the development of Fertility Preservation guidelines and improve patient outcomes at the Royal Children’s Hospital Melbourne, which include:

1. An audit of fertility preservation consultations for patients seen at The Royal Children’s Hospital between 2002 and 2014. This project is ethics approved. Specifically the audit will report the proportion of subjects who underwent such discussions, the procedures offered, barriers to uptake of the procedures, and complications. 

2. Evaluation of a ‘Fertility Preservation Toolkit’. This is a recently introduced resource for health providers, patients and families which aims to improve knowledge and awareness of fertility preservation options for patients and families by providing information in a standardized manner.

3. Mining the haematology oncology database at the Royal Children’s Hospital to examine recovery of gonadal function according to cancer treatment in the young.
**Benefits to student:** A multi-collaborative project encompassing basic research and clinical interaction. Publication. Requirements for students: Dedicated, passionate, sensitive and committed. Has done well academically.

**CARDIOLOGY**

**65. Cardiac benefits by delayed reperfusion after acute myocardial infarction in mice**

**Supervisors:** A/Prof Xiao-Jun Du, Dr Xiao-Ming Gao  
**Project Site:** Experimental Cardiology Laboratory, Baker IDI Heart and Diabetes Institute, AMREP (Prahran)  
**Contact:** A/Prof XJ Du. T: 85321267; E: xiao-jun.du@bakeridi.edu.au

**Project Description:** Acute myocardial infarction (AMI) occurs following occlusion of a coronary artery. It is important to re-open the blocked artery to re-establish blood supply to the ischemic myocardium (reperfusion) to save ischemic myocardium from necrosis, i.e. infarct size limitation. Clinically, post-ischemia reperfusion can be achieved most commonly by catheter-based percutaneous primary coronary intervention (PCI) or by thrombolytic drugs. It is usually believed that significant delay (i.e. over 12 hours after onset of ischemic symptoms) in reperfusion does not provide clinical benefits, rather, reperfusion per se may exacerbate further injury to the ischemic heart muscle.

AMI in mice can be induced surgically by coronary artery occlusion. Like human patients, mice with AMI develop cardiac wall rupture, a malignant complication due to post-infarct myocardial inflammation and damage to the extracellular matrix (ECM) architecture of the infarct myocardium. In our recent study on mice, reperfusion was done following 1, 2 or 4 hours after coronary artery occlusion. We observed that the onset of cardiac rupture was completely prevented not only by early, but also by delayed reperfusion (Gao XM, et al: 2012. Due to significantly high metabolic rate in mice, reperfusion following a 4-hour period of ischemia in mice is equivalent to a major delay of reperfusion to humans). This finding clearly indicates benefits achieved by delayed reperfusion. This project is designed to explore the mechanism responsible for such cardiac protection by delayed reperfusion focusing on the extent of inflammation and ECM damage.

The specific aims of this project are:
- To compare delayed reperfusion versus non-reperfusion on the extent of inflammation in the infarct myocardium;
- To determine the extent of ECM damage by biochemical and histological means, between hearts without and with delayed reperfusion;
- To measure the degree of post-infarct ventricular remodelling by non-invasive echocardiography.

**Skills:** The project will enable the student to gain skills in: understanding the principal of reproducing heart disease models in mice, quantitative histology, biochemical assays, echocardiography in mice, data analysis using a variety of statistical methods.

**References**

**66. High resolution ultrasound evaluation of cardiac abnormalities in a mutant strain of mice with rheumatoid arthritis**

**Supervisor/s:** Xiao-Jun Du, Helen Kiriazis  
**Project site:** Experimental Cardiology Laboratory, Baker IDI Heart and Diabetes Institute, AMREP (Prahran)  
**Contact:** A/Prof XJ Du. T: 85321267; E: xiao-jun.du@bakeridi.edu.au

**Research Focus:** A strain of mice has recently been developed with simultaneous development of rheumatoid arthritis (RA) and cardiac abnormalities particularly aortic valve dysfunction [1]. This is due to a single mutation of gene resulting in elevated tumor necrosis factor α (TNFα). The aim of this project is to determine the initiation and progression of cardiac abnormalities by serial echocardiography in relation to the development of RA and circulating levels of TNFα.

**Keywords:** tumour necrosis factor α, echocardiography, rheumatoid arthritis

**Project description:** Chronic inflammatory conditions such as RA are known to influence adversely on the development of cardiovascular disease [2]. While there has been no animal model of RA that simultaneously develops heart abnormalities, a recent study by Dr Bouille and his team has revealed a mutant strain of mice with RA and heart disease, particularly aortic valve abnormalities due to regional inflammation and dilatation [1]. However, the time-course of initiation and progression of heart disease in relation to the development of RA has not been documented. This project is designed to illustrate the development and nature of heart disease in the mutant mice by conducting serial
echocardiographic imaging using our in-house high-resolution ultrasound system (Vevo2100). Experiments will be performed on mutant and control mice during 2 to 6 months of age and ventricular diastolic and systolic function, as well as valvular function of the aortic valves and mitral valves will be determined. Echocardiographic findings will be related to cardiac histological examination. This project is expected to significantly advance our understanding of the influence of chronic inflammatory disease on the cardiovascular system.

**Project related methods/skills/technologies:**
- echocardiography
- quantitative histology

**References:**
2. Symmons DP, Gabriel SE: Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011;7(7):399-408.

**67. Feasibility and effects of inorganic sodium nitrate in decompensted heart failure**

**Supervisors:** Associate Professor Christopher Neil, Head of CCU and Cardiac Ambulatory Care, Western Health, Clinical Associate Professor, University of Melbourne, Professor Jason Allen, Research Program Leader, Clinical Exercise Science, ISEAL Director, Victoria University

**Project Site:** Melbourne Medical School, Sunshine Hospital, St Albans

**Contact:** Email: Christopher.Neil@wh.org.au

**Project description:** Millions worldwide live with chronic heart failure and acute decompensation of heart failure (ADHF) remains a frequent problem. Elevated vascular resistance is of primary importance in the genesis of ADHF, whilst poor bioavailability of nitric oxide (NO, the body's major paracrine blood vessel relaxant) has also been described in the acute phase: dysfunction of the endothelial NO synthase (eNOS)/L-arginine pathway of NO generation may be at the nexus of vascular dysfunction and decompensation.

NO can be supplied to the body in a way which bypasses the dysfunctional eNOS/L-arginine pathway, via oral supplementation of sodium nitrate (NaNO₃, present in foods such as beetroot). Given the implications for vasodilation, this novel strategy has generated intense interest in various cardiovascular pathologies, including hypertension, coronary artery disease and peripheral arterial disease. A recent study in stable heart failure demonstrated safe administration of 8.4mmol NaNO₃, without hypotension.

NaNO₃ supplementation may be an ideal means of treating ADHF during hospital admission, since existing NO-donor drugs such as glyceryl trinitrate have limited effectiveness in HF due to pharmacological resistance, as well as frequent pharmacological tolerance within 24 hours. The aim of this honours project is to execute a 32 patient pilot study (randomised double blind, placebo controlled), to evaluate the feasibility and effectiveness of sodium nitrate (NaNO3 8.4mmol administered twice daily) over 48 hours as a treatment for ADHF.

The student will be involved in the recruitment and randomization of subjects and will assess the efficacy of NaNO₃ supplementation through impedance cardiography as well as in chemiluminesence assays of NO, over the treatment period. This project is suitable for the honours student who wishes to experience translational cardiovascular research in a clinical and laboratory environment. This project is furthermore advantageous for those applicants who may wish in the future to pursue hospital-based employment in the long term or as a prelude to further study in biomedicine.

**68. Prospective evaluation of non-invasive cardiac haemodynamic assessment for therapeutic guidance in acute and ambulatory heart failure**

**Supervisors:** Associate Professor Christopher Neil, Director of CCU and Cardiac Ambulatory Care, Western Health, Clinical Associate Professor, University of Melbourne, Lynnette Reid-Price, Manager, Medical Specialty Diagnostics. Dept Respiratory & Sleep Disorders, Medicine and Dept Neurology & Neuropsychology, Western Health

**Project Site:** Melbourne Medical School, Sunshine Hospital, St Albans

**Contact:** Email: Christopher.Neil@wh.org.au

**Project description:** Acute decompensated heart failure (ADHF) is the single largest reason for acute hospital bed occupancy, and represents a large public health problem and is therefore a major focus of attention for health professionals and health funders alike. Major goals include efficient optimisation in the acute phase, which often revolves around decongestion with diuretics, without excess duration of hospitalisation. However, ADHF represents a diverse group, in which a broad based “one size fits all” therapeutic strategy may not be appropriate. Hence, failure to appreciate
this heterogeneity in cardiovascular and haemodynamic status and to tailor therapeutic maneuvers accordingly, has been suggested to lie at the root of the problem, and specifically the failure to develop evidence-based treatment. The implications of this thought are significant and it is argued that haemodynamically guided application of the existing “therapeutic toolkit”, especially vasodilators such as organic nitric oxide donors and hydralazine (in the case of residually elevated systemic vascular resistance), may actually translate to better outcomes.

Therapeutic guidance will be aided with the use of the Non-Invasive Cardiac system or NICA5. NICA5 is a system based on the ICG (impedance cardiography) technique, measuring changes in the voltage of an electrical signal applied across an area of the body. This project aims to assess the potential of the NICA5 to guide tailored therapy in heart failure patients by accurately describing the patient’s unique circulatory state, especially their vascular resistance, which is otherwise difficult to assess by standard clinical measures (such as clinical examination or blood pressure measurement).

This proposal will consist of a prospective randomised protocol and will aim to determine the place of the NICA5 in guiding clinicians to optimise cardiovascular status in the acute phase of deteriorated HF with use of specific heart failure therapies in inpatients.

The student will be involved in the inpatient phase of this project, on the ward with enrolled patients, utilising NICA5 to collect data. The student will also be involved in the randomisation of subjects. The student will analyse the efficacy of NICA5-guided treatment in accordance with the primary outcome measure (a greater and more consistent fall in BNP from admission to discharge) and nominated secondary outcome measures.

This project is suitable for honour students who wish to experience translational cardiovascular research in a hospital environment. Specific skills to be developed will include,

- performing and understanding basic clinical measurements with a novel technology (NICA5);
- patient interaction, recruiting and randomising patients;
- appropriate/effective interaction with ward staff i.e. nurses, ward doctors.
- data collection, management and analysis
- understanding complex pathophysiology and therapeutics in a clinical context.

This project is furthermore advantageous for those applicants who may wish in the future to pursue hospital based employment in the long term, (e.g. as a hospital scientist, technician) or as a prelude to further study in biomedicine.

Feasibility: We have already obtained Human Research Ethics Committee approval. Furthermore, working on the project will guarantee a publication for the work involved.

69. Novel ways of Detecting and Managing Chronic Diseases (Chronic Kidney Disease/Diabetes/Cardiovascular Disease) in Primary Care

Supervisors: A/Prof Craig Nelson; Professor Edward Janus; Dr Shane Hamblin
Project Site: Melbourne Medical School, Sunshine Hospital, St Albans
Contact: A/Prof Craig Nelson; Craig.Nelson@wh.org.au; +61412412376

Project description: Funding from the Victorian Department of Health Renal Health Clinical Network and Aboriginal Health has enabled Western Health to pilot a successful early detection program targeting patients at risk of developing kidney disease in the West of Melbourne. We now plan to extend this program to encompass Diabetes and Cardiovascular Disease with granted funds from the Macedon Ranges and North Western Melbourne Medicare Local. It is estimated 80% of primary care practices in Australia have Electronic Healthcare Records (EHR) that are compatible with the eHealth tools to be developed. It is a powerful tool enabling monitoring of chronic disease risk, testing and management on large populations at the primary care level. Population Health data will be available on over 100,000 people for analysis and reporting. This would be an excellent experience in bridging the gap between primary care and hospitals and skills gained will include experience in population health and epidemiology.

70. Do the coronary small vessels respond less well to medication in patients with diabetes or renal failure – also offered as MBiomedSc

Supervisors: Professor Judy Savige and A/Prof Deb Colville
Project Site: NWAC, Northern Hospital, Epping.
Contact: Professor Judy Savige, T 8344 3260, j.savige@unimelb.edu.au

Project description: Most research into the causes of heart disease has focused on disease in the coronary arteries but the importance of small vessel disease is recognized increasingly. However the coronary small vessels are difficult to study. Nevertheless whenever the small vessels in the heart are affected, small vessels are diseased throughout the body. This includes the vessels in the retina, which are very accessible using a retinal camera and photography. So we propose to examine the retinal small vessels as a model for the coronary arterioles and determine whether renal failure or diabetes means these vessels are diseased and respond less well to medication.
This study involves recruiting patients from the wards with renal failure or diabetes and testing the effect of a tablet that usually dilates small vessels. You will help the patient fill out a questionnaire and also take their blood pressure and retinal photographs, and then review the photographs under the supervision of an ophthalmologist. In addition the retinal photos will be sent to the Centre for Eye Research Australia for the vessel diameters to be measured precisely. The aim of this project is then to determine whether small vessels are less responsive in diabetes and renal failure, and whether medication doses should be increased. The analysis includes univariate and multivariate statistics and backwards linear regression (we will help you with the statistics).

Techniques to be used and skills acquired: This project involves a lot of patient contact, going onto the wards and getting to know hospital staff, learning how to take retinal photographs, and how to interpret abnormalities, as well as statistics. Feasibility: We already have Human Research Ethics Committee Approval for this project and many of the medical students who have undertaken similar projects during an AMS year have achieved a publication from their work.

71. Natural History of Coronary Plaque Evolution Through Optical Coherence Tomography– ONLY offered as MBiomedSc

Supervisor/s: A/Prof. Peter Barlis, Dr. Vikas Thondapu; Prof Andrew Ooi, Dr. Eric Poon
Project Site: Department of Mechanical Engineering, Parkville
Contact: Dr Vikas Thondapu E: vthondapu@gmail.com

Project description: Despite groundbreaking advances in cardiology over the past several decades, cardiovascular disease remains the most common cause of death worldwide. The unfortunate reality is that many coronary plaques remain asymptomatic until acute rupture and vessel occlusion, forming a clear impetus for the earlier identification and treatment of high-risk lesions. Intracoronary optical coherence tomography (OCT), a light-based analog of intravascular ultrasound, provides a tenfold improvement in resolution, allowing in vivo imaging of coronary plaques with near-histologic clarity.

This project aims to evaluate the natural history of coronary plaque over 6 months through analysis of angiographic and OCT-derived plaque features. Students will also have the opportunity to engage in state-of-the-art computational fluid dynamic modeling to better understand the role of local micro-hemodynamics in plaque evolution. This work will improve our fundamental understanding of plaque evolution, better define the role of intravascular imaging in the identification of high-risk plaques, and has a potentially high impact in the prospective diagnosis and treatment of coronary artery disease.

Baseline and follow-up angiography and OCT imaging has already been completed in a series of 60 patients. Students will be trained in quantitative coronary angiography and OCT plaque analysis. Those interested in computational modeling will be guided in 3D coronary artery reconstruction and computational fluid dynamic methods.

72. Evaluation of Coronary Stent Apposition and Intimal Healing Through Optical Coherence Tomography – ONLY offered as MBiomedSc

Supervisor/s: A/Prof. Peter Barlis, Dr. Vikas Thondapu; Prof Andrew Ooi, Dr. Eric Poon
Project Site: Department of Mechanical Engineering, Parkville
Contact: Dr Vikas Thondapu E: vthondapu@gmail.com

Project description: Stent placement is the standard of care in the treatment of occlusive coronary artery disease. The vast majority of patients show improvement and remain asymptomatic after stent placement, however a small but significant subset of patients are prone to adverse long-term complications such as in-stent restenosis and stent thrombosis. The causes of these potentially catastrophic late outcomes remain unclear, but early evidence points to features such as incomplete stent strut apposition and persistently uncovered stent struts. Optical coherence tomography, a high-resolution intravascular imaging technique, offers unprecedented in vivo visualization of individual stent struts and tissue coverage patterns, and is thus an ideal tool to evaluate potential risk factors for late adverse stent complications.

This project aims to compare the stent apposition and late tissue healing characteristics of two commonly used second-generation drug-eluting stents. Students will also have the opportunity to explore the effect of stent malapposition on local micro-haemodynamics through state-of-the-art computational fluid dynamic modeling. Given that over 4 million stents are placed annually around the world, this high-impact project has potentially great clinical significance.

Baseline and follow-up angiography and OCT imaging has already been completed in a series of 60 patients. Students will be trained in quantitative coronary angiography and OCT stent analysis. Those interested in computational modeling will be guided in 3D coronary artery reconstruction and computational fluid dynamic methods.
CENTRAL CARDIOVASCULAR REGULATION

73. **Unravelling the neural circuits that drive increases in sympathetic nerve activity in heart failure**

**Supervisors:** Dr Song Yao  
**Project Site:** Florey Institute of Neuroscience and Mental Health, UoM, Parkville  
**Contact:** Dr Song Yao, E: song.yao@florey.edu.au

**Project description:** Heart failure (HF) is a major global healthcare problem because of its high prevalence, morbidity, mortality and cost. Patients with heart failure are three times more likely to die within three years than patients diagnosed with cancer. While there has been some improvement in HF treatment over last 30 years, morbidity and mortality remain high. One of the major contributors to disease progression is the rise in sympathetic nerve activity. However, the brain areas responsible for this detrimental increase in sympathetic nerve activity has not been well characterised.

This project will investigate which cardiovascular brain centres are activated in the short and long term after myocardial infarction. This project will be relatively demanding and involve using a number of different techniques including surgery, echocardiography, neuroanatomy and electrophysiology if time permits. The successful completion of the project will expand our understanding of the neural circuitry driving sympathetic nerve increases in heart failure.

For this project we will be asking the following questions:
1. Which areas of the brain are activated in the short and long term after a myocardial infarction?  
2. What are the chemical phenotypes of activated neurons?  
3. Can this neuronal activation be prevented using the anti-inflammatory compound pentoxifylline?

**Techniques involved:** small animal surgery (induction of myocardial infarction), echocardiography, tissue sectioning, immunohistochemistry (DAB and fluorescence), microscopy (light, fluorescence, confocal), in vivo electrophysiology (if time permits).

**Further Reading:** Ruchaya et al. (2014) Experimental Physiology, 99(1) 111-122

74. **Central cardiovascular control: uncovering the role of inflammatory cytokines in the area postrema**

**Supervisors:** Dr Song Yao  
**Project Site:** Florey Institute of Neuroscience and Mental Health, UoM, Parkville  
**Contact:** Dr Song Yao, E: song.yao@florey.edu.au

**Project description:** The area postrema is a circumventricular organ located in the brain stem. Because it lacks a blood-brain barrier the area postrema is exposed to a wide range of factors found in the circulation. There is much evidence to suggest that inflammatory cytokines are increased in a number of cardiovascular diseases such as hypertension and heart failure. However, the cardiovascular effect of these cytokines when exogenously applied to the area postrema is not currently known.

This project will investigate the effects of different cytokines such as CX3CL1 (fractalkine) and tumor necrosis factor-alpha (TNF-α) within the area postrema. The successful completion of the project will increase our understanding of the role of cytokines in driving changes in blood pressure at the level of the area postrema and how this signaling might be altered in disease states such as hypertension and heart failure.

For this project we will be asking the following questions:
1. What are the cardiovascular effects of CX3CL1 and TNF-α when applied directly to the area postrema?  
2. Are the cardiovascular effects of these cytokines altered in hypertension and heart failure?

**Techniques involved:** small animal surgery (induction of myocardial infarction and hypertension), stereotaxic microinjections, tissue sectioning, microscopy (light, fluorescence, confocal).  
**Further Reading:** Ruchaya et al. (2014) Experimental Physiology, 99(1) 111-122

CARDIOLOGY - PAEDIATRICS

75. **Body composition and cardiovascular risk in children: The Longitudinal Study of Australian Children’s Child Health Check Point – also offered as MBiomedSc**

**Supervisors:** Professor David Burgner, Dr Richard Liu  
**Project Site:** Murdoch Childrens Research Institute  
**Contact:** David Burgner E: david.burgner@mcri.edu.au

**Project description:** Cardiovascular disease (CVD), the leading cause of morbidity and mortality in Australia and worldwide, has its origins in early life, but is asymptomatic until adulthood. Understanding the childhood factors that
increase CVD risk earlier in life – before disease develops – would allow earlier intervention and prevention. Obesity is recognised as a major public health emergency and carries a significant CVD risk. 1 in 4 Australian children are overweight or obese. Measurement of growth parameters (anthropometry) including weight, body mass index, fat mass, lean mass, and waist circumference allows assessment of body composition in a number of ways. It is unknown which of these measures are most strongly associated with early subclinical atherosclerosis in asymptomatic children. Working within the Longitudinal Study of Australian Children’s (LSAC) Child Health CheckPoint, this project will address these clinically important questions, while also providing a rare opportunity to work within one of Australia’s most important and exciting national research projects. The Child Health CheckPoint is providing a detailed physiologic profile of a nationally-representative sample of ~2000 children at age 11-12 years; including sophisticated body anthropometry measures and a comprehensive cardiovascular assessment including carotid intima-media thickness, a well-studied marker of subclinical atherosclerosis. The project will involve analysis of the relationships between the different anthropometric measures and their association with markers of early atherosclerosis. The findings will be of clinical importance, as they will inform decisions as to how to assess anthropometry optimally to target cardiovascular risk. The project will involve some hands-on experience assessment of children and analysis of the unique data that are being generated.

76. Which measures of growth and body composition best predict cardiovascular risk in adults? A study of the parent cohort from The Longitudinal Study of Australian Children’s Child Health Check Point – also offered as MBiomedSc

Supervisors: Professor David Burgner, Dr Richard Liu
Project Site: Murdoch Childrens Research Institute
Contact: David Burgner E: david.burgner@mcri.edu.au

Project description: Cardiovascular disease (CVD), the leading cause of morbidity and mortality in Australia and worldwide. Obesity is recognised as a major public health emergency and carries a significant CVD risk. Two thirds of Australian adults are overweight or obese. Measurement of growth parameters (anthropometry) including weight, body mass index, fat mass, lean mass, and waist circumference allows assessment of body composition in a number of ways. It is unknown which of these measures are most strongly associated with subclinical atherosclerosis in asymptomatic adults. Published data largely relate to American males; much less is known about women and there are few Australian studies. Working within the Longitudinal Study of Australian Children’s (LSAC) Child Health CheckPoint, this project will address these clinically important questions, while also providing a rare opportunity to work within one of Australia’s most important and exciting national research projects. The Child Health CheckPoint is providing a detailed physiologic profile of a nationally-representative sample of ~2000 parent-child dyads, including sophisticated body anthropometry measures, and a comprehensive cardiovascular assessment including carotid intima-media thickness, a well-studied and validated marker of subclinical atherosclerosis. The project will involve analysis of the relationships between the different anthropometric measures and their association with markers of atherosclerosis in the parents enrolled in the study. The findings will be of clinical importance, as they will inform decisions as to how to assess anthropometry optimally to target cardiovascular risk. The project will involve some hands-on experience assessment of parents and children and analysis of the unique data that are being generated.

CLINICAL RESEARCH

77. Hospital acquired electrolyte disorders – also offered as MBiomedSc

Supervisors: A/Prof Terri Jackson, Dr Anastasia Hutchinson, Prof Peter Brooks, Ms Karen Barclay
Project Site: Melbourne Medical School, Epping Hospital
Contact: Dr. Terri Jackson T: 044 872 7240 E: terri.jackson@unimelb.edu.au

Project Description: Routine hospital diagnosis data in Australia includes ‘condition onset’ (timing) markers that distinguish co-morbidities (diagnoses documented as present on admission) from hospital-acquired diagnoses. This project uses a one-year sample of the Victorian Admitted Episodes Database to investigate the correlates of hospital-acquired electrolyte disorders arising from active treatment rather than dehydration. These range from minor biochemical imbalances to major multi-organ disorders. They have been found to be the most costly single complication in hospital data from both Canada and Australia. A better understanding of the factors affecting their clinical course will assist in efforts to reduce incidence.

The specific aims of this project are:
• To identify the patient characteristics and diagnoses most frequently associated with hospital-acquired electrolyte disorders
• To describe patterns of multiple complications causing or arising from electrolyte imbalances
• To estimate the health care implications of these disorders, including incremental additional days of stay, days of ICU care, in-hospital death
• To review the literature on approaches to fluid and electrolyte management to support reduction in the rates of these disorders.

Skills: The project will enable the student to gain skills in: secondary analysis of large hospital data sets (including data validation and cleaning), data linkage, descriptive statistics and multivariate logistic regression. The student will develop an understanding of key concepts in clinical medicine.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

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**CLINICAL RESEARCH – SURGICAL**

78. **The utility of colonoscopy in women of child bearing age**
   Supervisors: Ms Karen L Barclay
   Project Site: Melbourne Medical School, Epping Hospital
   Contact: E: karen.barclay@nh.org.au or kbarclay@unimelb.edu.au;

   AIM: To establish the outcomes of colonoscopies performed for women of child-bearing age and attempt to assess the utility of haematinsics and occult-blood testing in prioritization.

   Colonoscopy is a scarce resource and has potential risks. Women of child-bearing age are more likely to have abnormal haematinic indices which may result in referral for colonoscopy. In our clinical setting, the outcomes of colonoscopy performed for this indication are unknown, as is the utility of laboratory measures.

   The student would review colonoscopies performed at the Northern hospital in women of child-bearing age and match the results with clinical and laboratory measures. The information would be used to provide evidence for or against tests and colonoscopy in this group.

79. **Opportunities to diagnose Colorectal Cancer – are we missing them?**
   Supervisors: Ms Karen L Barclay
   Project Site: Melbourne Medical School, Epping Hospital
   Contact: E: karen.barclay@nh.org.au or kbarclay@unimelb.edu.au;

   AIM: To establish the proportion of people treated for CRC at TNH for whom an opportunity for earlier diagnosis may have been present

   The researcher would conduct a retrospective clinical record review of patients managed for Colorectal Cancer and establish which patients have been present within the institution within the last few years in order to see if earlier diagnosis may be possible by the introduction of a generalised screening process. Patients with Colorectal Cancer would be identified from the colorectal database and clinical records and databases used to identify hospital attendances. The information would be recorded and analysed to assess the proportion of patients for whom a generalised screening process may allow earlier diagnosis of CRC.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

80. **A scoring system for the assessment of process in rectal cancer management**
   Supervisors: Ms Karen Barclay
   Project Site: Melbourne Medical School, Epping Hospital
   Contact: Ms Karen Barclay karen.barclay@nh.org.au

   **Project description:** Standards of care are critical in any type of oncologic surgery. In the management of rectal cancer, key processes in the pathway of care have been shown to lead to improved outcome. Although audit processes are in place in most centres of repute, it is difficult to demonstrate due process simply and quickly. The current study looks at an original scoring system for assessing key areas of practice. The aim is to show the scoring system is easy, reproducible and a simple way of showing practice standard is adequate or highlighting areas for improvement.

Potential students are requested to forward a CV, Academic transcript and statement of interest.
81. **The presentation of colorectal cancer in the era of screening**

**Supervisors:** Ms Karen Barclay  
**Project Site:** Melbourne Medical School, Epping Hospital  
**Contact:** Ms Karen Barclay karen.barclay@nh.org.au

**Project description:** Since the introduction of the National Bowel Cancer Screening Programme in 2006, little information is available about the effect on presentation of Colorectal Cancer (CRC). With an increase in awareness of screening and numbers of people offered screening over time, it could be expected that more people would be presenting with screen-detected rather than symptomatic tumours. This project looks at the presentation of CRC over time to see whether this has occurred or not.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

82. **In patients with a foot wound undergoing revascularization surgery, what is the time frame for improvement in ankle and toe systolic pressures? A pilot study**

**Supervisors:** Elise Gillies – Grade 3 Podiatrist (Primary Researcher), Kate Harper – Grade 3 Podiatrist (Associate Researcher)  
**Project Site:** Northern Centre for Health, Research and Education (NCHER) at Northern Health, Cooper Street, Epping, 3076.  
**Contact:** Tanya Gilliver: Associate Director Allied Health at Northern Health Tanya.gilliver@nh.org.au

**Project description:** Many people with foot wounds and poor peripheral arterial supply will undergo a revascularisation procedure by a Radiologist or Vascular Surgeon, as part of their wound management. These may include: arterial bypass, angioplasty, stenting and/or endarterectomy. The aim of these procedures is to improve peripheral blood flow and optimise arterial potential for wound healing.

The primary aim of this study is to determine the time period it takes for TP to be maximised following revascularisation surgery in people with a foot wound. This observational, prospective pilot study will use a within-subjects, repeated measures study design. It will involve measuring the ABI and TP of Northern Hospital patients with a foot wound who undergo a revascularisation procedure. The authors will compare the findings before, then at specific time periods up to 2 weeks after the procedure, to determine the time period of magnitude of improvement in these measures following surgery. The authors hypothesise that this study will provide a time period in which optimal arterial perfusion of the foot occurs after revascularisation surgery. Based on the results, the authors may be able to make clinical recommendations on the timing of initiation of moist wound healing principles, amputation and debridement, when TP is optimised so arterial potential for wound healing is maximised.

COLORECTAL MEDICINE AND GENETICS

83. **Serrated Polyposis Syndrome - also offered as MBiomedSc**

**Supervisors:** Professor Finlay Macrae  
**Project Site:** The Royal Melbourne Hospital  
**Contact:** E: finlay.macrae@mh.org.au

**Project description:** Serrated polyposis syndrome is the last polyposis syndrome without a known genetic predisposition identified. Working with Dr Dan Buchanan in the Dept of Pathology, this project will be the clinical arm of phenotype data collection from the records of the Familial Cancer Clinic which will form the basis for the selection of cases for next gen whole genome sequencing in Dan’s lab in the Dept of Pathology.

84. **Prospective studies on penetrance for cancer in Lynch Syndrome – also offered as MBiomedSc**

**Supervisors:** Professor Finlay Macrae  
**Project Site:** The Royal Melbourne Hospital  
**Contact:** E: finlay.macrae@mh.org.au

**Project description:** Well-designed studies on prospectively collected data for studying penetrance, survival and treatment effects of cancers occurring in Lynch Syndrome are scarce. This project will collaborate with European investigators on a common design template to provide important data to guide clinical practice. Two consortia are already formed with whom the candidate will collaborate: the International Mismatch Repair Consortium (leads Robert Hale, Stanford, Mark Jenkins and Finlay Macrae (Melbourne) and Gabriela Moeslein (Dusseldorf, Germany); and the Majorca Group (lead Pal Moller, Norway)
85. **CAPP3: a randomized controlled trial of aspirin dosage in Lynch Syndrome**  
*also offered as MBiomedSc*

**Supervisors:** Professor Finlay Macrae  
**Project Site:** The Royal Melbourne Hospital  
**Contact:** E: finlay.macrae@mh.org.au

**Project description:** CAPP2 proved aspirin reduces the incidence of LS associated cancers by over 50%. CAPP3 is a dose finding RCT testing 100mg vs 300mg vs 600mg. This is an international study lead from Newcastle UK, with Australian leadership from RMH. Students will learn about multi centre, multi national RCTs, be immersed in aspirin science and cancer genetics, and participate in the clinical aspects of management of Lynch Syndrome.

86. **The Human Variome Project (HVP) and familial bowel cancer**  
*also offered as MBiomedSc*

**Supervisors:** Professor Finlay Macrae Head, Colorectal Medicine and Genetics, Professor Richard Cotton, Director, Genomic Disorders Research Institute, University of Melbourne  
**Project Site:** Dept of Colorectal Medicine and Genetics, RMH; or GDRC, Alan Gilbert Building, Uni of Melb.  
**Contact:** Tel: 61 3 9347 0788 E: Finlay.macrae@mh.org.au

**Project Description:** This important project forms a component of the HVP, which aims to document all DNA variants across all genes in man. The International Society for Gastrointestinal Hereditary Tumours is well advanced in formulating processes for the vision, with committees of experts world wide working on different aspects. A range of Honours and higher degree opportunities are available within the HVP and InSiGHT’s engagement with the HVP. Its aims to position itself as a lead locus for the HVP

87. **Biogrid and IBD data basing**  
*also offered as MBiomedSc*

**Supervisor:** Professor Finlay Macrae, Head, Colorectal Medicine and Genetics  
**Project Site:** Royal Melbourne Hospital, Parkville  
**Contact:** Professor Finlay Macrae T: +61 3 9347 0788 E: finlay.macrae@mh.org.au

**Project Description:** The development of a common database for recording clinical management and outcomes for IBD clinics in Melbourne is being coordinated through the Department of Colorectal and Genetics. This project will bring students into close contact with the management of IBD, and working alongside a dedicated team of doctors and nurses focusing on IBD. The project will lead to linkage with other similar databases through the Australian BioGrid. [http://www.biogrid.org.au](http://www.biogrid.org.au)

88. **Locus Specific Databases in Hamartomatous polyposis syndromes:**

**Supervisors:** Professor Finlay Macrae  
**Project Site:** Department of Colorectal Medicine & Genetics, Royal Melbourne Hospital  
**Contact:** Professor Finlay Macrae E: Finlay.macrae@mh.org.au

**Project description:** Hamartomatous polyposis syndromes include: Peutz Jeghers Syndrome (gene locus STK11), Juvenile Polyposis (gene loci SMAD4 & BMPR1A, Cowden’s Syndrome (gene locus PTEN). Diagnostic laboratories around the world identify in the gene loci, sometimes clearly pathogenic, other times uncertain. International centralisation of gene variant information with clinical and familial information is one of the best ways to progress the interpretation of variants of uncertain significance. The Human Variome Project, at the University of Melbourne, aims to document variation in all genes across all countries in the world. The Hamartomatous Polyposis Syndrome project will relate to the HVP. The International Society for Gastrointestinal Hereditary Tumours (InSiGHT) hosts LSDB's for genes responsible for inherited gastrointestinal cancers. The InSiGHT mismatch repair gene database is curated at the HVP and Department of Colorectal Medicine and Genetics at The Royal Melbourne Hospital. The Hamartomatous Polyposis LSDB Project will develop similar database, ascertaining variant and clinical data across the published literature, contacting the InSiGHT membership for unpublished information and assembling the data on a LOVD platform. The project will involve extensive international collaboration, understanding genetic variation and variants of uncertain significance, bioinformatics and clinical management of these syndromes.

89. **The Structure and Functions of an Inflammatory Bowel Disease Service:**

**Supervisors:** Professor Finlay Macrae  
**Project Site:** Department of Colorectal Medicine & Genetics, Royal Melbourne Hospital  
**Contact:** Profess Finlay Macrae E: Finlay.macrae@mh.org.au

**Project description:** This project will assist the IBD Service and the IBD Nurse Consultant to refine the structure required for the Inflammatory Bowel Disease Service through: Development of clinical guidelines to manage well defined IBD Clinical management issues (eg. acute colitis)/ Integration with the new Pharmaco-genetics Service at The Royal Melbourne Hospital (ie. TPMT genotyping). Thiopurine metabolite testing. Transition arrangements of IBD patients from paediatric to adult care. Bone density monitoring and intervention.
"Off label" use of anti TNF therapies eg. in ulcerative colitis. The Royal Melbourne Hospital IBD Database. The functions of one of several of these will be tested through “before and after” assessment, where appropriate and audits and /or surveys.

The project will provide an outstanding opportunity for clinical engagement in a busy IBD Service, collaboration with other Australian IBD services, understanding of the evolving role of IBD Nurse Practitioners in IBD care, endoscopy in IBD, and interaction of the clinical IBD service with a range of clinical research projects (microbiota pharma trials).

90. **C-reactive protein (CRP) and Crohn’s disease – CRP as a potential phenotypic marker for disease**
    
    **Supervisors:** Dr Suresh Sivanesan, Prof. Finlay Macrae
    
    **Project site:** Royal Melbourne Hospital, Parkville
    
    **Contact:** Dr Suresh Sivanesan T: 03- 8417 9900 or 03- 9342 7584 E: suresh.sivanesan@mh.org.au
    
    **Project description:** Crohn’s disease is a chronic inflammatory condition which can affect any part of the gastro-intestinal tract to cause significant symptoms and morbidity. The condition can affect and segment of the gastrointestinal tract including the perianal region. It can develop into more complex disease resulting in abscesses, luminal strictures, fistulas and perforation. Clinicians have sought to classify Crohn’s disease in terms of the disease distribution or complications that it has caused. The currently used classifications are helpful but they do not assist in reliably predicting appropriate treatment or outcomes.

    CRP is a serum inflammatory protein that is commonly elevated in conditions such as rheumatoid arthritis, infection and Crohn’s disease. It is produced by hepatocytes and is upregulated by cytokines IL-6, IL1β and TNFα. It has been described that not all patients with Crohn’s disease exhibit a rise in CRP. We hypothesize that if there are a subgroup of patients with active Crohn’s disease and a express a normal serum CRP.

    We intend to study our cohort of patients with active Crohn’s disease to determine their levels of CRP, disease phenotype and assess their response to treatment. In particular if the hypothesis is true, we would hope to extend this work in the future to include cytokine and genotypic profiling of these patients.

    This work could open the door toward a better understanding of Crohn’s disease using widely available tools such as CRP. In future identifying subgroups of patients with Crohn’s disease based on cytokine and genetic profiling will enable a more tailored approach to patient care.

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**ELECTROPHYSIOLOGY**

91. **How do Anti-Epileptic Drugs Work? - also offered as MBiomedSc**
    
    **Supervisor:** Dr Chris French
    
    **Project Collaborators –** Prof T O’Brien, Prof D Williams
    
    **Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital
    
    **Contact:** Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
    
    **Website:** [http://sites.google.com/a/hfbg1.net/crf_lab/](http://sites.google.com/a/hfbg1.net/crf_lab/)
    
    **Project Description:** Despite many years of use and research, it is still not clear how even some of the oldest forms of anti-epileptic drugs work. That which is known is generally based on the effects of these compounds on single neurons, rather than examining how activity of the whole inter-connected neural network of the mammalian CNS is modulated. This project involves studying the effects of AED’s at several levels of organization of the CNS – single channel (voltage-gated sodium, potassium and calcium channels), single neuron, principal neuron/interneuron dynamics, as well as glial cell effects. Patch clamp techniques are used for recording dissociated neuron and neurons in the intact brain slice, and these observations will be extended with high-speed calcium imaging with conventional microscopy as well as multiphoton techniques. This projects affords excellent opportunities for skill development in electrophysiology, pharmacology, advanced microscopy and computational neuroscience.

92. **How do Antipsychotic Drugs Trigger Seizures? - also offered as MBiomedSc**
    
    **Supervisor:** Dr Chris French
    
    **Project Collaborators –** Prof T O’Brien, Prof D Williams
    
    **Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital
    
    **Contact:** Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
    
    **Project Description:** The treatment of psychosis and schizophrenia has been greatly improved with the use of anti-psychotic drugs such as chlorpromazine, haloperidol and newer drugs such as clozapine. One significant side effect of
these drugs is that they tend to lower the threshold for epileptic seizures to occur. The aim of this project is to quantify enhanced seizure activity with this type of drug using the in vitro brain slice technique. Seizure provocation threshold, synaptic transmission and single neuron properties will be assessed using rat hippocampal brain slices after acute application of these drugs.

93. **Multi-Electrode Recording in the Rat Brain** - *also offered as MBiomedSc*
   
   **Supervisor:** Dr Chris French  
   **Project Collaborators –** Prof T O'Brien, Dr P O'Brien  
   **Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital  
   **Contact:** Dr Chris French  
   **Tel:** 8344 3276  
   **E-mail:** frenchc@unimelb.edu.au  

   **Project Description:** Although immense advances have occurred in recording electrical signals from the CNS, these observations tend to be of single cells in a matrix of many millions of neurons and hence give very limited information about how the whole highly interconnected network functions. One solution to this problem is to use banks of tetropdes, bundles of four 10-20 micron diameter electrodes to record many cells simultaneously, either from a single region or from different parts of the brain. Up to 32 electrodes can be implanted with our system, and sophisticated spike detection and analysis algorithms are available to organize the complex multiple signals recorded. This recording technique can also be easily adapted to exploring epileptiform discharges in models of both focal and generalised epilepsy (including drug effects), which will be the main aim of this project. This project provides opportunity to learn cutting-edge electrophysiological and computing analysis techniques for assessment of function of the mammalian nervous system.

**ENDOCRINOLOGY, DIABETES & BONE DENSITY**

94. **Assessment of the effect of ankle arthrodesis on muscle and bone function using an integrated experimental and computational approach— also offered as MBiomedSc**
   
   **Supervisors:** A/Prof Christine Rodda and A/Prof Peter Pivonka  
   **Project Collaborators:** A/Prof Peter Lee  
   **Project Site:** Melbourne Medical School, Sunshine Hospital, St Albans.  
   **Contact:** Dr Christine Rodda, Tel: 8395 8161; email: Christine.rodda@unimelb.edu.au  

   **Project Description:** Ankle arthrodesis is the fusion of the ankle joint in patients with severe ankle arthritis that leads to a significant reduction in joint flexibility and stability. While this orthopaedic surgical procedure is very effective for pain relief and joint stability only a limited amount of data is available on the functional outcomes of this procedure on muscle and bone. Some of the observed intermediate and long-term effects are reduction of muscle strength (e.g., calf muscle) and stress fractures in the tibia and fibula. In order to address this problem we will apply an integrated experimental and computational approach to quantitatively assess the functional outcomes of ankle arthrodesis on muscle and bone. We plan to recruit 30 adult patients who have undergone ankle fusion at least 2 years previously, from a single orthopaedic surgeon. In order to assess muscle function we will use gait analyses and metatarsal pressure analyses. To assess bone changes we will collect regional DEXA (dual energy X-ray absorptiometry) bone density and peripheral QCT (quantified computerised tomography) measurements of the affected tibia and compare these with the control group. Calf muscle bulk on affected and unaffacted sides will also be assessed using pQCT. Data from the gait analyses will be used for a musculoskeletal model of the lower limb (using OpenSim i.e. an open source software to simulate dynamic human movement developed in Stanford University) in order to quantify muscle strength and muscle activation patterns. Using the obtained muscle forces together with the bone material properties (from pQCT) we can calculate the mechanical stress distribution in the tibia. The magnitude of stresses together with the frequency of loading will serve as an indicator of the risk of stress fracture. Findings from this study will enable us to anticipate and inform the intermediate and longterm local musculoskeletal sequelae of ankle arthrodesis, and form the basis for future intervention studies.

**EPILEPSY AND NEUROPHARMACOLOGY**

95. **Reducing Epilepsy Deaths – Learning from the NCIS (National Coronial Information System)**
   
   **Supervisors:** Dr Rosemary Panelli  
   **Project Site:** The Melbourne Brain Centre, The Department of Medicine (RMH)  
   **Contact:** Dr Rosemary Panelli  
   **E-mail:** rpanelli@unimelb.edu.au  

   **Project Description:** The most common epilepsy-related cause of death remains a mystery. Epilepsy carries a risk of premature death that is 2-3 times higher than for the general population and a risk of sudden death 20 times higher. The mean age of death is low and the number of Years of Life Lost is high. Sudden Unexpected Death in Epilepsy (SUDEP) is
the term now used to describe these unexplained deaths but recognition and appropriate reporting is inconsistent internationally and the incidence is difficult to assess.

The Australian National Coronial Information System is unique internet-based data storage and retrieval system and research access to such a comprehensive database is rare in the international context. The objective of this study is to identify and analyse all information held in the NCIS database concerning epilepsy-related deaths. The NCIS data is extensive and valuable due to the large number of these deaths which occur in the community setting. A systematic examination of the NCIS documents (police reports, post-mortem results, toxicology, and coroners’ findings), will allow the researchers to clarify the frequency of SUDEP and to identify any patterns or common factors associated with the deaths, thus enabling a more informed characterisation of epilepsy-related death and risk in this country. The project will include extensive assessment and interpretation of forensic and police reports, database development, critical analysis of the data, and preparation of information for publication.

96. Keeping the Brain and the Heart in Sync – HERG channels in the CNS - also offered as MBiomedSc

Supervisors: Dr Chris French,
Project Site: Melbourne Brain Centre
Contact: Chris French frenchc@unimelb.edu.au

Project description: (H)ERG (“human ether a go-go”) ion channels are important in for pacing the heart. Genetic disorders of this channel or drug inhibition lead to serious cardiac arrhythmias. It is known that (H)ERG channels are also in the mammalian CNS, but there is almost no data on their effects on neural function. Recent studies in this lab have disclosed evidence of electrical activity of these channels in rat hippocampus, and that they are exquisitely sensitive to antipsychotic drugs. Additionally, computer simulations show activity of this channel may modulate brain rhythms known to be important in epilepsy and schizophrenia. The project will involve further characterization of these channels in single neurons, as well as looking at how brain rhythms and epileptic activity in brain slices are affected by these channels, especially their modulation by antipsychotic drugs. Additionally, we will have the unique opportunity of studying these channels in human brain tissue obtained from neurosurgical procedures.

97. Modelling Epilepsy and Epilepsy Drug Effects–Computational Neuroscience Project

Supervisor: Dr Chris French
Project Site: Department of Medicine, MBC Neurosciences Building, Parkville
Contact: Dr Chris French T: 9035 6376 E: frenchc@unimelb.edu.au

Project Description: It is unclear how large scale electrical oscillations in the CNS are produced with epileptic seizures. Simple hyper-excitability of individual ion channel types and abnormalities of synaptic transmission are undoubtedly important. However, at the network level, recurrent excitation and inhibition from interneurons must be crucial, and may explain why some anti-epileptic drugs (AED’s) produce paradoxical exacerbation of seizures. This project involves modelling small networks (initially just 2 neurons) to examine the dynamics of seizure production, as well as how certain anti-epileptic drugs suppress or occasionally exacerbate network oscillations. This modelling involves incorporating novel experimental data from this laboratory on normal and drug affected ion channel mechanisms, as well as the effect of glial (supporting cells) cell interactions. The program “Neuron” will be mainly used for the simulations. Some programming experience is necessary, but the modelling language is relatively simple. This project provides an opportunity to gain an in-depth understanding of ion channel kinetics and non-linear behaviour of individual neurons and networks, with a strong clinical relevance.

98. Sodium Channels in Epilepsy - also offered as MBiomedSc

Supervisors: Dr Chris French, Prof Terence O’Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr Chris French T: 9035 6376 E: frenchc@unimelb.edu.au

Laboratory Overview. The O’Brien Laboratory in the Department of Medicine, University of Melbourne, has a wide range of research activities related to the neurological disorder epilepsy. Projects include molecular biological studies, in vivo and in vitro electrophysiology, advanced imaging techniques, animal behaviour models, pharmacogenomics as well as comprehensive clinical

Project Overview. The project will be to study voltage-gated sodium channels, membrane proteins that are the basis of almost all electrical signaling in the nervous system, and so of the greatest significance in normal function, as well as disease states including epilepsy. Properties of normal channels in rat brain cells and cloned channels in tissue culture will be studied, as well as the effects of common anti-epileptic drugs (AED’s). We are particularly interested in examining how minor genetic variations impact on AED action. Opportunities for mathematical modeling and computational simulations of nerve cell activity are also available.
The project thus offers a very wide range of possibilities for advanced skill acquisition, including molecular biological techniques, patch-clamping and computational neuroscience. Several publications are anticipated. Additionally, a very high priority is placed on basic research skill acquisition, including experimental design and analysis, statistical techniques, familiarity with common molecular biological methods, as well as public presentation of research findings.

99. **Long-term outcome of newly diagnosed epilepsy - also offered as MBiomedSc**
    
    **Supervisors:** Prof. Patrick Kwan
    
    **Projects site:** Department of Medicine (RMH), University of Melbourne
    
    **Contact:** Professor Patrick Kwan, E: patrick.kwan@unimelb.edu.au
    
    **Project description:** Seventy million people have epilepsy with 34–76 per 100,000 developing the condition every year. To formulate rational treatment plans, it is important to understand the different clinical courses and patterns of response to antiepileptic drugs, ideally by following outcomes from the point of treatment initiation.

    This project will perform analysis focusing on response to the initial therapies and their relationship with long-term treatment outcomes and development of pharmacoresistance in newly treated epilepsy patients. The student will be involved in recruiting and following up eligible patients. Basic knowledge and skills in biostatistics is preferred

100. **Does epilepsy cause a secondary cardiac channelopathy?**
    
    **Supervisors:** Dr. Kim Powell, Prof Terence O’Brien, Dr. Marian Todaro
    
    **Project Site:** The Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne.
    
    **Contact:** Dr KimPowell E: kpowell@unimelb.edu.au; Prof Terence O’Brien E: obrientj@unimelb.edu.au
    
    **Project description:** People with epilepsy are at a higher risk of death than the general population. People with epilepsy may die suddenly without an obvious pathologic cause for death. Such deaths are termed Sudden Unexpected Death in Epilepsy (SUDEP), and this is the major clinical problem facing epilepsy patients, accounting for 17-38% of all epilepsy related deaths. Basic research investigating the causal mechanisms underlying SUDEP is lacking. Alterations in function or expression of ion channels expressed in both cerebral and cardiac tissue represent strong candidate mechanisms for SUDEP - defects in membrane excitability could predispose an individual to a dual phenotype of epilepsy and cardiac arrhythmia. In both a genetic and an acquired animal model of epilepsy we have identified altered cardiac electrophysiological function with an associated down-regulation of the cardiac pacemaker HCN channel. Based on this data We have hypothesised that the development of epilepsy itself can result in secondary changes in cardiac ion channel expression and function that could contribute to an increased risk of cardiac arrhythmias and therefore SUDEP.

    **Aims:** To investigate whether patients with chronic epilepsy have alterations in cardiac electrophysiology and ion channel expression compared to matched non-epileptic control subjects.

    **Methods:** This will be investigated by examining cardiac tissue from patients with chronic epilepsy collected during open heart surgery at the Royal Melbourne Hospital and Melbourne Private. This tissue collected will be atrial muscle, which is routinely excised, and discarded as part of the routine cannulation of patients that are being placed on cardiopulmonary bypass for cardiac surgery. These patients would be identified by using a screening questionnaire given to all patients during the pre-admission clinic assessment. Identified patients will then be given a more detailed interview collecting data about their epilepsy syndrome, aetiology, duration, seizure frequency, and medication history. Control subjects will be patients without a history of epilepsy matched to the epilepsy patients for age, sex, cardiac disease status in a ratio of 1:3 (i.e. three controls for each patient with epilepsy). The mRNA and protein levels for the ion channels, HCN2 and 4 channels, which are expressed both in the heart and the brain will be measured, and compared between the epilepsy and control patients. The patients’ ECG recordings will also be compared for significant electrophysiological difference. Any significant molecular or electrophysiological changes identified will be correlated with the epilepsy syndrome (i.e. genetic vs. acquired), the duration of epilepsy and the seizure frequency. Parrellel studies are being undertaken in animal models of chronic epilepsy to enable the mechanisms causing the epilepsy-associated cardiac changes to be better elucidated.

    **Outcome:** This study has the potential to identify the mechanism responsible for epilepsy-associated cardiac dysfunction and thereby provide an opportunity to target interventions that can prevent the cardiac dysfunction, and mitigate the risk of SUDEP.

101. **Investigations into the role of neuropeptide Y in a genetic rat model of absence epilepsy - also offered as MBiomedSc**
    
    **Supervisor:** Prof Margaret Morris, Prof Terence O’Brien, Dr Kim Powell
    
    **Project Site:** Department of Medicine and Department of Pharmacology, University of New South Wales.
    
    **Contact:** Prof Terence J O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au
    
    **Professor Margaret Morris E: m.morris@unsw.edu.au**
**Project Description:** Absence epilepsy is one of the most common idiopathic generalised epilepsy syndromes. The underlying neurophysiological correlate of absence epilepsy is a pathological activation of rhythmic thalamocortical activity. However, the underlying aetiology for this disorder is still unknown.

There is increasing evidence that neuropeptide Y has a role in modulating seizures in acquired focal epilepsies, however there has been little investigation of its possible role in generalised epilepsy syndromes. This study will investigate the effect of intracerbral microinfusions of neuropeptide Y into selected intracerebral thalamocortical brain regions on the number and total duration of absence seizure in the Genetic Absence Epilepsy Rats of Strasbourg (GAERS) model. Absence seizures will be quantified on the basis of the SWDs recorded on EEG for 90 minutes following the infusion. The effect of infusion antagonists and agonists of various neuropeptide Y receptors will also be evaluated.

The second stage of the project will investigate the effect of enhancing NPY expression focally in selected thalamocortical using a recombinant adenovirus viral vector.

**Skills:** Small animal handling and neurosurgery (electrode implantations, microinjection catheter implantations), rat electroencephalography recordings, brain perfusion, fixation and histological preparation, immunohistochemistry.

### 102. Stargazin and AMPA receptor expression at cortical synapses in epileptic rats - also offered as MBiomedSc

**Supervisors:** Dr Kim Powell, Professor Terence O’Brien

**Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville

**Contacts:** Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au

**Project Description:** Absence seizures, one of the most common seizure types in humans with idiopathic generalised epilepsy (IGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Absence seizures most commonly affect children and adolescents who can experience hundreds of seizures per day and if left untreated can lead to disruptions in learning. Despite the important recent identification of genetic mutations in some rare families with IGEs showing a monogenic inheritance, in the common situation (>95% of sufferers) with complex inheritance patterns the genetic determinants of the absence seizures are still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and how they interact to result in epilepsy remains to be determined. GAERS are a strain of rats which spontaneously develop generalized absence seizures.

AMPA receptors are ionotropic transmembrane receptors for the excitatory neurotransmitter glutamate, which mediates fast synaptic transmission in the central nervous system. Stargazin is the archetypal member of a family of proteins called Transmembrane AMPA Receptor regulatory Proteins (TARPs), and is critical for the trafficking and anchoring of AMPA receptors to synaptic membranes. Stargazin also influences electrophysiological properties of AMPA receptors including the slowing of deactivation and reducing desensitization rates. This newly identified TARP role for stargazin may have major functional implications on the homeostatic balance of neuronal excitation, and potentially for the pathophysiology of epilepsy. Recent work from our lab has shown increased expression of stargazin at neuronal membranes in the somatosensory cortex of epileptic GAERS animals, a brain region thought to be involved in the generation of absence seizures. These animals also show increased membrane AMPA receptor expression, which may be driven by elevated stargazin levels. Stargazin is known to interact with other synaptic proteins to localise AMPA receptors to the postsynaptic density (PSD), the region of the postsynapse opposite sites of neurotransmitter release.

The specific aims of this project are

- To biochemically isolate the PSD from the somatosensory cortex of epileptic GAERS and non-epileptic control (NEC) rats
- To compare PSD localization of stargazin, AMPA receptor subunits and other synaptic proteins in GAERS and NECs
- To correlate membrane and synaptic expression of stargazin and AMPA receptors with seizure parameters

**Skills:** The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), EEG recordings and analysis, and biochemical and molecular analysis (subcellular fractionation, western blotting)

### 103. Investigating the role of a Cav3.2 calcium channel mutation in contributing to the epileptic phenotype using congenic rat strains and a knock in mouse model - also offered as MBiomedSc

**Supervisors:** Dr Kim Powell, Professor Terry O’Brien

**Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville

**Contact:** Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au; Prof. Terry O’Brien E: obrientj@unimelb.edu.au
Project Overview: Absence seizures, one of the most common seizure types in humans with genetic generalised epilepsy (GGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Absence seizures most commonly affect children and adolescents who can experience hundreds of seizures per day and if left untreated can lead to disruptions in learning. Despite the important recent identification of genetic mutations in some rare families with IGEs showing a monogenic inheritance, in the common situation (>95% of sufferers) with complex inheritance patterns, the genetic determinants of the absence seizures is still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and the mechanisms by which they act to result in epilepsy remains to be determined. In an important, well characterised model of GGE with absence seizures, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), our research group has discovered a homozygous, missense, single nucleotide (G to C) mutation in the Ca,3.2 T-type calcium (Ca2+) channel gene (Cacna1h) resulting in an amino acid from arginine to proline (R1584P). The R1584P mutation correlates with the epileptic phenotype in GAERS doubled crossed with Non-Epileptic Control (NEC) rats. Additionally, the R1584P mutation increases the rate of recovery from channel inactivation in a splice variant specific manner, producing a predicted gain-of-function phenotype.

We have a knock-in mouse model of the R1584P Ca,3.2 mutation as well as two congenic rat strains; a NEC strain expressing the R1584P mutation and a GAERS congenic rat strain without the R1584P mutation which we will use as tools to investigate the neurobiological mechanisms by which the R1584P mutation results in is pro-absence effects. These experiments will explore further the specific role played by the R1584P mutation in the absence phenotype of GAERS and the effect of genetic background.

Project 1: To examine the expression of spike-wave-discharges (SWD) in two different congenic rat strains, an NEC congenic strain expressing the R1584P mutation and a GAERS congenic rat strain without the R1584P mutation.

Project 2: To characterise the epileptic phenotype of a knock-in mouse expressing the R1584P mutation and to investigate the effect of genetic background.

Skills: The skills expected to be learnt from this project include: Small animal handling and surgery, EEG recording and analysis.

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104. Investigating molecular and physiological determinants of Sudden Unexplained Death in Epilepsy in acquired and genetic animal models of epilepsy - also offered as MBiomedSc

Supervisors: Dr Kim Powell, Professor Terry O’Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au;

Project Description: Epilepsy is associated with an increased risk of sudden unexplained death (SUDEP), possibly due to cardiac arrhythmias, although the precise mechanism remains unknown. SUDEP is considered the most important direct epilepsy-related mode of death and accounts for up to 30% of all deaths in the epilepsy population, being particularly prevalent amongst young patients with uncontrolled or drug-resistant, frequent and severe generalized tonic-clonic seizures.

Ion channels that coexist in the brain and heart would make ideal candidates for SUDEP because defects in intrinsic membrane excitability could predispose an individual to a dual phenotype of epilepsy and cardiac arrhythmias culminating in sudden death. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and T-type calcium channels play an important role in the generation of pacemaker activity in the brain and heart. Furthermore, its functional role becomes more marked in the process of pathological cardiac hypertrophy and heart failure. Thus HCN and T-type calcium channels are attractive candidates for investigating molecular mechanisms of SUDEP. Our research has identified a cardiac transcriptional channelopathy of HCN2 and Ca,3.1 and Ca,3.2 T-type calcium channels, with associated detrimental cardiac electrophysiological changes, in rat models of both genetic generalised epilepsy (GAERS) and acquired temporal lobe epilepsy (kainic acid (KA) induced post-status epilepticus (SE)).

Several projects will be offered to investigate different aspect of SUDEP and cardiac dysfunction in animal models of genetic and acquired epilepsy

Project 1: To investigate the molecular mechanisms contributing to the cardiac dysfunction on genetic and acquired animal models of epilepsy.

Project 2: To investigate if decreased HCN2 expression translates to a decrease in HCN channel current (Ih) in cardiomyocytes in animal models of genetic and acquired epilepsy.

Project 3: To investigate if by pharmacologically suppressing seizures we can alleviate the altered cardiac electrophysiological function and HCN2 and T-type calcium channel transcriptional repression.
**Skills:** The skills expected to be learnt from this project include: Small animal handling and surgery, Drug testing in animal models of epilepsy, electrophysiology recordings and analysis, biochemical and molecular analysis (real time PCR, western blotting).

### 105. Serotonin in epilepsy

**Supervisor:** A/Prof. Nigel Jones ncjones@unimelb.edu.au  
**Project Site:** Department of Medicine RMH, MBC Neurosciences Building Parkville  
**Contact:** A/Prof Nigel Jones E: ncjones@unimelb.edu.au

**Project description:** Any type of brain injury can result in epilepsy, a chronic neurological condition associated with seizures or 'fits'. The pathological processes occurring in the brain which drive the development of epilepsy following brain injury are not clear, but certain drugs acting at serotonin receptors, including SSRI antidepressants, accelerate these processes. Using animal models, this project will investigate serotonin signalling in epilepsy, and attempt to understand why SSRIs accelerate the development of disease following injury. We will utilise a variety of techniques, including assessment of serotonin levels, molecular consequences of serotonin activity, immunocytochemical identification of serotonin receptors, and pharmacological manipulation of the serotonin system, all in the context of epilepsy. Available as Honours, Masters or PhD projects.

**Skills:** Small animal handling; animal models of epilepsy; small animal surgery and EEG recording; pharmacology; microdialysis; fast-scan cyclic voltammetry; molecular biology techniques, such as real-time qPCR, Western blotting; histology, including immunocytochemistry.

### THE IOIN CHANNELS AND DISEASE LABORATORY

Our laboratory is located on the first floor in the Melbourne Brain Centre, Kenneth Myer Building, and is fully equipped with state-of-the art neurophysiological and imaging capabilities. We are a 20 person multidisciplinary team working on individual and joint projects in the neurosciences. Our primary interest is in diseases and therapies that involve ion channels with a particular focus on epilepsy. In epilepsy our work begins with clinical and genetics collaborators who identify gene mutations. Many of these are in ion channels and we seek to understand how these mutated genes lead to behavioural seizures. We use a range of methods, appropriate to the scale of investigation and combine, genetic, molecular, biophysical, computational, neurophysiological and behavioural approaches. In addition, our laboratory houses the Australian Optogenetics Repository and we are well positioned to exploit this exciting new method. The projects below give a sample of the work being undertaken and available for suitable candidates.

### 106. Projects in network analysis of genetic epilepsy

**Supervisors:** A/Professor Steve Petrou & A/Professor Chris Reid  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au;  
Chris Reid E: careid@unimelb.edu.au

**Project description:** Epilepsy impacts around 3% of the population and in many cases has clear genetic underpinnings. Our laboratory has created several genetically engineered models of epilepsy that have helped provide the most detailed understanding of how a single gene mutation can lead to behavioural seizures. Perhaps the largest gap in our understanding lies at the level of the network that bridges cellular and synaptic function with the actual seizure phenotype itself.

### 107. Multi-site patch clamp recording of cortical micro networks

**Supervisors:** A/Professor Steve Petrou & A/Professor Chris Reid  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au;  
Chris Reid E: careid@unimelb.edu.au

**Project description:** In this project the candidate will be trained in the use of an emerging method in brain slice electrophysiology that allows for the simultaneous intracellular recording of 4 connected neurons. Using this recording mode it is possible to examine how neurons function in coupled micro networks in epileptic and normal brains to lead to a deeper understanding of the functional basis of epilepsy. If the candidate makes sufficient progress and is motivated this project may also expand into network analysis using multiphoton imaging where 50 or more neurons in a living brain can be labelled with a Ca**2+ indicator dye and imaged in real time.
108. **High density multi-electrode array recording of in vitro networks in epilepsy**

**Supervisors:** A/Professor Steve Petrou, A/Professor Chris Reid  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au; Chris Reid E: careid@unimelb.edu.au

**Project description:** In this project the candidate will use high density extracellular multielectrode array recordings to investigate large scale network function. This a level of organization beyond that studied in Project 1 and will reveal fundamental properties of how the hippocampal and thalamocortical networks are altered in genetic models of epilepsy. The goal of these studies is to not only understand more about the neurobiology of epilepsy but also to create novel disease state models for creating anti-epileptic drugs. The method will involve cutting fresh brain slices and using 60 site multi-electrode arrays that enable electrical stimulation and recording from all sites simultaneously. Slices will be subject to various stimulation and pharmacological protocols to reveal aspects about excitability, synaptic transmission and plasticity.

109. **In vivo electrophysiological analysis in mouse models of genetic epilepsy**

**Supervisors:** A/Professor Steve Petrou  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg.  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au;

**Project description:** In this project the candidate will use multi-site in vivo unit recording in mouse models of genetic epilepsy to investigate network function and dysfunction in freely moving mice. Using digital high density electrode recording the candidate will implant multiple sites and then record from mice housed in a controlled environment with video monitoring. One possible addition to these experiments is the incorporation of optogenetic stimulation whilst recording to probe network function in connected networks of behaving mice. This will provide some of the first views into how real time intervention of networks modulates seizure initiation and termination.

110. **“CLARITY” based glass brain imaging in health and disease**

**Supervisors:** A/Professor Steve Petrou, Dr Verena Wimmer, Dr Kay Richards  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au; Kay Richards E: kay.richards@florey.edu.au

**Project description:** Recent improvements in the histochemical method of optically clearing whole tissues and the joint development of special optics that can image deep into them have created unprecedented views into the wiring of networks. Changes in wiring of cortical neurons have been implicated in a number of disorders such as epilepsy, schizophrenia and depression. In this project the candidate will prepare brains from mice with fluorescently labelled neurons and use 2-photon excitation or custom light sheet based microscopy to create 3D images in regions of the mouse cortex. By comparing normal and epilepsy models this work will begin to unravel the changes that occur prior to and after the occurrence of seizures. This will shed important light on the scale on which structural changes occur in epilepsy and will guide future experimental and clinical work.

111. **MRI tractography in mouse models of genetic epilepsy: Creation of prognostic and diagnostic structural biomarkers**

**Supervisors:** Dr Kay Richards, A/Professor Chris Reid, Professor Alan Connelly, A/Professor Fernando Calamente, A/Professor Steve Petrou,  
**Project Site:** Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
**Contact:** Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au; Kay Richards E: kay.richards@florey.edu.au

**Project Description:** Our earlier classical histological analyses have shown that neuronal numbers and positioning are both altered in genetic forms of epilepsy prior to the appearance of overt seizures suggesting that structural changes precede epilepsy. These changes, however, would be below the level of detection of current clinical MRI scanning technology and have led to the potentially erroneous conclusion that idiopathic generalised epilepsy (IGE) is characterised by a complete absence of structural change. By combining recent developments in super resolution MRI (developed by members of the supervisory team) and high field MRI acquisition (16.4T) the candidate will seek to reveal structural changes, or biomarkers, that precede or are a consequence of epilepsy. Because these approaches are directly translatable into the clinic any finding could be rapidly tested in patients. The candidate will develop skills in preparing fixed mouse brains for MRI scanning at 16.4T at the Queensland Brain Institute for analysis using the MRtrix suite of software on a custom workstation to compare brains from control and genetic mouse models.
112. High content automated analysis of ion channels in epilepsy  
Supervisors: Dr Carol Milligan & A/Professor Steve Petrou  
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
Contact: Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au;  
Carole Milligan E: carol.milligan@florey.edu.au  
Project Description: Discovery of gene mutations in neurological disorders such as epilepsy is outstripping the ability to functionally validate them. Because many epilepsy genes code for ion channels we have established high content automated patch clamp platforms based on the Nanion Patchliner 16 and the Fluxion HT 64 systems to bridge the “discovery” gap between genetics and functional validation. Several new mutations have been found by our geneticist collaborators that are awaiting detailed functional analysis and the candidate will first have to produce mutant cDNAs then transiently transfected into HEK293 or CHO cells prior to analysis on the automated platforms. Candidates will be trained in the necessary molecular biological methods and then in ion channel electrophysiology and will work closely with a senior member of the team to ensure success.

113. Optogenetic modulation of the area tempestas – an epilepsy hot spot  
Supervisors: Kay Richards, A/Professor Steve Petrou, A/Professor Chris Reid  
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
Contact: Steven Petrou T: 9035 3628 E: spetrou@unimelb.edu.au;  
Kay Richard E: kay.richards@florey.edu.au  
Project description: Several lines of study have recently converged to reveal a new target for controlling epileptic seizures. Early work by Piredda and Gale (Nature 1985, 317:623) provided unequivocal evidence that the prepiriform cortex, subsequently coined the “area tempestas”, was a hot spot for initiation and spread of epileptic seizures. Within this region a population of specialised inhibitory neurons called neurogliaform cells (NG) shows a stereotypic pattern of firing that implicates them seizures. In this project the candidate will use in vivo electrophysiological recording and optogenetic stimulation to examine real time modulation of the control of seizures to develop a role for the in vivo function of NG cells and explore their potential utility in seizure suppression.

114. Zinc and seizures  
Supervisors: A/Prof Chris Reid, A/Professor Steve Petrou, Dr Paul Adlard  
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
Contact: Chris Reid E: christopher.reid@florey.edu.au / careid@unimelb.edu.au  
Project description: Zn$^{2+}$ is an essential element having a multitude of biological functions throughout the body. Febrile seizures are common affecting approximately 3% of children. There is good evidence that febrile seizures can trigger a cascade of events that lead to more severe forms of epilepsy later in life. Clinically, several studies have suggested that Zn$^{2+}$ levels are significantly lower in blood and CSF of children that suffer febrile seizures but these studies are not conclusive. In this project we will directly test the hypothesis that low brain Zn$^{2+}$ may be one environmental factor in increasing the chance of having a febrile seizure. In this project the student will learn a range of experimental techniques aimed at understanding the role Zn$^{2+}$ plays in changing neuronal excitability. The results have clear clinical implications and could be particularly important in for developing countries, where epilepsy rates are high and nutritional supplementation is a potential practical therapy.

115. Will HCN channel antagonists be good antiepileptic drugs?  
Supervisors: A/Prof Chris Reid, A/Professor Steve Petrou  
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg  
Contact: Chris Reid E: careid@unimelb.edu.au  
Project description: Our laboratory has discovered that some antiepileptic drugs act on certain HCN channel subtypes. We now need to address whether this mechanism is part of the anti-seizure effect of these drugs. In this project we will use a combination of selective HCN subtype-selective channels in a variety of seizure models to establish this. We will also extend the project to look specifically at mechanisms using electrophysiological methods that directly measure neuron excitability. Establishing if these channels are good targets will motivate drug discovery programs. These channels are also thought to be important to the generation of pain and may be useful in this condition as well.

116. Inhibitory neuron subtypes in cortical circuits: an examination of their structure, function, and connectivity  
Supervisors: Verena C Wimmer, Kay Richards, Steven Petrou, Ion Channels and Disease Group, Florey Neuroscience Institutes, The University of Melbourne, Parkville, 3010.  
Project Site: Florey Neuroscience Institutes, The University of Melbourne, Parkville.  
Contact: Verena Wimmer E: vwimmer@florey.edu.au
Project 1: In the brain there are numerous subtypes of inhibitory neurons with specific functions and connectivity. While some of these subtypes are well understood the role of others remains enigmatic, for example VIP (vasoactive intestinal polypeptide) expressing GABAergic neurons. Using a mouse model expressing a fluorescent protein in VIP-positive neurons and quantitative anatomy approaches we will study the distribution of VIP-cells throughout the brain, their morphology and examine the ion channel composition that governs the function of those cells. We aim to develop a better understanding of the neuronal circuits VIP neurons are involved in and generate a testable model of input integration. Methods include immunohistochemistry, state-of-the-art confocal microscopy, mosaic imaging and automated analysis of large data sets.

Project 2: Historically, some epilepsy syndromes have been defined as ‘idiopathic’ or ‘of unknown origin’, because the anatomy of the brain seems normal. Our group has recently shown that genetic ‘idiopathic’ epilepsy mutations impact the formation of neuronal networks during embryonic development and lead to microscopic changes in the wiring of the cortex, specifically affecting inhibitory neurons. This project looks at the exact changes in synaptic connectivity and aims to quantify the synaptic contacts made between parvalbumin-positive inhibitory neurons and excitatory neurons across the cortical layers in normal and epileptic mice. These results will greatly aid our understanding of how epileptic seizures develop and reveal novel mechanisms by which genetic mutations lead to long term changes in the brain of epilepsy patients. Methods include immunohistochemistry, state-of-the-art high resolution confocal microscopy and super-resolution techniques as well as deconvolution and automated analysis of large data sets.

GASTROENTEROLOGY

117. Barrett’s Oesophagus – also offered as MBiomedSc
   Supervisor:  Professor Finlay Macrae and Dr Andrew Metz
   Project Site:  The Royal Melbourne Hospital
   Contact:  E: Finlay.macrae@mh.org.au

   Project description: Barrett’s oesophagus is a premalignant condition which is challenging to manage. Detection of dysplasia is difficult but new advanced imaging modalities are assisting, and new treatments such as radio frequency ablation are allowing the condition to be treated without surgical resection. This project will evaluate new imaging and treatment modalities. It will involve close engagement with the Barrett’s clinical service.

GENOMICS

118. GAERS versus NEC: Genetics of epileptic and non-epileptic rat strains– also offered as MBiomedSc
   Supervisor:  Dr. Slave Petrovski and Prof. Terence J. O’Brien
   Project Site:  Department of Medicine RMH, Kenneth Myer Bldg
   Contact:  Slave Petrovski E: slavep@unimelb.edu.au

   Project description: Whole genome sequence data is available for the GAERS epilepsy rat and its sibling strain the NEC non-epileptic rat. Moreover, whole-genome sequencing is available for four F2 pups born from breeding GAERS and NEC strains. This project will explore the whole genomes of these strains to identify potential genetic aberration markers of epilepsy. This project will require interest in genetics, bioinformatics and big data.

119. When synonymous mutations aren’t silent – also offered as MBiomedSc
   Supervisor:  Dr. Slave Petrovski
   Project Site:  Department of Medicine RMH, Kenneth Myer Bldg
   Contact:  Slave Petrovski E: slavep@unimelb.edu.au

   Project description: Synonymous mutations are generally dismissed as neutral ‘background’ mutations. Yet, there are many examples of cryptic splice synonymous mutations that cause severe genetic disorders. This project will compare catalogs of synonymous mutations ascertained from patients with epilepsy, autism, schizophrenia and severe ID and compare them to catalogs of mutations from healthy controls of convenience. The aim will be to use in silico tools to pinpoint potentially pathogenic cryptic splice variants followed by functional splicing assessment.

120. Neurocognitive complaints and epilepsy prognosis – also offered as MBiomedSc
   Supervisor:  Dr. Slave Petrovski and Prof. Terence J. O’Brien
   Project Site:  Department of Medicine RMH, Kenneth Myer Bldg
   Contact:  Slave Petrovski E: slavep@unimelb.edu.au
**Project description:** It has been previously reported that patients with pre-treatment neuropsychiatric symptomatology are less likely to respond efficaciously to anti-epileptic drug (AED) therapy. Given what we already know about the potential for neurocognitive side-effects induced by AEDs, this study extends the original observation to investigate whether patient-reported neurocognitive adverse drug reactions (ADRs) within the first three months of therapy along with pre-treatment neuropsychiatric symptomatology could together provide a more sensitive and specific prediction of pharmacoresponse in this population of newly-treated patients.

**121. Genomics of adverse response to antiepileptic drugs - also offered as MBiomedSc**
**Supervisors:** Prof. Patrick Kwan
**Projects site:** Department of Medicine (RMH), University of Melbourne
**Contact:** Professor Patrick Kwan, E: patrick.kwan@unimelb.edu.au

**Project description:** Although highly efficacious, antiepileptic drugs (AEDs) are associated with a range of side effects. This project will focus on two types of side effects: skin reactions and psychosis, which are severe and largely unpredictable by clinical risk factors but likely to have a strong genetic basis. Identifying the genetic markers will help patient selection and inform future drug development.

Severe cutaneous adverse drug reactions (cADRs), such as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are among the most feared adverse effects of antiepileptic drugs (AEDs) not only because of their high mortality and morbidity, but also because of their unpredictability. Dissecting the genetic basis for these ADRs will have major impact on “personalised” drug selection, and the insights gained on the chemico-biological pathways will help future design of safer medications.

This project represents an exceptional opportunity to effectively and efficiently discover these variants in a unique subject cohort (drug-exposed cases and controls) using the latest genotyping and sequencing platforms. More than one student will be needed for various aspects, including patient recruitment and phenotyping. In addition, there will be opportunity for the student to be part of the data analysis team, thus basic knowledge in bioinformatics and genetic statistics is essential.

**IMAGING**

**122. Neuroimaging**
**Supervisors:** Dr Chris Steward, Professor Patricia Desmond, Dr Brad Moffat
**Project Site:** The Brain Imaging Laboratory, Department of Radiology, Level 2, 1B building, Royal Melbourne Hospital.
**Contact:** Dr Chris Steward T: 9342 8337 E: csteward@unimelb.edu.au

**Project Description:** There is presently a paradigm shift in the way in which patients with neurological diseases (such as Brain Tumours, Stroke and Epilepsy and Dementia) are treated. Old methods are being replaced by individualised patient management protocols using spatially, molecularly and genetically targeted therapies. Similarly, there is also currently a paradigm shift occurring in the field of Neuroimaging. Imaging (MI) Biomarkers are being developed to image biological, molecular and functional targets of interest to neuroscientists and clinicians. With this in mind The Brain Imaging Laboratory is currently works closely with clinicians to better understand and predict patient disease and response to treatment. Imaging techniques being studied are: Structural imaging, Functional Diffusion Mapping, Diffusion Tensor Imaging, Magnetic Resonance Spectroscopy and Perfusion MRI, functional MRI. The following are a subset of possible projects:

**Project 1:** Diffusion tensor MRI techniques for clinical assessment of white matter integrity in mild cognitive impairment and healthy aging.

**Project 2:** MRI in healthy aging (also available as MBiomedSc)

**123. Network Activity in Brain Tissue Recorded with Combined Calcium and Voltage-Sensitive Dye Imaging and Electrophysiology - also offered as MBiomedSc**
**Supervisor:** Dr Chris French
**Project Collaborators – Prof T O’Brien, Prof D Williams**
**Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital
**Contact:** Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
**Website:** [http://sites.google.com/a/hfbg1.net/crf_lab/](http://sites.google.com/a/hfbg1.net/crf_lab/)

**Project Description:** Understanding the normal function as well as pathophysiological states of neural systems requires sampling information from many points in the network simultaneously. One way to do this is using optical methods that allow the activity of many neurons to be imaged simultaneously. Calcium-sensitive fluorescent dyes can be loaded into
neurons, so that the “firing” of neurons can be observed as a change in fluorescence in real time across many neurons. Voltage-sensitive dyes have the advantage of better time resolution, but the signal obtained is much smaller than calcium indicators. This project involves imaging groups of neurons in rat hippocampal brain slice in normal and epileptic states, with concomitant electrophysiological recording to better understand epileptogenesis in this structure. Additionally, the effects of anti-epileptic drugs will be examined at the network level using these techniques. In particular, we will be looking for key parameters that permit the stable network to enter oscillatory modes. Confocal and multi-photon imaging will be used for imaging the neurons loaded with dyes, combined with patch-clamp recording.

INFECTION DISEASES AND IMMIGRANT HEALTH

124. Monitoring the efficacy of a training program in gastroenterology in the Pacific - also offered as MBiomedSc
Supervisors: Professor Finlay Macrae
Project Site: Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital
Contact: Professor Finlay Macrae  T: +61 3 9347 0788  E: finlay.macrae@mh.org.au

Project Description: Diseases in the GI tract are common in the South Pacific. GI Endoscopy access is limited, and training even less available. In association with the World Gastroenterology Organization, we have recently introduced a training program in gastroenterology to support postgraduate training in gastroenterology at the Fiji School of Medicine, with expertise provided from Australia. The project is designed to monitor the effects of this across the South Pacific, through documentation of higher levels of service delivery in the region, epidemiology of disease detection (eg helicobacter pylori) and skills’ acquisition by graduates of the program that can be applied in remote communities in the South Pacific with high GI disease burdens.

The applicant would be required to visit South Pacific regions to assess qualitatively and quantitavely, disease burdens and the provision of services to address these needs, with a view to reports for Faculty, the Gastroenterological Society of Australia, the World Gastroenterology Organization and the Australian Government (AusAid).

INJECTING DRUG USE

125. Investigating blood/blood product donation practices among Australian people who inject drugs (PWID)
Supervisors: Professor Margaret Hellard, Dr Brendan Quinn
Project Site: Burnet Institute
Contact: E: brendanq@burnet.edu.au

Project description: In Australia, potential blood donors are ‘deferred’ permanently if they report a history of injecting drug use (IDU). This is due to IDU being a key transmission route of various transfusion-transmissible infections, particularly hepatitis C. A recent review of the appropriateness of this policy was conducted by the Burnet Institute in collaboration with the Australian Red Cross Blood Service. One key finding was that more research needs to be conducted to address various knowledge gaps – including on the prevalence of blood donation practices among PWID – before any changes can be made to the current IDU-related blood donation criteria. The Burnet Institute is collecting such data from PWID in Victoria and across Australia throughout 2015. This project is the first of its kind in Australia. Findings will be vital for informing any potential changes to the Blood Service’s IDU-related guidelines. The study will also inform targeted education of PWID about blood donation.

This project will involve analysis of quantitative data collected during 2015 from the Illicit Drug Reporting System (IDRS), an annual, national cross-sectional survey of PWID in Australia, in addition to data from the Melbourne Injecting Cohort Study (MIIX), a prospective cohort study running since 2008 with over 700 PWID as participants. Findings will provide an indication of the prevalence of lifetime blood donation practices among Australian PWID and the characteristics of those who report doing so.

126. Exploring the similarities and differences of hepatitis C treatment and opiate substitution treatment therapy in people who inject drugs to inform increasing access HCV treatment in this population
Supervisors: Prof Margaret Hellard, Dr Peter Higgs
Project Site: Burnet Institute
Contact: E: peterh@burnet.edu.au
Project description: Pharmacotherapy, when used with regard to substance dependence refers to the replacement of a person’s drug of choice with a legally prescribed and dispensed substitute. Known as opioid substitution therapy (OST) in Victoria over 14,000 people are currently being dosed daily with methadone or suboxone for their heroin dependency.

Currently few PWID receive treatment but the advent of new direct-acting antiviral (DAA) treatment provides opportunity for increased uptake of therapy which will have the dual benefit of curing the PWID’s HCV and also potentially reducing HCV transmission (through treatment as prevention (TasP)) leading to HCV elimination in Australia.

Working with participants from the Treatment and Prevention (TAP) Study, a world first study of community based treatment for PWID and HCV elimination, this honours project will explore the PWIDs attitudes and understandings of the new DAA HCV treatment, the best mechanism to provide DAA to the – separate to or with OST. The overall aim is to identify mechanism to increase PWIDs access to DAs and compliance with DAA treatment so as to inform HCV elimination in Australia and globally.

The study will use qualitative methods including in-depth semi-structured interviews to achieve the research aims. An interview guide will be developed to map broad areas of investigation and to lead the semi-structured interview process, which will be inductive to allow for the generation of new ideas and knowledge that may otherwise remain uncovered.

127. The outcomes of transitioning between prison and community for people with a history of injecting drug use
Supervisors: Prof Paul Dietze, A Prof Mark Stoove
Project Site: Burnet Institute
Contact: E: pauld@burnet.edu.au

Project description: Injecting drug use contributes disproportionately to the health and social burden of illicit drug use in Australia. Sustained patterns of problematic injecting drug use are influenced by a complex interaction of social, health, structural, and policy factors, including the ongoing criminalisation of drug use and the routine incarceration of people for drug-related crime.

People who inject drugs (PWID) are vastly over-represented in the prison and broader criminal justice system. Transition out of prison represents a particularly vulnerable period for PWID that is characterised by challenges associated with social reintegration, housing, employment, accessing health and other support services, and relationships with significant others. Return to dependent patterns of drug use following prison release is also common, resulting in very high rates or mortality, morbidity, recidivism and re-incarceration in this population.

Burnet Institute is undertaking Australia’s first prison-to-community prospective cohort study of people with injecting drug histories. This study provides an opportunity for analysis pre- and post-release data collected from 500 participants in the weeks preceding prison release and in the first three months following their release. A range of post-release outcomes are available for investigation, including but not restricted to patterns of drug use, engagement and retention in treatment and health care, overdose, housing stability and blood borne virus risk. Univariate descriptive and prospective analyses examining the pre- and post-release predictors of outcomes will be undertaken to help inform policy and practice in the Justice and Health arenas.

128. The persistence of risk among people who inject drugs - also offered as MBiomedSc
Supervisor: Professor Paul Dietze, Co-Head , Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute
Project Site: Burnet Institute
Email: Paul Dietze E: pauld@burnet.edu.au

Project Description: The prevalence of risk behaviours such as sharing of injecting equipment among people who inject drugs (PWID) has been well described in the Australian context. However, little is known about transitions in risk behaviours among PWID over time and whether Australian PWID moderate their behaviours in response to their changing circumstances. In this study data from the Melbourne Injecting Drug User Cohort Study (MIX) will be examined to determine the extent to which risk behaviours change over time in the cohort and what impact any changes have on key health outcomes such as blood borne virus transmission.

129. Mapping public injecting drug use in urban Melbourne - also offered as MBiomedSc
Supervisor/s: Paul Dietze, Rebecca Winter, Peter Higgs
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Paul Dietze E: pauld@burnet.edu.au; Peter Higgs E: peterh@burnet.edu.au
Project Description: The risks associated with injecting drug use are determined by interactions between individual injecting behaviours and the ‘environment’ (e.g., physical, social, legislative) in which injecting occurs. Using a mixed methods approach, this project will undertake ethnographic mapping and quantitative secondary data analysis to document aspects of public injecting drug use in inner urban Melbourne. The ethnographic mapping exercise will involve neighbourhood-level observational research to examine sites of public injecting, levels of public injecting and document associated injecting practices and potential risks. Additional secondary data analysis will be undertaken to examine indicators of the impacts of public injecting, such as fatal and non-fatal overdose and impacts on public amenity.

130. Understanding and reducing the barriers to community based point of care hepatitis C testing in people who inject drugs

Supervisor/s: Margaret Hellard
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Margaret Hellard, Hellard@burnet.edu.au, T: +61 3 9282 2163

Project description: Hepatitis C infection predominately infects people who inject drugs with around 50% becoming infected within five years.

Surprisingly, despite this high risk of infections, there are no Australian guidelines on how frequently PWID should be tested. Also there are many barriers to PWID being tested for HCV including limited engagement with health services due to stigma and discrimination and the lack of a licensed rapid point of care HCV test in Australia despite them being available elsewhere in the world.

This means that many people infected with hepatitis C may have their diagnosis delayed. If someone is not aware of their infection they are a) at greater risk of accidently transmitting the infection to other and b) delaying their presentation for hepatitis C care and treatment.

This project will identify the best rapid-point of care HCV tests available and licensed world-wide. It will also examine PWIDs attitudes to rapid point of care tests administered in the community by peers or outreach workers or that are self-administered test.

This will be a qualitative research study where the student will conduct an estimated 20 to 30 interviews with PWID about their attitudes and understandings of HCV point of care tests. As well they will interview key informants from key community based organisations - Harm Reduction Victoria and Hepatitis Victoria.

The student will also review the gray and standard literature to identify jurisdictions that have implemented community based point of care testing for HCV. They will also examine the legislative barriers to making these tests available in Australia.

INNATE IMMUNITY AND HOST DEFENCE

131. Immune Cell Signalling Regulation During Inflammation

Supervisors: Dr Paul Licciardi and Dr Rodney Luwor
Location: Murdoch Childrens’ Research Institute, The Royal Children's Hospital and Dept of Surgery, RMH, Level 5, Clinical Sciences Building, Royal Melbourne Hospital
Contact: Dr Paul Licciardi; T: 9345-5554, E: paul.licciardi@mcri.edu.au or Dr Rodney Luwor; T: 8344 3027, E: rluwor@unimelb.edu.au

Project Description: Infections with Streptococcus pneumoniae (pneumococcus) are a major cause of morbidity and mortality in children <5 years of age globally with ~1.5 million deaths per year due to invasive pneumococcal diseases (IPD) such as pneumonia, meningitis and sepsis. There has been recent interest in understanding the host response to pneumococcal infection, particularly on innate immunity and inflammation. Following infection, recognition of S. pneumoniae (and their bacterial components) occurs by pattern recognition receptors such as Toll-like receptors (TLRs-2,4) on monocytes and neutrophils as well as on airway epithelial cells. Activation of TLRs lead to inflammation characterised by cytokine and chemokine secretion (e.g. TNF-α, IL-1β, IL-6, IL-8) which further recruit innate immune cells mainly under the control of NFκB. In addition, large multi-protein complexes known as inflammasomes regulate caspase-1-mediated IL-1β and IL-18 release and are critical in this response. Recent studies have shown that the NLRP3/NALP3 inflammasome is integral in the host inflammatory response to pneumococcal infection but can also contribute to the associated pathology. Therefore, novel anti-inflammatory therapies that target the inflammasome would be effective in limiting the pathological consequences of pneumococcal infections. Dietary short-chain fatty acids (SCFAs) such as
butyrate are widely recognised to possess potent anti-inflammatory effects. SCFAs are also produced by probiotic bacteria, and represent a possible mechanism by which they exert their reported beneficial effects on inflammation, immune modulation and pathogen colonisation. This study aims to assess the biological role of butyrate on NFKB- and inflammasome-driven responses using a bacterial infection model recently developed in the laboratory.

Skills/Techniques acquired: Cell biology techniques including Cell transfections, western blotting, luciferase reporter assays, RT-PCR and potentially animal handling and injecting.

**INNATE PHAGOCYTOSIS & NEURODEGENERATION**

132. Leukocyte surface and functional biomarkers for prognosis of age-related macular degeneration  
Supervisors: Dr. Ben J. Gu, Prof. Robyn Guymer, Prof. Erica Fletcher, Prof. James S. Wiley  
Project Site: Florey Institute, Kenneth-Myer Building  
Contact: E: ben.gu@florey.edu.au Ph: 03 9035 6317  
Project description: Age-related macular degeneration (AMD) is a multifactorial disease and is a leading cause of irreversible vision loss in Australia. AMD at its early stage is characterized by accumulation of debris (lipid rich drusen) in retina, which is believed due to reduced clearance capacity. While AMD can be easily diagnosed with high resolution retina imaging, early prognosis biomarkers are needed to identify people with high risk for preventive treatment. Our previous study has shown that genetic variants leading to defective phagocytosis are risk factors for AMD. In this study, we will measure the phagocytosis ability of monocytes and monocyte subsets from AMD patients as well as age-matched healthy controls, using a real-time tri-colour flow cytometry method developed by our group. Meanwhile, the monocyte surface expression of scavenger receptors, e.g. P2X7, TREM-2, SCARA1 and CD36, will be examined. Cell surface biomarkers will be examined on peripheral blood leukocytes from patients and healthy controls. The sensitivity and specificity of promising parameters will be analysed and validated in a follow-up study. This study will not only identify a useful pattern for early prognosis of AMD, but also provide insights on the pathogenesis and development of this disease.

133. Identification of serum glycoproteins inhibiting innate immunity - also offered as MBiomedSc  
Supervisors: Dr Ben Gu, Professor James Wiley  
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building, Parkville  
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au James Wiley E: james.wiley@florey.edu.au  
Project description: Innate immunity is the first line defense of host against invading pathogens. Phagocytosis of non-opsonized particles (bacteria or viruses not coated by immunoglobulin, complement, etc) is an important part of innate immunity. Our recent findings show that innate phagocytosis is completely abolished by a group of serum glycoproteins, i.e. serum inhibits innate immunity. These proteins play an important role in regulation of innate immunity and the most potent protein remains unknown. Identifying this protein will lead to a new therapies to boost resistance against infectious diseases. Techniques involved are chromatography, cell culture, flow cytometry, electrophoresis, western blotting and mass spectrometry.

134. How does the brain remove the excess number of neurons during development and aging - also offered as MBiomedSc  
Supervisors: Dr Ben Gu, Professor James Wiley  
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building, Parkville  
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au James Wiley E: james.wiley@florey.edu.au  
Project description: Many more neurons are produced during development than are present in the adult brain. Also many neurons are lost during aging, however the process of innate phagocytosis, which removes unwanted and superfluous neurons is poorly defined. The unwanted neurones enter apoptosis but subsequent clearance of these dying cells is important for our body to avoid autoimmunity or inflammation in the brain. Apoptotic cells express unique markers which enable them to be recognized and engulfed by phagocytes. The knowledge of these unique markers is limited at present to certain cell membrane lipids, e.g. phosphatidylserine. Recent novel finding from our laboratory suggests that a unique protein epitope is expressed early in apoptosis and this is recognized by P2X7 receptors on phagocytes. This project will examine how apoptotic cells are recognized and cleared by phagocytes both in health and in disease. This result will have relevance to many neurological diseases as well as early neurodevelopment. Techniques involved are cell culture, immunoprecipitation, western blotting, flow cytometry, peptide screen, molecular biology and mass spectrometry.
135. Identify the transcriptional regulatory factors of the P2X7 receptor - also offered as MBiomedSc

Supervisors: Dr Ben Gu, Professor James Wiley
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building, Parkville
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au
James Wiley E: james.wiley@florey.edu.au

Project description: P2X7 is an ATP-gated purinergic receptor and plays a broad role in infection, inflammation, autoimmunity, neurodegeneration and oncogenesis. Several isoforms of P2X7 have been identified to be associated with cancer or other diseases. High expression of non-functional P2X7 has also been found in a broad range of tumour tissues. However, the transcriptional regulatory factors leading to these isoforms and non-functional P2X7 are unclear. This project will identify the transcriptional factors in the P2X7 promoter region, and how these transcriptional factors regulate production of P2X7 isoforms and non-functional P2X7. The results will provide insights on how cancer cells avoid removal by innate immunity.

Techniques involved include molecular biology, including primer extension, transfection, fluorescent super electrophoresis mobility shift assay and chromatin-immunoprecipitation, as well as cell culture, flow cytometry.

MALARIA

136. Hiding out in the Placenta. Investigating how glycosaminoglycans can modulate the immune system during malaria and pregnancy.

Supervisors: Dr Louise Randall and Professor Stephen Rogerson
Project Site: Department of Medicine, University of Melbourne. The laboratory is located at the Peter Doherty Institute for Infection and Immunity
Contact: Dr Louise Randall E: louise.randall@unimelb.edu.au T: 8344 2181

Project description: Malaria during pregnancy can impact both the mother and the developing fetus, resulting in increased morbidity and mortality. Placental malaria is characterised by the accumulation of P. falciparum-infected red blood cells in the placenta. Parasite-derived proteins on the infected red blood cell membrane bind to chondroitin sulfate A, a glycosaminoglycan associated with the syncytiotrophoblasts and the intervillous spaces of the placenta. Studies performed in our laboratory suggest that this glycosaminoglycan can modulate the immune system response to the malaria parasite. This new project aims to examine this modulation more closely and to understand the interaction between the parasite, the placenta and the mother’s immune system.

Techniques involved: enzyme-linked immunosorbent assay (ELISA), cell culture, measurement of cytokines, real-time PCR.

137. Cross reactive antigens expressed in severe malaria

Supervisors: Dr Michael Duffy
Project Site: Department of Medicine (RMH), Peter Doherty Institute, Cnr Grattan St and Elizabeth St, University of Melbourne
Contact: Dr Michael Duffy; T: 8344 3264; E: mduffy@unimelb.edu.au

Project description: Severe, cerebral malaria is caused by Plasmodium falciparum and is associated with adhesion of infected erythrocytes to microvasculature via the PFEMP1 variant surface antigen. Each parasite encodes 60 different PFEMP1s that also differ between isolates and regions. Different PFEMP1s adhere to different host receptors. Antibodies to PFEMP1 correlate with protective immunity, but parasites avoid immunity by switching between the PFEMP1s expressed. Recently a subset of PFEMP1 domain cassettes were shown to be associated with severe disease and to bind a novel receptor, these domains may be vaccine targets.

Hypothesis: That parasites causing severe malaria express a conserved subset of PFEMP1 variant surface antigens that elicit cross-reactive antibodies.

Aim: To test PFEMP1 domains abundantly transcribed in severe malaria for cross-reactivity with severe malaria sera. We have identified the PFEMP1 domains expressed in patients with severe and non-severe malaria in West Papua. Sera from these patients will be tested for reactivity with recombinant PFEMP1 domains from their infecting strain and from both severe and non-severe heterologous infections. We predict that patients with acute severe malaria will lack antibodies to their infecting strain PFEMP1s and to PFEMP1s from other parasites causing severe malaria whilst patients with non-severe malaria will be immune and possess antibodies to the PFEMP1s expressed by parasites causing severe malaria.
Significance: Discovery of conserved PfEMP1 domains expressed in severe malaria in West Papua will be an essential step towards a globally effective vaccine to prevent adhesion.

138. Are novel bromodomain proteins required for malaria parasite growth and gene regulation?
Supervisors: Dr Michael Duffy
Project Site: Department of Medicine (RMH), Peter Doherty Institute
Contacts: Dr Michael Duffy; T: 8344 3264; E: mduffy@unimelb.edu.au

Novel anti-malarial drugs are urgently required to combat the increasing resistance to existing anti-malarials. Inhibition of factors binding acetylated histones has recently emerged as a totally novel therapeutic strategy targeting a central epigenetic pathway. This approach has shown promise for the treatment of cancer, inflammation and HIV.

Histone acetylation is a fundamental epigenetic mechanism; it affects the packaging of DNA into chromatin and the histone acetylations bind regulatory protein complexes that determine gene activity. Bromodomains are protein motifs that bind selectively to different acetylated lysine residues in histones. They are present in a range of proteins that modify chromatin structure directly or recruit enzymatic complexes to specific positions in the genome.

We hypothesise that unique P. falciparum proteins containing bromodomains interact with acetylated histones and are essential for gene regulation and survival of the malaria parasite. We will determine the role in parasite biology and gene regulation of six novel P. falciparum bromodomain proteins and will identify and characterize specific, small molecule inhibitors that interfere with their function.

The specific aims of this project are:
1. To analyse the function of the bromodomain proteins using mutant parasites.
2. To characterize six putative P. falciparum bromodomain proteins by determining their location across the genome and how their presence correlates with gene transcription.

139. Gene regulation mechanisms in the transmissible stages of the malaria parasite - also offered as MBiomedSc
Supervisors: Dr Michaela Petter and Dr Michael Duffy
Project Site: Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne
Contacts: Dr Michael Duffy and Dr Michaela Petter; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

Project Description: During infection with the malaria parasite Plasmodium falciparum, some malaria parasites infecting red blood cells differentiate into sexual stages called gametocytes. Gametocytes are transmitted to the mosquito when it feeds on an infected human. The mechanisms that trigger the differentiation of malaria gametocytes are poorly understood. In many eukaryotes, epigenetic mechanisms are crucial for the regulation of cellular differentiation processes. This project aims to identify epigenetic gene regulation mechanisms which are important during the differentiation of malaria gametocytes. The project will involve cultivating P. falciparum gametocytes in vitro and the analysis of the expression of candidate epigenetic regulators by using advanced molecular and imaging techniques such as fluorescence microscopy, Western Blot analysis, and chromatin immunoprecipitation, combined with classical molecular biology.

140. Characterizing new surface proteins of the malaria parasite - also offered as MBiomedSc
Supervisors: Dr Michaela Petter
Project Site: Department of Medicine (RMH), Peter Doherty Institute
Contacts: Dr Michaela Petter; T: 8344 3264; E: mpetter@unimelb.edu.au

Project Description: The malaria parasite evades the host immune system by constantly changing its appearance, a process called antigenic variation. This is mediated by large protein families encoded in the parasites genome. Due to their important role in the patho-physiology of the disease, a better understanding of these surface proteins may reveal new targets for interventions. This project aims to characterize members of a particular protein family, called RIFIN. You will generate and analyse transgenic parasite lines expressing RIFIN proteins fused to fluorescent markers and use these tools to characterize the protein family with respect to their expression, cellular localization, membrane topology and function.

Techniques include: Cell culture, PCR and cloning, SDS-PAGE and Western blotting, FACS analysis, Immunofluorescence microscopy.
141. Investigating the effects of GM-CSF and M-CSF derived human macrophages on phagocytosing \textit{P. falciparum} infected erythrocytes and cytokine production - \textit{also offered as MBiomedSc}

\textbf{Supervisors:} Dr. Adrian Achuthan and Professor Stephen Rogerson  
\textbf{Project site:} Department of Medicine (RMH), University of Melbourne  
\textbf{Contact:} Dr. Adrian Achuthan T: 8344-3298 E: aaa@unimelb.edu.au

\textbf{Project Description:} An important way in which the body clears malaria infection is through opsonisation of \textit{P. falciparum}-infected erythrocytes (IE) and phagocytosis by monocytes/macrophages. This process leads to activation of signalling pathway and cytokine production. Current studies utilize human monocytes cultured in vitro in the presence of either granulocyte-macrophage colony stimulating factor (GM-CSF) or M-CSF to produce monocyte-derived macrophages (MDMs). Classical activation of monocytes by GM-CSF yields “M1-like” MDMs with a pro-inflammatory cytokine profile while M-CSF promotes “M2-like” MDMs that produce an anti-inflammatory cytokine repertoire. In this project you will explore the effects of IE phagocytosis by M1-like and M2-like MDMs on cytokine production and trafficking. Furthermore, you will be investigating the expression and function of signalling proteins that govern phagocytosis and cytokine secretion in these two types of MDMs.

Techniques: The project involves a range of molecular and cell biology techniques including culture and purification of \textit{P. falciparum}-infected erythrocytes, isolation and culture of human monocytes/macrophages, qPCR to assess cytokine mRNA, ELISA to measure cytokine secretion and Western blotting and confocal imaging to determine protein expression and localisation.

142. A role for Adipose Tissue in Malaria? - \textit{also offered as MBiomedSc}

\textbf{Supervisors:} Dr Elizabeth Aitken & Professor Stephen Rogerson  
\textbf{Project site:} Department of Medicine (RMH), Peter Doherty Institute  
\textbf{Contact:} Dr Elizabeth Aitken T: 03 8344 1972 E: Elizabeth.aitken@unimelb.edu.au and Professor Stephen Rogerson T: 03 8344 3259 E: sroger@unimelb.edu.au

\textbf{Project description:} The pathology associated with malaria is partly caused by a strong inflammatory immune response to the \textit{Plasmodium} parasite. Adipose (fat) tissue has recently been shown not to be an inert energy store, but a tissue which actively regulates the immune response. Interestingly, we know that the parasite likes to sequester in the adipose tissue but we don’t know much else. With increasing obesity worldwide, this could be important for development of severe malaria. In this project you will study adipose tissue from people and mice infected with \textit{Plasmodium} parasites. You will discover where in the adipose tissue the parasites are, if (and which) immune cells are also there and if there are any other changes in adipose tissue associated with infection. Techniques will include: Immunohistochemistry, light microscopy, image analysis software.

143. Investigating the acquisition and maintenance of immunity to malaria in infants and pregnant women

\textbf{Supervisor:} Dr Freya Fowkes, Head, Malaria Epidemiology Group, Centre for Population Health, Burnet Institute  
\textbf{Project site:} Burnet Institute  
\textbf{Email:} Fowkes@burnet.edu.au

\textbf{Project Description:} Immunity to infectious diseases during pregnancy remains an intriguing area with immunologic and physiologic changes during pregnancy rendering pregnant women to be more susceptible to, and more severely affected by, infectious diseases. Malaria is one of the most important pathogens in pregnancy and world-wide it is estimated that 50 million women living in malaria endemic areas become pregnant. Despite acquiring substantial pre-existing blood-stage immunity pregnant women typically develop higher parasite densities compared to non-pregnant adults, placental infection and associated complications. Very little is known about antibody acquisition, maintenance and boosting during or after gestation. Furthermore little is known about maternal transfer of antibodies and subsequent maternal antibody decay and infant antibody acquisition in infants born in malaria endemic areas.

We have samples from several established longitudinal cohorts of pregnant women and infants that can address questions of antibody acquisition and maintenance through antibody assays and epidemiological analyses. Findings will help us understand how immunity develops and is maintained against infectious diseases.

144. Identifying antigen targets of the acquired immune response during severe malaria

\textbf{Supervisor:} Professor James Beeson, Dr Freya Fowkes, Dr Jack Richards, Professor Stephen Rogerson  
\textbf{Project site:} Burnet Institute  
\textbf{Email:} Professor James Beeson E: beeson@burnet.edu.au T: 9282 2111

\textbf{Project Description:} Malaria caused by \textit{Plasmodium falciparum} is a leading cause of mortality and morbidity globally, particularly among young children. After repeated exposure, individuals develop effective immunity that controls blood-
stage parasitaemia, thereby reducing clinical symptoms and life-threatening complications. Antibodies are important mediators of this acquired immunity. The demonstration that naturally acquired antibodies are associated with protection from malaria is one of the criteria used to objectively prioritize malaria antigens for malaria vaccine development.

We have recently completed a case-control study of severe malaria in children living on the North coast of Papua New Guinea. Cases were identified at Madang hospital and were defined as having severe malaria according to the World Health Organization criteria. Each case of severe malaria was matched to a healthy community control. Blood samples were taken from cases at the time of hospital admission and when the patient had recovered. For controls, samples were taken at the time of enrolment into the study. We would like determine levels of antibodies to a range of malaria antigens by Enzyme-linked immunosorbent assay (ELISA), flow cytometry and functional antibody assays. The levels of these antibodies will then be related to clinical outcome using statistical analysis including regression techniques.

These findings will help us understand how immunity contributes to protection from severe malarial disease progression. The findings are valuable for advancing vaccine development by providing evidence supporting certain malaria antigens as targets of protective immunity.

145. Understanding the targets and mechanisms of human immunity to malaria
Supervisor: Professor James Beeson, Dr Jack Richards, Dr Freya Fowkes
Project site: Burnet Institute
Email: beeson@burnet.edu.au Richards@burnet.edu.au, Fowkes@burnet.edu.au
Project Description: This project will focus on identifying the key antigens that are targets of protective immunity against malaria and understanding the mechanisms mediating immunity, which includes antibodies and cell-mediated responses. This knowledge is crucial for the development of effective vaccines against malaria. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect children from malaria, or protect pregnant women and their developing babies from the devastating consequences of malaria in pregnancy. The studies would particularly focus on understanding antibody acquisition, maintenance and boosting and how antibodies neutralize and clear malaria parasites in the blood, and examine interactions with monocytes/macrophages and dendritic cells, and understanding the nature and specificity of antibody responses.

146. Developing new diagnostics and treatments for malaria
Supervisor: Professor James Beeson, Dr Jack Richards, Dr Freya Fowkes
Project site: Burnet Institute
Email: beeson@burnet.edu.au Richards@burnet.edu.au, Fowkes@burnet.edu.au
Project Description: Access to affordable malaria diagnostics and antimalarial treatments are vital for the effective management of individuals and for malaria control at a population level. With an increasing emphasis on malaria elimination in some parts of the world, there is a need to develop diagnostics with improved sensitivity to detect low levels of parasites and to identify individuals with glucose-6-phosphate deficiency. There is also an urgent need to develop new anti-malarial drugs to combat drug resistance. This project seeks to develop and assess new tools for the diagnosis of malaria and to identify and develop novel drug compounds that block the blood stage replication of malaria parasites.

147. Vaccines against malaria
Supervisor: Professor James Beeson, Dr Jack Richards, Dr Freya Fowkes
Project site: Burnet Institute
Email: beeson@burnet.edu.au Richards@burnet.edu.au, Fowkes@burnet.edu.au
Project Description: The aim of this project is to evaluate candidate antigens as potential malaria vaccines, understand what combinations of antigens could be used to generate the most effective immune responses, and understand the protective activity of vaccine-induced immune responses. These studies will focus on several leading candidate antigens (AMA1, EBAs, PfRh, MSP2), and other promising antigens. They will use novel approaches in molecular biology, cell biology and immunology to address these aims. In addition, the project could include working on optimising vaccine approaches to induce potent protective immune responses (e.g. improving antigen presentation). The project could focus on vaccines for P. falciparum and P. vivax, which are the two main causes of human malaria.
148. Identifying targets and mechanisms of the acquired immunity to severe malaria in children

Supervisors: Professor James Beeson, Dr Freya Fowkes, Dr Jack Richards, Professor Stephen Rogerson
Project Site: Burnet Institute
Contact: Professor James Beeson E: beeson@burnet.edu.au T: 9282 2111

Project description: Malaria caused by Plasmodium falciparum is a leading cause of mortality and morbidity globally, particularly among young children. After repeated exposure, individuals develop effective immunity that controls blood-stage parasitaemia, thereby reducing clinical symptoms and life-threatening complications. Antibodies are important mediators of this acquired immunity. The demonstration that naturally acquired antibodies are associated with protection from malaria is one of the criteria used to objectively prioritize malaria antigens for malaria vaccine development.

We have recently completed a case-control study of severe malaria in children living on the North coast of Papua New Guinea. Cases were identified at Madang hospital and were defined as having severe malaria according to the World Health Organization criteria. Each case of severe malaria was matched to a healthy community control. Blood samples were taken from cases at the time of hospital admission and when the patient had recovered. For controls, samples were taken at the time of enrolment into the study. We would like to determine levels of antibodies to a range of malaria antigens by Enzyme-linked immunosorbent assay (ELISA), flow cytometry and functional antibody assays. The levels of these antibodies will then be related to clinical outcome using statistical analysis including regression techniques. These findings will help us understand how immunity contributes to protection from severe malarial disease progression. The findings are valuable for advancing vaccine development by providing evidence supporting certain malaria antigens as targets of protective immunity.

149. Understanding mechanisms that mediate human immunity to malaria

Supervisors: Professor James Beeson, Dr Jack Richards, Dr Freya Fowkes
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au richards@burnet.edu.au fowkes@burnet.edu.au

Project description: This project will focus on identifying the key antigens that are targets of protective immunity against malaria and understanding the mechanisms mediating immunity, which includes antibodies and cell-mediated responses. This knowledge is crucial for the development of effective vaccines against malaria. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect children from malaria, or protect pregnant women and their developing babies from the devastating consequences of malaria in pregnancy. The studies would particularly focus on understanding antibody acquisition, maintenance and boosting and how antibodies neutralize and clear malaria parasites in the blood, and examine interactions with monocytes/macrophages and dendritic cells, and understanding the nature and specificity of antibody responses.

150. Developing new diagnostics and treatments for malaria

Supervisors: Professor James Beeson, Dr Jack Richards, Dr Freya Fowkes
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au richards@burnet.edu.au fowkes@burnet.edu.au

Project description: Access to affordable malaria diagnostics and antimalarial treatments are vital for the effective management of individuals and for malaria control at a population level. With an increasing emphasis on malaria elimination in some parts of the world, there is a need to develop diagnostics with improved sensitivity to detect low levels of parasites and to identify individuals with glucose-6-phosphate deficiency. There is also an urgent need to develop new anti-malarial drugs to combat drug resistance. This project seeks to develop and assess new tools for the diagnosis of malaria and to identify and develop novel drug compounds that block the blood stage replication of malaria parasites.

151. Healthy Mothers, Healthy Babies in Papua New Guinea – The impact of Nutrition, Malaria and STIs on pregnant women and infants

Supervisors: Professor James Beeson, Dr Freya Fowkes
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au fowkes@burnet.edu.au

Project description: In many resource-poor regions globally, pregnant women experience high rates of malaria, undernutrition and sexually transmitted infections (STIs) which can lead to maternal morbidity and mortality and in infants, low birth weight (LBW) resulting in a significant number of infant deaths each year. In these settings, LBW is due to fetal growth restriction and preterm delivery. However the link between nutrition, malaria and STIs and these birth outcomes have yet to be elucidated.
At the Burnet Institute, we have initiated a unique research program in rural PNG, called Health Mothers Health Babies, in partnership with the PNG Institute of Medical Research, East New Britain Provincial Government, University of PNG, the National Department of Health, and others. We have undertaken a longitudinal study of 700 pregnant women attending antenatal care, and followed them through to delivery. Among these women we will measure markers of nutrition and evaluate micronutrient deficiencies, determine malaria and STIs. The association of nutrition, malaria, and STIs during pregnancy with respect to birth outcomes will then be assessed using epidemiological techniques. The objective of this project is to determine the major preventable causes of poor maternal health and LBW to enable the development of future interventions to improve health and pregnancy outcomes. This project is offered as a laboratory or epidemiological project, or a combination of the two depending on student interests.

152. Development of novel point-of-care diagnostics tests and surveillance tools

Supervisors: Professor James Beeson, Dr Philippe Boeuf, Associate Professor David Anderson
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au  Philippe.Boeuf@burnet.edu.au  anderson@burnet.edu.au

Project description: There is an urgent need for diagnostic and surveillance tests that could be used in resource-poor settings. These include vaccine antibody testing (malaria, measles, HBV, pneumonia and others) to assess vaccine coverage in populations, and sero-surveillance tools for monitoring and tracking major infectious diseases. The limited resources and health care infrastructure in many disease-endemic countries means that tools for evaluating the vaccine status of patients, vaccine coverage in populations and for disease surveillance need to be simple to perform without a requirement for laboratory facilities or advanced equipment. The tests need to be being semi-quantitative, have a long shelf-life, stable for periods at ambient temperature, and easy to perform and interpret to ensure their suitability to the specific conditions to resource-poor settings. This project will work towards the development of novel semi-quantitative point-of-care rapid tests and investigate different approaches to improve sensitivity and quantitation. This will build on Burnet’s extensive expertise in diagnostic test development and strong links to communities that experience a high burden of disease and have an urgent need for new point-of-care tests. The development of new low cost point-of-care tests for major diseases would facilitate major advances in disease control in resource-limited settings.


Supervisor: Dr Paul Gilson, Dr Freya Fowkes and Professor James Beeson
Project site: Burnet Institute
Email: Gilson@burnet.edu.au Fowkes@burnet.edu.au

Project Description: Malaria parasites invade and replicate within human red blood cells which can cause debilitating disease symptoms and even death. Parasites recognize, attach to and penetrate red blood cells using a surfeit of surface ligands, the understanding of which is important for vaccine development. We have recently established the potential functions of several malaria surface proteins and the order in which they work. This project aims capitalize on this discovery by finding the best combinations of invasion inhibitory antibodies to block the surface proteins and prevent growth. This work could prove highly informative for future vaccine development.

Techniques involved: Cell culture, luciferase based growth assays, live cell microscopy of parasites.

154. Host cell modification in malaria parasites. – also offered as MBiomedSc

Supervisor: Dr Paul Gilson, Dr Freya Fowkes and Professor James Beeson
Project site: Burnet Institute
Email: Gilson@burnet.edu.au Fowkes@burnet.edu.au

Project Description: Malaria parasites extensively modify the red blood cells they infect to enable them to grow rapidly and to avoid host immunity. To modify their host cells, the parasites make and then export hundreds of proteins into the host compartment. These proteins traffic to different regions within the host and form a number of complexes and structures that contribute to parasite virulence. We have made a number of key discoveries regarding the methods used by parasites traffic their virulence proteins and this project hopes to extend this work further to assess the value of the trafficking systems as future targets for anti-malarial drugs.

Techniques involved: Cell culture, parasite molecular cell genetics, fluorescence microscopy, flow cytometry.
MEDICATION SAFETY

155.  How do cognitive and functional impairment relate to the use of anticholinergic medications in patients aged 65 years and over in rehabilitation and geriatric evaluation and management settings?  – also offered as MBiomedSc

Supervisors:  Professor Elizabeth Manias and Dr Snezana Kusljic  
Project Site:  Royal Melbourne Hospital, Royal Park Campus; Melbourne School of Health, The University of Melbourne  
Contact:  Professor Elizabeth Manias T: 0450 308 060 E: emanias@unimelb.edu.au

Project description:  Anticholinergic medications can cause many adverse events such as drowsiness, urinary retention, tachycardia, constipation, blurred vision, dry mouth and increased intraocular pressure. These medications can reduce levels of cognition, therefore causing decreased arousal, sedation, and confusion. These effects are more likely to be pronounced in older people because of altered pharmacokinetics and reduced levels of cognition that occur with increased age. Examples of anticholinergic medications include tricyclic antidepressants, antihistamines, and ocular mydriatic agents. This study will involve the conduct of a prospective audit of anticholinergic medications prescribed to older patients (aged 65 years and over) admitted to hospital. Data will also be collected on all medications prescribed to these patients. Prescription of anticholinergic medications will be considered in relation to the cognitive levels experienced by older patients as determined by the Mini-Mental State Examination. The prevalence and severity of anticholinergic symptoms, including dry mouth, constipation, blurred vision, confusion, urinary hesitation, dry eyes, and drowsiness will also be assessed. Following conduct of this study it will be possible to make recommendations about how medication safety can be improved in the use of anticholinergic medications in older people.

156.  Safe and appropriate medication prescribing of older patients with coronary heart disease in hospital  – also offered as MBiomedSc

Supervisors:  Professor Elizabeth Manias and Dr Snezana Kusljic

Project Site:  Royal Melbourne Hospital, Parkville Campus; Melbourne School of Health, The University of Melbourne

Contact:  Professor Elizabeth Manias T: 0450 308 060 E: emanias@unimelb.edu.au

Project description:  In Australia, coronary heart disease in older people is commonly associated with a large burden of care, in terms of patient disability and mortality, and cost of treatment. Coronary heart disease can manifest as angina and acute myocardial infarction (or a heart attack). In order to treat coronary heart disease, older people have to use many medications. In addition to coronary heart disease, older people also have a number of chronic conditions, such as osteoarthritis and diabetes. Older people are prescribed many medications to treat these conditions, which has important implications for medication safety. They are at risk of developing adverse events such as falls, gastrointestinal bleeding, and cognitive impairment. In addition, older people are often denied potentially beneficial medications without a valid reason. In this study, the STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria will be applied to a random sample of older people admitted to hospital following a diagnosis of unstable angina, a symptom of coronary heart disease. Use of these screening tools will determine what medications have been inappropriately commenced in older people and what medications have been inappropriately stopped or not commenced in older people. The adverse events experienced by older people will also be examined to determine whether the medications they are prescribed may be associated with these adverse events. Medical histories of older people will be examined retrospectively on admission, at three days following admission and at discharge. Following completion of the study recommendations will be made about the safety and appropriateness of medication prescribing for older people with coronary heart disease in hospitals.

MOTOR NEURON DISEASE

157.  Neurodegeneration – Stimulating autophagy to improve intracellular proteostasis in MND - also offered as MBiomedSc

Supervisors:  Dr Bradley Turner, Dr Bec Sheean

Project Site:  Florey Institute, Kenneth Myer Building

Contact:  Bradley Turner E: Bradley.turner@florey.edu.au  T: 9035 6521

Project description:  Motor neuron disease (MND) is a neurodegenerative and protein misfolding disorder linked to defects in proteostasis pathways, or protein homeostasis, within affected motor neurons. MND is associated with cytoplasmic accumulation and aggregation of key proteins (SOD1, TDP-43 and FUS) which are implicated in motor neuron death. Strategies that improve proteostasis and clear these misfolded proteins in motor neurons are therefore an attractive candidate therapeutic approach for MND. Our group is interested in autophagy, the main catabolic pathway in neurons that eliminates misfolded proteins, aggregates and damaged organelles by targeting these substrates to lysosomes for digestion.
This project will investigate the therapeutic effect and action of stimulating autophagy in genetic cell culture and mouse models of MND. The effects of newly identified autophagy enhancing drugs will be evaluated on clinical progression, neuropathology and misfolded and aggregated protein load in mouse models of MND. This project will employ transgenic mice, behavioural studies, advanced microscopy, immunohistological and biochemical techniques.

158. **Neurodegeneration – Transcriptional profiling of motor neuron populations in development and MND** - **ONLY offered as MBiomedSc**

**Supervisors:** Dr Bradley Turner  
**Project Site:** Florey Institute, Kenneth Myer Building  
**Contact:** Bradley Turner E: Bradley.turner@florey.edu.au T: 9035 6521

**Project description:** Motor neuron disease (MND) is an adult-onset and progressive neurodegenerative disorder that results from combined upper and lower motor neuron loss. Although MND presents late in life, there is increasing evidence for a long preclinical or presymptomatic period before diagnosis of overt clinical symptoms. It is likely that a combination of genetics, epigenetics and exogenous factors determine motor neuron sensitisation and seed the development of MND early in life. Motor neuron sensitisation and susceptibility in MND is likely to be coupled to stress and remodelling associated with developmental milestones of motor neurons.

This project will employ a transcriptomic approach to understand the genetic factors orchestrating motor neuron development and disease. Newly available fluorescent reporter mice will be exploited to isolate different motor neuron populations at key developmental stages for RNA sequencing and pathway analysis in healthy or transgenic MND mice. This project is likely to yield proximal gene candidates seeding the development of MND for future target validation and functional studies.

This project will employ transgenic mice, next-generation sequencing, bioinformatics, molecular biology and biochemical techniques.

**MULTIPLE SCLEROSIS/NEUROLOGY**

159. **Defining cervical dysplasia incidence and management in immune-compromised patients with Multiple Sclerosis**

**Supervisors:** Dr Ananne van der Walt, Dr David Wrede and A/Prof Julia Brotherton  
**Project Site:** Department of Medicine, Royal Melbourne Hospital, The University of Melbourne and Department of Gynaecology, Royal Women’s Hospital.  
**Contact:** Dr Ananne van der Walt, Ananne.vanderwalt@mh.org.au

**Project description:** The exact incidence of cervical dysplasia and cervical cancer in immune-compromised women is not known. Current guidelines recommend two-yearly pap smears for the general female population and yearly pap smears for immuno-compromised patients. Patients with multiple sclerosis are increasingly being treated with higher potency immunomodulatory drugs. Defining the incidence of cervical dysplasia in this population will critically inform screening programs and reduce the risk of lower genital cancers.

Pap smear results of consented women with MS from the Royal Melbourne and Box Hill Hospitals will be identified from the Victorian Cervical Cytology Registry. There is the potential for expansion of the project to other populations of immune-compromised women at RMH.

This project will suit students with interest in gynaecology and/or neurology in addition to health outcome analysis. During the project, you will improve your statistical skills and will be required to work across several clinics at the RMH and RWH to facilitate recruitment. You will contribute to the evidence-based clinical management of MS.

160. **Investigating the effects of vitamin D treatment on immune cells of people with Multiple Sclerosis** - **also offered as MBiomedSc**

**Supervisors:** Melissa Gresle and Helmut Butzkueven  
**Project Site:** Department of Medicine, Royal Melbourne Hospital.  
**Contact:** E: mgresle@unimelb.edu.au

**Project description:** In Australia, someone growing up in North Queensland is 7 times less likely to get Multiple Sclerosis (MS) than a person in Tasmania. It is very likely that this is, at least in part, due to higher levels of Vitamin D, which is produced by sun exposure in the skin; as sun intensity, duration and exposure are much higher in North Queensland. Thus, low circulating vitamin D levels are considered a risk factor for MS.

Our laboratory has produced some preliminary data to suggest that there are potential differences in way that vitamin D regulates the expression of some genes in MS cases compared to unaffected controls. As this has not previously been
reported we need to independently validate these findings. For this project we will culture lymphocyte immune cells from MS cases and healthy controls in the presence and absence of vitamin D to confirm that (1) vitamin D regulates the expression of our candidate genes and (2) to test if there are any differences in the way that vitamin D regulates the expression of these genes in MS cases compared to controls.

This work will provide novel insights into the immune mechanisms of vitamin D therapy in MS cases and healthy controls.

161. Management of radiologically active relapsing remitting multiple sclerosis - also offered as MBiomedSc
Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven
Project Site: Department of Medicine, Royal Melbourne Hospital, The University of Melbourne
Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au
Project description: Regular imaging of the central nervous system is a common practice in relapsing-remitting multiple sclerosis (MS). Only approximately 1 in 10 new MS-related brain lesions present with clinical symptoms of a relapse. It is unclear whether silent brain lesions observed on routine brain MRI’s warrant change of disease modifying therapy or whether these lesions do not add any prognostic information to the management algorithm.

This project compares disease outcomes (relapse and disability outcomes) in patients with multiple sclerosis with recent clinically silent MRI activity. It utilises MSBase - a large international, observational database of MS patients, to conduct retrospective analysis of prospectively recorded data.

This project will suit students with interest in statistics and health outcome analysis. During the project, you will improve your statistical skills, learning some of the more complex statistical analytical techniques, including propensity score matching procedures. Knowledge of elementary statistics is a requisite. You will contribute to the evidence-based clinical management of MS.

162. How does therapy change the course of multiple sclerosis relapses? - also offered as MBiomedSc
Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven
Project Site: Department of Medicine, Royal Melbourne Hospital, The University of Melbourne
Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au
Project description: Clinical relapses triggered by episodic inflammatory activity are a typical feature of multiple sclerosis (MS). Typically, patients experiencing relapses of MS activity receive short courses of high-dose intravenous steroids. While evidence showed that remission is facilitated by steroid therapy, the evidence regarding the completeness of the steroid-induced remission is scarce.

This project will examine the outcomes of steroid therapy for MS relapses. We hypothesise that intravenous steroids decrease duration of MS relapses and improve recovery. This project will also examine difference in the clinical presentations of relapses, their severity and recovery on various disease modifying agents. The project is an extension of our recently published work on relapse incidence and phenotype. It will utilise a large longitudinal collection of data recorded in the international observational MS registry based at Melbourne Brain Centre - MSBase.

This project will suit students with interest in statistics and health outcome analysis. During the course of the project, you will become familiar with quasi-randomisation and the analysis of observational data. Knowledge of basic statistics including its applied use is essential. You will contribute to the evidence-based clinical management of MS.

163. Does disease modifying therapy change the phenotype of multiple sclerosis relapses? - also offered as MBiomedSc
Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven
Project Site: Department of Medicine, Royal Melbourne Hospital, The University of Melbourne
Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au
Project description: A number of disease modifying therapies are available for long-term treatment of relapsing-remitting multiple sclerosis (MS). While the overall effect of these therapies has been well described in the literature, individual response to therapy varies widely among patients. Our understanding of individual treatment response is limited.

This project will examine the effect of two potential modifiers of treatment response - sex and age - on the individual response to disease modifying agents in MS. We hypothesise that female sex and younger age are associated with higher treatment effect. This project is an extension of our recently published work on the association between sex, age and relapse activity in MS. It will utilise a large longitudinal collection of data recorded in the international observational MS registry based at Melbourne Brain Centre - MSBase.

This project will suit students with interest in statistics and health outcome analysis. During the project, you will improve your statistical skills, learning some of the more complex statistical analytical techniques. Knowledge of elementary statistics is a requisite. You will contribute to the evidence-based clinical management of MS.
NEPHROLOGY

164. Finding genetic mutations in new types of inherited kidney disease: focal segmental glomerulosclerosis – also offered as MBiomedSc

Supervisors: Professor Judy Savige and Dr Yanyan Wang
Project Site: NWAC, Northern Hospital, Epping
Contact: Professor Judy Savige, T 8344 3260, jsavige@unimelb.edu.au

Project description: To date, more than 120 different inherited kidney diseases due to mutations in 160 different genes have been identified. However there are still many diseases where the genes are not known. We have an Inherited renal disease clinic and are referred many families with unclassified kidney diseases. We have a number where the mutant genes are not known, and in the first instance are looking at some candidate genes. The aim of this project is to help characterize the patients (many have hearing loss and eye abnormalities too) and determine the mutant gene that is responsible for the disease in each family. For example, we have 12 families with inherited focal segmental glomerulosclerosis (FSGS), and also some candidate genes. Patients with focal segmental glomerulosclerosis have proteinuria and invariably develop renal failure, requiring life long dialysis or a renal transplant. The aim of this project is to determine which genes are affected in FSGS and some other inherited renal diseases.

Techniques to be used and skills acquired: This study involves extracting DNA from peripheral blood, designing amplification/PCR primers, amplifying DNA, purifying it, sequencing it, and determining if the DNA change is pathogenic. This work is likely to result in a publication and could easily lead on to a PhD. This project involves working with a kidney specialist (Prof Judy Savige in her clinic) and with A/Prof Deb Colville an ophthalmologist.

Feasibility: We already have DNA stored from 12 families with FSGS and have Human Research Ethics Committee Approval for this project. This project has plenty of patient contact and also good laboratory experience.

NEUROPSYCHIATRY AND STRESS BIOLOGY

165. The relationship between dietary quality, nutrient biomarkers, and major depressive disorder – also offered as MBiomedSc

Supervisors: Dr Jerome Sarris
Project Site: The Melbourne Clinic (Richmond)
Contact: Dr Jerome Sarris jsarris@unimelb.edu.au

Project description: Emerging data is showing there is a relationship between mental health and a person’s dietary quality and nutrient status. We have novel data assessing dietary quality, in addition to serum levels of essential fatty acids, zinc, folate, and B12, in a sample of adults with current major depressive episode (n=150). This sub-project (from an NHMRC-funded study) will explore the relationships between these factors to determine any meaningful associations. Matched control data will be collected by the successful research student, to determine any differences between depressed and healthy people in respect to their dietary quality and nutrient status.

166. Integrative modelling of a microglial response to neuroinflammation and the role of mGluR5: Implications for neuronal homeostasis.

Supervisors: Dr. Gursharan Chana, Dr. Karen Gregory, Dr. Mirella Dottori, Professor Christos Pantelis, Professor Arthur Christopoulos, Professor Stan Skafidas.
Project Site: Centre for Neural Engineering/Monash Institute of Pharmaceutical Sciences
Contact: Dr. Gursharan Chana T: 03 9035 6741 E: gchana@unimelb.edu.au
Dr. Karen Gregory E: karen.gregory@monash.edu

Project description: The role of microglia in neurodevelopment and synaptic pruning has recently been characterized. This has important implications with regard to the role of these key brain immune cells in neuronal connectivity and how potential disruption in their normal functioning due to neuroinflammation may lead to aberrant over or under pruning of synapses. This is of relevance to neuropsychiatric disorders such as autism and schizophrenia, which have a neurodevelopmental origin and where increased microglial numbers have been seen before in the dorsolateral prefrontal cortex (DLPFC). In addition, we have recently observed decreased neuronal expression of the metabotropic glutamate receptor-5 (mGluR5) in the DLPFC in Autism, in a subset of patients where we previously reported increased microglial numbers and activation status, together with increased microglial numbers in an mGluR5 knockout mouse. We propose a project that will adopt an integrative in vitro approach to assessing the role of mGluR5 in microglial activation and consequences for restoring synaptic integrity.
Skill Acquisition: The project involves tissue culture, real-time PCR, pharmacological profiling with binding and signaling assays together with state of the art helium ion microscopy to assess how mGluR5 expression levels, function and localization are altered following a neuroinflammatory insult and the resulting effect on markers of neuronal and synaptic integrity.

167. 3D Cortical Modelling Using Biomaterials

Supervisors: Dr. Gursharan Chana, Ms. Cristiana Mattei, Dr. Giovanna D’Abaco, Dr. Mirella Dottori, Dr. Babak Nasr, Professor Stan Skafidas.

Project Site: Centre for Neural Engineering

Contact: Prof. Stan Skafidas T: 03 9035 3630 E: sskaf@unimelb.edu.au
Dr. Gursharan Chana T: 03 9035 6741 E: gchana@unimelb.edu.au

Project Description: The need for developing 3D models of the brain is imperative not only to increase our understanding of the central nervous system but also for disease modelling. Modelling the layered structure and organization of the cerebral cortex presents a significant and important challenge as this is the site of higher order brain functioning and complex processing. We propose a project that utilises state of the art facilities at the Centre for Neural Engineering with regard to biomaging and fabrication and builds upon current work already being conducted towards 3D modelling of the brain.

Skill Acquisition: The project will utilise tissue culture techniques, immunofluorescence, real time PCR, microelectrode arrays, as well as tissue embedding and high end imaging using helium ion microscopy.

168. Towards a brain-based measure of human anxiety sensitivity (offered as MSc only) – ONLY available as MBiomedSc

Supervisors: Assoc Prof Ben Harrison and Dr Chris Davey

Project Site: Melbourne Neuropsychiatry Centre, and Department of Psychiatry, The University of Melbourne

Contact: Assoc Prof Ben Harrison; T: 03 8344 1876 E: habj@unimelb.edu.au

Project Description: Anxiety disorders are the most prevalent and costly of all mental disorders for Australians aged between 18 and 45 years. Despite this, we lack a clear understanding of the biological mechanisms that give rise to their symptoms and how to effectively treat them.

This PhD project will test the hypothesis that human anterior insular cortex activity underlies individual differences in trait “anxiety sensitivity”: an established psychological risk factor for clinical anxiety disorders. The project will recruit a large cohort of adolescent and young adult participants and assess them with functional magnetic resonance imaging (fMRI) combined with psychophysiological monitoring. As well as characterising the brain basis of human anxiety sensitivity, it is expected that this project will identify a novel biological risk marker of clinical anxiety, in particular, panic disorder. We have close collaborations with Orygen Youth Health and headspace Western Melbourne, and there is scope for the project to be extended to patient groups from these clinics.

Candidates (Masters only) with an interest in psychology, biological psychiatry and imaging neuroscience are encouraged to apply. Further detail about this project is available upon request.

169. Predicting treatment response in young people with major depression using functional neuroimaging – ONLY available as MBiomedSc

Supervisors: Dr Chris Davey and Assoc Prof Ben Harrison

Project Site: Melbourne Neuropsychiatry Centre, and Department of Psychiatry, The University of Melbourne

Contact: Dr Chris Davey, T: 03 9342 2800 E: c.davey@unimelb.edu.au

Project Description: Mental illnesses are the "chronic diseases of the young", and the mental illness that causes most disability in young people is depression. While antidepressant medications are an effective treatment for adolescent depression, only about two-thirds of patients will demonstrate a clinical response, and less than a third will reach remission. The identification of valid biomarkers to assist in the prediction of treatment response is therefore of great clinical relevance.

This Masters project will use functional magnetic resonance imaging (fMRI) combined with novel emotional provocation tasks. We will test the hypothesis that individual differences in pretreatment activity of the medial frontal cortex will predict treatment response in young patients experiencing their first episode of depression. Patients will be recruited from Orygen Youth Health and headspace Western Melbourne, where Dr Davey works as a psychiatrist.

Candidates (Masters only) with an interest in psychology, biological psychiatry and imaging neuroscience are encouraged to apply. Further detail about this project is available upon request.
170. **Mapping the Human Schizophrenia Connectome – Also offered as MBiomedSc**

**Supervisors:** Dr Andrew Zalesky (Melbourne Neuropsychiatry Centre), Dr Alex Fornito (Monash Biomedical Imaging), Dr Luca Cocchi (Queensland Brain Institute), Professor Christos Pantelis (Melbourne Neuropsychiatry Centre)

**Project Site:** Melbourne Neuropsychiatry Centre

**Contact:** Dr Andrew Zalesky: azalesky@unimelb.edu.au

**Project description:** This project aims to comprehensively map the entire human connectome in schizophrenia. The student will complete one of the largest clinical connectome mapping studies undertaken in the world by analysing high-quality brain imaging data in more than 330 individuals with schizophrenia provided by the Australian Schizophrenia Research Bank (ASRB). The ASRB is the largest brain research project ever undertaken in Australia. This project will apply advanced fibre tracking algorithms to the diffusion-MRI brain imaging data acquired in each patient, with the goal of comprehensively mapping all disrupted connections comprising the entire schizophrenia connectome. VLSCI computational resources may be utilised for this purpose.

*Figure:* Disruptions to functional brain connectivity in schizophrenia.

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171. **Human Connectome Bioinformatics – Also offered as MBiomedSc**

**Supervisors:** Dr Andrew Zalesky, Professor Christos Pantelis

**Project Site:** Melbourne Neuropsychiatry Centre

**Contact:** Dr Andrew Zalesky: azalesky@unimelb.edu.au

**Project description:** The connectome refers to a comprehensive network description of the brain’s internal wiring. Advances in magnetic resonance imaging (MRI) have enabled reliable mapping of the large-scale connectome in the living human brain. Comparing the human connectome between healthy and diseased brains has identified disease-specific anomalies in brain circuitry that may provide novel therapeutic targets and potential biomarkers to assess risk and predict patient outcomes. This project aims to develop and apply tools that capitalise on these advances.

*Figure:* The human connectome mapped using diffusion-MRI and tractography.

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172. **Neuroimaging in schizophrenia-spectrum disorders – Also offered as MBiomedSc**

**Supervisors:** Dr Vanessa Cropley, Dr Tamsyn Van Rheenen, Dr Chad Bousman, Professor Christos Pantelis

**Project Site:** Melbourne Neuropsychiatry Centre, The Alan Gilbert Building, 161 Barry Street, Carlton South, The University of Melbourne.

**Contact:** Dr Vanessa Cropley; T: (03) 8344 1876; E: vcropley@unimelb.edu.au or Dr Tamsyn Van Rheenen: Tamsyn.van@unimelb.edu.au

**Project description:** The Melbourne Neuropsychiatry Centre (MNC) is a joint centre of Melbourne Health (North Western Mental Health) and The University of Melbourne (Department of Psychiatry). Research at MNC focuses on improving our understanding of the neurobiological processes involved in disorders of the brain and mind.

Our group has structural Magnetic Resonance Image (MRI) scans previously collected from the Australian Schizophrenia Research Bank (ASRB). The ASRB is an Australian register and storage facility of medical research data that links clinical and neuropsychological information, blood samples and structural MRI scans from people with schizophrenia and healthy non-psychiatric controls. This data is collected across five research sites within Australia, including the MNC. The data is accessible to researchers wanting to undertake research using the resources of the ASRB.

The Psychosis and Developmental Neuropsychiatry Stream of MNC has several projects available that will investigate gene x environment interactions on structural neuroimaging parameters and behaviour in schizophrenia or risk for psychosis. These projects will utilise MRI scans and associated clinical, cognitive and genetic data collected as part of the ASRB. Projects for 2016 include:

- Investigating the influence of prefrontal and striatal dopaminergic genes, cannabis exposure and their interaction on cognition and prefrontal-striatal volumes in high and low schizotypy
- Examining the interaction between the brain derived neurotrophic factor (BDNF) gene and childhood adversity on hippocampal subfield volume in schizophrenia and healthy controls
- Investigating the impact of neurodevelopmental genes (e.g. neuregulin) on neurological soft signs and its association with cortical gyrification, cognition and age of illness onset in schizophrenia
The student will be responsible for pre-processing, tracing (if applicable) and statistical analysis of MRI scans and associated clinical and genetic data. The student will also be trained in the application of imaging analysis in neuropsychiatry.

There are 2 honours places available for 2016

173. **Effects of oxytocin genetic variants on brain and behavior in schizophrenia**

**Supervisors:** Dr Cali Bartholomeusz (Orygen); Dr Chad Bousman (Melbourne Neuropsychiatry Centre); Prof Cyndi Shannon-Weickert (Neuroscience Research Australia); Prof Christos Pantelis (Melbourne Neuropsychiatry Centre)

**Project site:** Orygen, The National Centre of Excellence in Youth Mental Health and Centre for Youth Mental Health, 35 Poplar Road, Parkville; and Melbourne Neuropsychiatry Centre, The Alan Gilbert Building, 161 Barry Street, Carlton South.

**Contact:** Dr Cali Bartholomeusz Email: barc@unimelb.edu.au

**Project Description:** Oxytocin (OXT), a neurohypophysial hormone and neurotransmitter, is widely recognized as having an important role in human social cognition and prosocial behavior. These domains, which contribute to general social functioning, are significantly impaired in schizophrenia. Variation in OXT single nucleotide polymorphisms (SNPs) and OXT receptor (OXTR) SNPs have been linked to risk for schizophrenia. In addition, several of these SNPs have been associated with the severity of psychopathology, as well as social cognitive impairment in schizophrenia. A number of neuroimaging studies support a link between structural differences in social brain areas and OXTR variants in the healthy population, however no study has yet examined the relationship that these variants have to brain volumes in schizophrenia.

**Aims:** To examine the relationships between genetic load for previously identified OXT/OXTR SNPs and cognition, symptoms, and social functioning, in Australians with schizophrenia and healthy control participants. We will also investigate whether these relationships are linked to and potentially mediated by, brain volumes, particularly of the amygdala, nucleus accumbens and medial prefrontal/anterior cingulate cortices.

**Method:** Pre-existing data from the Australian Schizophrenia Research Bank will be utilised for the current study. Correlation statistics, and mediation analyses where appropriate, will be conducted to explore the associations between genetic variants and outcome measures and brain volumes. ANOVAs will also be conducted to explore differences between patients and healthy controls.

**Outcome:** This project will increase our understanding of how variants in key OXT and OXTR SNPs are related to risk for schizophrenia, symptomatology, cognition and general social functioning in an Australian sample.

174. **MRI volumetry and shape analysis in frontotemporal dementia and schizophrenia**

**Supervisors:** Dr Dennis Velakoulis and Dr Mark Walterfang

**Project Site:** Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital

**Contact:** Dr Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.org.au

**Project Description:** It has been well recognised for over a century that some patients with schizophrenia develop a dementia but the nature of this dementia has remained unclear. Recent clinical, neuropathological and genetic studies have identified a previously unrecognised association between chronic schizophrenia and frontotemporal dementia. This project aims to examine whether the volume and shape changes identified in schizophrenia are quantitatively and qualitatively similar to patients with a frontotemporal dementia. In addition to demographic and diagnostic information a subset of the subjects have neuropsychological and bedside screening cognitive testing which can be correlated with brain structural volumes and shape.

**Aims:** To estimate and compare brain structure volume and shape in an existing database of MRI images of patients with chronic schizophrenia and frontotemporal dementia compared to control subjects.

**Methods:** Specific regions of interest to examine would include:
- Frontal and temporal lobes
- Orbitofrontal / dorsolateral / medial frontal cortex
- Hippocampus
- Insula cortex
- Superior temporal gyrus

Depending on the region of interest the project would require the learning of methods for analysing the region and developing a reliable method for this assessment.

**Outcome:** To assess and compare the nature and pattern of brain changes in chronic schizophrenia and FTD.
175. **Characterisation of physiological stress responses in patients with depression and epilepsy** - *also offered as MBiomedSc*

**Supervisors:** Dr Dennis Velakoulis, Dr Chris Turnbull and Professor Terry O’Brien

**Project Site:** Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital and Alan Gilbert Building, University of Melbourne

**Contact:** Dr Dennis Velakoulis  T: 93428750  E: dennis.velakoulis@mh.org.au

**Project Description:** Depression and epilepsy are disabling disorders that are common in the community. Both disorders have been shown to have effects on the human body’s physiological response to stress. These effects have been identified in both the autonomic nervous system (responsible for immediate responses to stress) and the hypothalamic-pituitary-adrenal axis (which mediates longer-term stress responses). However, it is not known whether these effects occur through similar mechanisms, partly because previous research has not focused extensively on patients with both disorders. This project will broaden our understanding of stress physiology in these disorders by assessing stress physiology in patients who have been admitted to hospital for assessment of seizures and have one or both disorders.

**Aims:** To compare the effects of depression and epilepsy, particularly temporal lobe epilepsy, human physiological stress responses and to assess whether these effects are additive or have a more complex interaction

**Methods:** The project will measure parameters of the physiological stress response in patients who have been admitted to investigate their epilepsy. Assessment of the autonomic nervous system will use a variety of measures of heart rate variability, and the HPA axis will be measured by the level of the hormone cortisol in saliva. Clinical data will be obtained by working with the clinical team caring for the patient and involves direct patient contact.

**Outcome:** To better understand stress physiology in depression (a psychiatric illness) and epilepsy (a neurological disorder) by assessing their interaction.

176. **Functional disconnections and the pathophysiology of psychosis** - *also offered as MBiomedSc*

**Supervisors:** Dr Nigel Jones and Prof Terence J O’Brien.

**Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville

**Contact:** Dr Nigel Jones  T: 9035 6402  E: ncjones@unimelb.edu.au

**Project Description:** Functional disconnections in cortico-thalamo-cortical (CTC) systems, the neuronal circuits of attention, cognition and perception, are thought to underlie dysfunctions of conscious integration such as those seen in schizophrenia. More than 80% of the neurons that make up the CTC systems are glutamatergic. There is considerable evidence to suggest that NMDA-type glutamate receptors are implicated in the pathophysiology of schizophrenia. Non-competitive NMDA receptor antagonists (PCP, ketamine, MK-801), at subanaesthetic doses, induce cognition impairment, schizophreniform psychosis, hallucinations, and exacerbate both positive and negative symptoms in schizophrenic patients. In rodents, ketamine produces a wide spectrum of abnormal behaviour relevant to schizophrenia. The neuronal mechanisms underlying transient disruption in NMDA receptor function remain to be determined. CTC circuits generate coherent synchronized gamma frequency (30-80 Hz) oscillations during conscious brain operations. Disruption of cognition-related coherences of gamma oscillations between cortical areas is a major functional abnormality in schizophrenic patients.

This project will explore the hypothesis that aberrant cortical gamma frequency activity induced by ketamine mediates alterations in behavioural activity, thereby linking NMDA-mediated dysfunction of neuronal activity to schizophrenic-like behaviour.

**Research plan:** Rats are surgically implanted with recording electrodes and connected to a computer facilitating measurement of the EEG and analysis of the effects of drugs on cortical brain rhythms in the gamma frequency. The resultant changes in cortical rhythms will be concurrently measured with either sensorimotor gating or working memory to establish a temporal and magnitudinal association between disruptions to gamma oscillations and behavior.

**Skills:** small animal surgery, EEG measurement, behavioural analysis.

177. **Antidepressants in epilepsy**

**Supervisor:** Dr Nigel Jones and Dr Sandy Shultz

**Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville.

**Contact:** Nigel Jones E: ncjones@unimelb.edu.au  Sandy Shultz E: sandy.shultz@unimelb.edu.au

**Project description:** Patients with epilepsy also frequently suffer from psychiatric disorders such as depression. As a consequence, many patients receive antidepressants to mitigate these mood disorders. While these are generally effective, the influence of antidepressants on the severity of the epilepsy in patients, and on the risk of developing epilepsy, has been little studied. Our provocative recent data suggest that antidepressants actually promote the development of epilepsy, which could have major implications for how these drugs are prescribed to patients. Using a
range of animal models, including post-traumatic epilepsy, this project seeks to characterise and understand the influence of antidepressants such as Prozac on epilepsy development. Available as Honours, Masters or PhD projects

Skills: Small animal handling; animal models of epilepsy; models of traumatic brain injury; small animal surgery and EEG recording; MRI, animal behaviour and cognition, molecular biology techniques, such as real-time qPCR, Western blotting; histology, including immunocytochemistry

178. Temporal lobe epilepsy, the HPA axis and depression - also offered as MBiomedSc

Supervisor: Prof Terence O’Brien, Dr Dennis Velakoulis
Project Site: Department of Psychiatry and Medicine Royal Melbourne Hospital
Contact: Terence O’Brien T: 8344 5490 E: obrientj@unimelb.edu.au
Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.org.au

Brief Summary: The key structures involved in mesial temporal lobe epilepsy – the hippocampus and amygdala – are critical components in the central regulation of the HPA axis. The implications of this have hardly been studied at all. Does the HPA axis function normally when someone has mesial temporal sclerosis (the usual pathology underlying TLE)? What happens to HPA axis function when a temporal lobe is excised to treat intractable TLE (temporal lobectomy)? There are good reasons to think the answers to these questions are very important for several reasons, e.g., glucocorticoids and stress have been shown in animal models of this kind of epilepsy to aggravate the disorder, to speed up its rate of development.

Project: We have a small preliminary study in progress, testing HPA function before and after temporal lobectomy. We’re using the dex/CRH test, doing this about 2 weeks before and at 6 and 12 weeks after surgery. We’re doing the same protocol with surgical control patients, having elective brain surgery for nonepilepsy conditions remote from the temporal lobe.

We think temporal lobectomy disinhibits the HPA axis, which may help explain the transient mood disturbance that occurs in temporal lobectomy patients in the early months following surgery.

This study will interest students interested in a topic that involves basic neuroscience and neuroendocrinology but also with a very immediate clinical relevance. It will involve contact with patients – in recruitment, obtaining informed consent, administering questionnaires and helping administer the dex/CRH test (a two hour procedure). It will also involve data analysis and writing-up in the usual way.

179. Does stress contribute to epilepsy? - also offered as MBiomedSc

Supervisor: Dr Nigel Jones and Prof Terence O’Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: Dr Nigel Jones T: 9035 6402 E: ncjones@unimelb.edu.au

Project description: Chronic stress is strongly linked to the development of psychiatric disturbances, such as depression and anxiety disorders. Interestingly, these disorders are prevalent in a high proportion of people suffering from epilepsy. Recent literature suggests that environmental exposures such as stress may also contribute to the development of epilepsy. This project aims to investigate this hypothesis, with a parallel focus on anxiety and depression-like behaviour.

Using rat models, this study will determine whether exposure to repeated stressful situations leads to a vulnerability to limbic epilepsy. It will also study whether psychiatric disturbances are enhanced in subjects who have experienced the stress.

The second stage of the project will investigate molecular and plasticity changes which occur after epilepsy to determine whether the stress can influence such parameters as stress receptor expression and neurogenesis.

Skills: Small animal handling and neurosurgery (electrode implantations), neurobehavioural testing and analysis, post-mortem stereology.

180. High Frequency Brain Wave Patterns in a Rodent Model of Schizophrenia

Supervisors: Dr Chris French, A/Prof Anthony Hannan, Dr Nigel Jones, Prof Terrence O’Brien
Project Site: Department of Medicine RMH, MBC Neurosciences Building, Parkville
Contact: Chris French frenchc@unimelb.edu.au

Project description: High frequency ("gamma") brain wave activity has been associated with higher cognitive activity in humans and animals, and has shown to be abnormal in psychosis and schizophrenia. Phospholipase C-β1 (PLCβ1) is an enzyme that is altered in human schizophrenia and a PLCβ1 knockout mouse displays deficits (locomotor hyperactivity, sensorimotor gating and cognitive impairment) homologous to those seen in schizophrenia. Remarkably, some of these deficits can be improved with antipsychotic drugs that are efficacious in humans.
The aim of these experiments is to characterize the gamma-frequency brain wave patterns of normal and PLCβ1 knockout mice, and to investigate whether the behavioural effects of antipsychotic drugs can be correlated with brain wave patterns.

These experiments are likely to lead to a better understanding of the functional abnormalities that lead to schizophrenia in humans and to suggest new and better forms of treatment.

181. Estrogen, antipsychotics and schizophrenia – also offered as MBiomedSc

Supervisors: Dr Andrea Gogos and Dr Snezana Kusljic
Project Site: The Florey Institute of Neuroscience and Mental Health
Contact: Dr Andrea Gogos E: andrea.gogos@florey.edu.au and Dr Snezana Kusljic E: skusljic@unimelb.edu.au

Project description: A role for sex hormones in the development of schizophrenia has been hypothesised to explain the observed gender difference in the age-of-onset with women presenting symptoms on average 3-4 years later than in men. Interestingly, clinical trials have shown that adjunctive estrogen treatment in women with schizophrenia can accelerate the beneficial effect of the antipsychotic treatment. Our laboratory is currently using a number of different rodent models to study the role of estradiol and testosterone in mediating several behaviours with relevance to schizophrenia and depression. The behavioural tests we use focus on drug-induced locomotor hyperactivity, sensorimotor gating, and learning and memory.

We have a number of projects available in this area. The aim of one study is to investigate the role of sex steroids in modulating the effects of antipsychotic treatment in rats. This will include both behavioural testing and analysis of cyclic adenosine monophosphate (cAMP) levels in the brains of these rats. Another study is focused on investigating the role of selective estrogen receptor modulators (SERMs) in regulating cognition. SERMs are potentially a safer alternative to estradiol, in terms of side-effects.

DEVELOPMENTAL PSYCHOBIOLOGY @ THE FLOREY

182. Early life stress and memory development

Supervisors: Dr Heather Madsen Co-supervisor: Dr Jee Hyun Kim
Project Site: Florey Institute, Parkville
Contact: heather.madsen@florey.edu.au

Project description: Early life experiences play a pivotal role in shaping personality and psychosocial functioning into adulthood. For example, early life adversity in humans is associated with increased risk of developing mental illnesses such as depression and anxiety. Given the importance of these first few years of life, it is interesting that most adults fail to recall autobiographical events from their early childhood years. Infantile amnesia is the term used to describe this phenomenon of accelerated forgetting during infancy, and it is not unique to humans. In fact, infantile amnesia has been observed in every altricial species examined; that is, animals that undergo extensive post-gestational development.

Many investigations into infantile amnesia have used Pavlovian fear conditioning in rats as a model of learning and memory. While adult rats exhibit excellent memory retention following just a single conditioning episode, infant rats rapidly forget fear associations over short intervals. Recently it has been shown that exposure to early life stress improves retention of learned fear in infant rats. The aim of this project is to investigate the neurobiological changes that underlie this early transition to adult-like memory.

183. Regulation of emotional memory across development

Supervisors: Dr Despina Ganella, Co-supervisor: Dr Jee Hyun Kim
Project Site: Florey Institute, Parkville
Contact: despina.ganella@florey.edu.au

Project description: Most anxiety disorders emerge during childhood, and individuals with childhood onset express more severe symptoms than do individuals who have adult onset. In fact, there is growing recognition that mental disorders may actually be developmental brain disorders and, as such, treatment strategies should focus on the young population. Currently, the effective treatments for anxiety disorders are cognitive-behavioural therapies that rely on inhibition of emotional memory. This project will examine inhibition of emotional memory throughout development using Pavlovian fear conditioning as a model of anxiety disorders in rats.
184. The role of dopamine receptor 1 vs 2 in adolescent vulnerability to anxiety.

Supervisors: Dr Jee Hyun Kim; Dr Heather Madsen
Project Site: Florey Institute, Parkville
Contact: Dr Jee Hyun Kim Ph: 9035 6623; Email: jeek@unimelb.edu.au

Project description: Anxiety disorders are a major worldwide public health concern, and according to the Australian Bureau of Statistics (ABS; 2007) ~1 in 4 Australians suffer from a clinically diagnosed anxiety disorder at least once in their lifetime. While these disorders can affect people of all ages, adolescence represents a particularly vulnerable period. For example, the median age of onset for anxiety disorders is 14, and people who experience anxiety early in life are more likely to exhibit more severe symptoms later on in life. One of the main focuses of our laboratory lies in determining what neurobiological factors underlie this increased vulnerability observed in adolescents, with the aim of developing more effective therapeutic interventions.

Fear conditioning is the most commonly used model for studying anxiety disorders in rodents. Extinction refers to the decrease in fear due to the fear-eliciting cue no longer being accompanied by an aversive event, and this forms the basis of exposure therapies used for the treatment of anxiety disorders in humans. Using a fear conditioning/extinction paradigm we have shown that extinction training is less effective in P35 (adolescent) compared to P70 (adult) rats due to maturational differences in the prefrontal cortex (PFC). This difference may be due to the well-established disrupted balance of dopamine receptor 1 (DR1) vs 2 (DR2) signalling during adolescence, however this has yet to be directly demonstrated.

The aim of this project is to investigate potential age-related differences in the activation of D1R vs D2R in the PFC of adult vs adolescent mice in response to extinction of conditioned fear. Mice that express green fluorescent protein- (GFP) tagged D1R and D2R will be utilised, and Fos/GFP immunohistochemistry will be performed to identify activated D1R and D2R neurons. The effect of the D2 partial agonist Aripiprazole upon extinction consolidation and D1R/D2R activation in the PFC will also be examined.

185. Neural circuitry underlying extinction of fear across development.

Supervisors: Dr Jee Hyun Kim; Dr Despina Ganella
Project Site: Florey Institute, Parkville
Contact: Dr Jee Hyun Kim Ph: 9035 6623; Email: jeek@unimelb.edu.au

Project description: Most anxiety disorders emerge during childhood, and individuals with childhood onset express more severe symptoms than do individuals who have adult onset. In fact, there is growing recognition that mental disorders may actually be developmental brain disorders and, as such, treatment strategies should focus on the young population. Currently, the effective treatments for anxiety disorders are cognitive-behavioural therapies that rely on the process of extinction. Extinction is the decrease in fear responses expressed to a fearful stimulus due to the repeated exposure to the stimulus without any aversive outcome. We have accumulated powerful evidence supporting that extinction is erasure in juvenile rats whereas extinction is new learning in adult rats. This developmental transition from erasure to new learning appears to be driven by changes in the functionality and the circuitry between the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC). This project will characterise the functional organisation of that neural circuitry using intracranial microinfusions of retrograde tracers (cholera toxin b subunit and fluorogold), using Pavlovian fear conditioning as a model of post-traumatic stress disorder in developing rats.
Early studies assessing adolescent brain development point toward a role for neurotrophins and sex steroid hormones in regulating cognitive ability during this period.

Current projects in the laboratory include investigations into the role of estrogen-based treatments in the regulation of neural firing and cognitive ability, utilizing electrophysiology and behavioural neuroscience techniques. Viral gene-knockdown studies are currently underway, investigating the cell-specific effects of specific genes in regulating GABAergic interneuron function, neuronal firing and cognitive function. So far, our research has led to a better understanding of the pathways that regulate cognitive ability.

**Project Site:** Behavioural Neuroscience Laboratory, The Florey Institute of Neuroscience and Mental Health
**Contact:** Rachel Hill  T: 9035 6661  E: rachel.hill@florey.edu.au

186. Understanding the transcriptional effects of estrogen based therapies in the CNS.
**Project description:** Involves a novel reporter mouse, recently imported from the University of Milan, Italy, in which a luciferase reporter has been inserted into an estrogen response element-containing promoter. Essentially this model allows us to visualize estrogen receptor transcription in the brain via bioluminescence imaging, during different physiological states and following drug administration. This highly novel model will allow us to determine the action of different selective estrogen receptor modulators (SERMs) with regional specificity in the brain. This knowledge, given the recent push for the use of these drugs in psychiatric disorders, is highly relevant in ensuring clinical safety and efficiency. In combination with the viral knockdown studies, the collective data generated by these studies may inform the development of more potent and safer SERMs.

187. Deciphering the receptor mediated pathways which regulate neural synchrony and cognitive ability
**Project description:** Our recent data have uncovered a role for estradiol in regulating cognitive function and neural oscillatory activity in the hippocampus. Neural oscillations in the high gamma frequency have been found to be disrupted in patients with schizophrenia. Importantly, our data demonstrate a specific effect of estradiol on this gamma frequency oscillatory activity recorded in mice while they are actively engaging in a spatial memory task. Project 2 will investigate which estrogen receptor pathway is involved in regulating gamma power during spatial memory recall. Mice will be ovariectomized and treated with selective estrogen receptor agonists. Recording electrodes will then be surgically positioned into the hippocampus and in vivo recordings will be taken during a number of learning and memory paradigms. This study will determine which receptor agonist shows the greatest effects on cognitive ability in both male and female mice and in doing so may guide the development of more potent SERMs that target specific estrogen receptors.

188. Towards preventative prenatal treatment strategies for schizophrenia
**Project description:** Our earlier studies found an important role for neurotrophins in adolescent brain development. In recent studies, we have also established a role for BDNF in early brain development (prenatal). Future studies, in collaboration with Prof. David Walker (Ritchie Centre), will investigate the effect of maternal infection, a significant risk factor for a variety of mental illnesses, on prenatal brain development — with a specific focus on neurotrophic factors. Here we hope to trial novel natural compounds with a high binding affinity for neurotrophin receptor, TrkB, following maternal infection to prevent developmental and behavioural disturbances caused by maternal infection. Overall these studies will provide a narrative of the molecular alterations throughout early development that precede behavioural disturbances, and in doing so, will identify novel therapeutic strategies to be used in the clinical setting.

189. Understanding the genetic contribution to schizophrenia
**Project description:** A major goal of this research team is to be able to translate this exciting basic neuroscience research to the clinical setting. Some of our preclinical data point to complex gene x environment and gene x treatment interactions whereby the treatment response to a cognitive task is highly dependent on the expression of a particular gene. Spring-boarding from these promising findings, future studies in collaboration with Prof. Jayashri Kulkarni and Prof. Suresh Sundram will aim to further explore these interactions in patients with psychiatric disorders, via genome sequencing and cognitive testing. These research projects may push the field towards more patient-specific treatment strategies, which, given the heterogeneity of these disorders, is the logical evolution of future treatment approaches. Furthermore, given the escalating rates of mental illnesses, low compliance rate of current antipsychotics, and the lack of truly effective drugs that treat the full spectrum of symptoms, these targeted treatment strategies provide a novel tangible avenue that is much sought after in the clinical setting.

Our collaborative research team will bridge the gap between basic neuroscience and clinical application by combining our multidisciplinary expertise to gain a complete understanding of the disease mechanism. Ultimately, our long-term goal is to provide the most effective and safe treatment strategies for people living with a mental illness.
190. Imaging predictors of neurological recovery post acute stroke intervention  
Supervisors: A/Prof. Bernard Yan, A/Prof. Peter Mitchell, A/Prof. Rick Dowling  
Project Site: Royal Melbourne Hospital  
Contact: Bernard.Yan@mh.org.au  
Project Description: Stroke is the second leading cause for death and the leading cause for disability worldwide. It accounts for significant financial burden up to $5 billion on health care costs associated with stroke in Australia in 2012 alone. Rapid treatment with thrombolyis (clot busting medication), within 4.5 hours of ictal onset, increases the chance of blood flow restoration to the ischemic area and decreases the risk of disability and dependence. This benefit diminishes and approaches parity at approximately 6 hours from stroke onset. CT scan is a widely used imaging modality for the initial evaluation of stroke. The Alberta Stroke Program Early CT Score (ASPECTS) tool was developed to provide a standard CT scan with a reproducible grading system. It is a semi-quantitative method of defining infarct extent in the middle cerebral artery (MCA) territory. However, very few studies have examined the impact of time on outcome as adjudicated by ASPECTS. The aim of this retrospective analysis study on an existing prospective database is to assess the impact of time on ASPECTS score and its correlation to functional outcome at 3 months after an acute ischemic stroke. We hypothesize that, in patients with acute ischaemic stroke treated with IV tPA, the predictive capacity of ASPECTS score of clinical outcome increases with time from stroke onset.

191. Continuous monitoring of motor recovery post acute stroke rescue: development of a broadband-based portable motion detector (REWIRE system) - also offered as MBiomedSc  
Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
Location: Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
Contact: Bernard.Yan@mh.org.au  
Project Description: Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. The clinical manifestation is acute loss of neurological function e.g. paralysis of arms and legs.  

One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) in order to unblock the blocked artery. A proportion of patients will experience recanalization (reopening) of blocked arteries with consequent recovery of arm and leg movements (motor recovery).  

The monitoring of motor recovery is by clinical observation is critical in the management of stroke patients. Patients who do not exhibit early motor recovery post thrombolysis may benefit from more aggressive treatment. However, the current clinical observation paradigm is time consuming and subjected to inter-observer bias. We aim to validate the clinical utility of a novel portable motion detector (REWIRE system) which allows for continuous monitoring of motor recovery in stroke patients treated with thrombolysis. The findings of the study may inform future decision to mandate continuous motor monitoring of patients post thrombolysis. We envisage that the study findings may lead to investigations of the REWIRE system in other neurological diseases e.g. Epilepsy.  

Research Plan: Human Ethics Committee approval has been obtained. The first phase of the project has been completed with 10 healthy controls. The second phase of the project aims to study the motor recovery of stroke patients. We hypothesize that the motion detector (REWIRE system) is able to better detect motor recovery compared to standard clinical observations. Inclusion criteria: acute stroke patients admitted to RMH Stroke Care Unit. Methods: study subjects will wear the REWIRE system on each limb for 4 hours. Accelerometry raw data will be continuously transmitted by WIFI to a base station for analysis. Study subjects are also examined by standard clinical examination for comparison.

192. Acute stroke rescue: clot retrieval. Does imaging characteristics predict the histopathology of clot composition? - also offered as MBiomedSc  
Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
Location: Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
Contact: Bernard.Yan@mh.org.au  
Project Description: Acute stroke is caused by a blockage of one of the arteries in the brain by clot(s). The clinical consequences result from acute neuronal failure secondary to precipitous decrease in arterial perfusion. Apart from intravenous thrombolytics, mechanical clot retrieval holds promise as an effective means to reopen blocked arteries.
However, the success clot retrieval depends partly on clot composition. It is known that clots undergo pathological change from red-cell dominant, then to fibrin dominant and finally to organized fibrin strands. It is thought that clots with organized fibrin are the most resistant to mechanical retrieval. The difficulty is that up till now, there are no reliable methods to judge clot composition prior to mechanical retrieval. In this project, we aim to employ advanced CT angiogram imaging pre-procedure and to correlate the imaging characteristics with histopathological examination of clots. The implication of the findings is that we may be able to more accurately predict the success rate of clot retrieval and to triage patients prior to invasive therapies.

**Research plan:** Human research ethics committee approval has been obtained. Acute stroke patients eligible for acute clot retrieval will be recruited prospectively into the study. Imaging modalities include plain CT, CT angiogram and CT perfusion (this is part of standard stroke treatment protocol). Clot retrieval will be performed by RMH neurointerventionists. Clot samples will be sent for standard H & E staining and immunohistochemistry for platelet markers. The imaging parameters will be correlated with histopathological examination of clots and the degree of success of clot retrieval and vessel recanalization.

**NEWBORN RESEARCH**

193. **Breathing support in extremely premature babies – reducing nasal trauma**  
**Supervisors:** Dr Louise Owen, Dr Brett Manley, Dr Jennifer Dawson, Prof. Peter Davis  
**Project Site:** The Royal Women’s Hospital  
**Contact:** E: louise.owen@thewomens.org.au / brett.manley@thewomens.org.au  
**Project description:** This exciting project is a clinical trial in very premature babies in the intensive care nursery at the Royal Women’s Hospital.

Very premature babies need help to breathe for many weeks after they are born. There are several ways to support breathing but none of them are perfect. One standard method uses short prongs placed in the babies’ nostrils to apply pressurised oxygen. This system increases oxygen levels and helps hold the lungs open. Unfortunately the prongs themselves can damage the delicate tissues around the nose, causing skin breakdown and bleeding. One potential way of reducing this nasal trauma is to place a special barrier dressing over the tip of the nose, but the dressings have not been rigorously tested. We are currently designing a year-long randomised trial to assess the impact of using these dressings. We are aiming to recruit 120 babies into the trial, commencing in February 2016. With comprehensive support from a dedicated, experienced clinical research team the successful applicant will be able to run this project. They will have direct patient contact, be able to attend preterm births, be responsible for recruiting babies to the trial, collecting and analysing data, and writing up the results for presentation and publication.

**OPHTHALMOLOGY**

194. **What are the genes affected in structural renal disease and renal complement diseases? – also offered as MBiomedSc**  
**Supervisors:** Prof Savige and A/Prof Deb Colville  
**Project Site:** Department of Medicine, Royal Melbourne Hospital  
**Contact:** Prof Savige on 8344 3260 or j.savige@unimelb.edu.au  
**Project description:** The genes for many forms of inherited renal disease are still unknown. We have several families with inherited disease in whom we will try to identify the abnormal genes. This involves carefully characterizing clinical features, collecting DNA, undertaking exomic sequencing, and checking for mutations in candidate genes. Any possible mutation will then be confirmed in other affected family members by DNA sequencing. Techniques to be used and skills acquired: This project involves patient contact, lab work and how to interpret DNA sequence abnormalities.

Feasibility: All the techniques for this project are already available in our laboratory.

195. **Small vessel disease causing stroke and dementia – also offered as MBiomedSc**  
**Supervisors:** Prof Savige, A/Prof Deb Colville  
**Project Site:** Department of Medicine, Royal Melbourne Hospital  
**Contact:** Prof Savige on 8344 3260 or j.savige@unimelb.edu.au
**Project description:** This project involves taking retinal photographs in patients undergoing brain MRI and correlating any small vessel disease in the retina with strokes/white matter ischemia. This study is to investigate whether retinal photographs might be useful in predicting patients who will develop a stroke and in whom greater attention to blood pressure control might prevent disability and even death.

Techniques to be used and skills acquired: This project involves patient contact, and learning how to take retinal photographs and how to interpret retinal abnormalities.

Feasibility: We already have Human Research Ethics Committee Approval for this project, and many of the medical students who have undertaken similar projects during a research year have achieved a publication from their work study. Nevertheless whenever the small vessels in the heart are affected, small vessels are diseased throughout the body. This includes the vessels in the retina, which are very accessible using a retinal camera and photography. So we propose to examine the retinal small vessels as a model for the coronary arterioles and determine whether renal failure or diabetes means these vessels are diseased and respond less well to medication.

This study involves recruiting patients from the wards with renal failure or diabetes and testing the effect of a tablet that usually dilates small vessels. You will help the patient fill out a questionnaire and also take their blood pressure and retinal photographs, and then review the photographs under the supervision of an ophthalmologist. In addition the retinal photos will be sent to the Centre for Eye Research Australia for the vessel diameters to be measured precisely. The aim of this project is then to determine whether small vessels are less responsive in diabetes and renal failure, and whether medication doses should be increased. The analysis includes univariate and multivariate statistics and backwards linear regression (we will help you with the statistics).

**196. The Contribution of Endothelial Progenitor Cells to Retinal Vascular Regeneration**

**Supervisor:** Dr R C Andrew Symons (Department of Ophthalmology, RMH; Department of Surgery (RMH), University of Melbourne)

**Project Site:** Department of Surgery, Royal Melbourne Hospital

**Contact:** Dr Andrew Symons Tel: 9342 2166 Email: andrew.symons@mh.org.au

**Aim:** To determine the role of endothelial progenitor cells in retinal revascularization in the oxygen induced retinopathy model of retinopathy of prematurity.

Retinal vasculopathies are some of the most important causes of blindness. Diabetic retinopathy is the most significant cause of visual disability in working adults in the developed world. Retinopathy of prematurity is one of the most significant causes of childhood blindness. It is unknown how important vascular regeneration is to delaying development of diabetic retinopathy, and it is unknown to what extent the arrest of vascular development that precedes the development of retinopathy of prematurity may be modulated by modifying angiogenic processes. Treatments that optimize vascular regeneration may potentially have an enormous impact on reducing visual loss in these diseases.

Our previous work has found a gene that controls numbers of endothelial progenitor cells in the bone marrow, and also the number of endothelial progenitor cells being recruited to the retina during vascular regeneration after hypoxic vaso-obliteration. The number of retinal endothelial progenitor cells appears to control the rate of revascularization and the severity of the pathological angiogenesis in the oxygen induced retinopathy model of retinopathy of prematurity.

This project involves the use of reporter mice expressing green fluorescent protein under the control of the Id1 allele to identify endothelial progenitor cells in the retina. Mice homozygous for this allele will be used to determine whether endothelial progenitor cell deficiency leads to a deficit in retinal vascular regeneration.

Future work on this project may lead to development of therapeutic strategies to reduce the severity of retinopathy of prematurity and diabetic retinopathy.

**Skills:** Animal handling skills, design of mouse breeding strategies, retinal fluorescein-dextran perfusions, immunofluorescence microscopy, flow cytometry, data analysis.

Please note: this subject is only offered for Round 2 - late applications. Late applications will open in early December. Please check the ‘How to Apply’ website for details: [http://sc.mdhs.unimelb.edu.au/how-apply](http://sc.mdhs.unimelb.edu.au/how-apply)
**PHARMACOGENETICS AND PERSONALISED MEDICINE**

197. **Pharmacogenomics in IBD - also offered as MBiomedSc**  
**Supervisors:** Professor Finlay Macrae and Prof Les Sheffield  
**Project Site:** Colorectal Medicine and Genetics, The Royal Melbourne Hospital  
**Contact:** Prof Finlay Macrae E: finlay.macrae@mh.org.au  
**Project description:** The Royal Melbourne Hospital, with GenesDX, is pioneering the implementation of a pharmacogenomics clinical support program. In the case of inflammatory bowel disease, this relates to the use of thiopurines. The project will assist in the implementation of the program and its evaluation. It will gauge the clinical utility of TPMT genotyping and the clinical decision support tools that will be built into the program, and thiopurine metabolite testing, in the management of inflammatory bowel disease.

198. **Development of a low cost, point-of-care diagnostic test to prevent abacavir hypersensitivity**  
**Supervisors:** Prof Patrick Kwan, Prof Stan Skafidas  
**Project sites:** Department of Medicine (Royal Melbourne Hospital), Centre for Neural Engineering  
**Contact:** Professor Patrick Kwan, Department of Medicine (RMH)  
E: patrick.kwan@unimelb.edu.au  
**Project description:** Abacavir is a nucleoside analog reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS. 5-8% people develop hypersensitivity to abacavir. It has been found that abacavir hypersensitivity is strongly associated with HLA-B*57:01, and pre-therapy HLA testing is recommended by regulatory agencies and all major treatment guidelines. However, conventional testing is laboratory based with long turnaround time and is not accessible or affordable for people living in developing countries where many people with HIV live.  
A monoclonal antibody that recognises HLA-B*57:01 has been developed. This project aims to use this antibody to develop a simple, rapid, low cost HLA-B*57:01 test kit.

199. **Express ambulatory point-of-care molecular diagnosis - also offered as MBiomedSc**  
**Supervisors:** Professor Patrick Kwan, Dr Marian Todaro  
**Project Site:** Department of Medicine (RMH), Melbourne Brain Centre (Parkville), Centre for Neural Engineering  
**Contact:** Patrick Kwan, Department of Medicine (RMH)  
E: patrick.kwan@unimelb.edu.au;  
Dr Marian Todaro, Department of Neurology  
E: Marian.Todaro@mh.org.au  
**Project Description:** This is an inter-disciplinary, technology driven program with multiple projects that aim to develop point-of-care molecular diagnostics for a range of important diseases, including epilepsy, HIV infection, coeliac disease, and malaria. Conventional laboratory tests have been indispensable for disease diagnosis. However, their high costs and need for skilled personnel to operate complicated equipment have limited their abilities to cope with escalating demand from the growing population, and the need for application in resource poor and remote areas. Therefore, development of portable, on-site, point-of-care (POC) testing devices has become increasingly important in medical research. POC testing performed at the time of consultation will allow the results to be used for making immediate, informed clinical decisions on patient care. In short, it will transform medical practice.  
This innovative project will combine novel biochemical and engineering technologies that will perform molecular diagnosis rapidly using compact ‘smart’ devices at the point of care. The platform technology can be customised for any molecule of interest, including DNA, RNA and protein. There is very strong potential for technological innovation and eventual application and commercialisation of the devices to meet the rapidly expanding need of molecular diagnosis.  
The global molecular diagnostic market is estimated to be US$21.7 billion in 2014 with projected 5-year compound annual growth rate (CAGR) of 12.5% to reach $45.2 billion in 2020. In this market, POC testing using lab-on-chip systems is the fastest growing segment, valued at >$2 billion in 2014 with CAGR of 16.5% (BCC Research, 2015).  
This project is open for different students with different skills and background, including:  
- Molecular biology  
- Electrical engineering  
- Electronic engineering  
- Software engineering  
Potential students are strongly encouraged to contact the supervisors to discuss their suitability for the project based on their interests and skills.
200. A decision support system for implementation of pharmacogenomics in epilepsy treatment - also offered as MBiomedSc
Supervisors: Professor Patrick Kwan, Professor Terence O’Brien, A/Professor Les Sheffield
Project Site: Department of Medicine (RMH)
Contact: Professor Patrick Kwan, Departments of Medicine and Neurology,
E: patrick.kwan@unimelb.edu.au

Project description: Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. Yet its uptake has been limited partly owing to the lack of appropriate systems that can support its widespread application in clinical practice. Through partnership with a business enterprise, The Royal Melbourne Hospital is pioneering the implementation of such a system in Australia. One of the projects relates to HLA genotyping prior to the prescription of certain antiepileptic drugs to prevent severe, life-threatening allergic skin reactions. This project will assist in the development, implementation and evaluation of the program by collecting and analysing the relevant clinical and test information.

201. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire - also offered as MBiomedSc
Supervisors: Professor Patrick Kwan, Dr Nicole Mifsud
Project Site: Department of Medicine (RMH), University of Melbourne, Department of Biochemistry & Molecular Biology, Monash University
Contact: Professor Patrick Kwan, Departments of Medicine and Neurology,
E: patrick.kwan@unimelb.edu.au

Project description: Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen derived peptide antigens selected by different HLA allotypes. Recently, a growing number of immunologically based drug reactions have been found to be strongly associated with specific HLA alleles. In particular, HLA-B*15:02 and HLA-A*31:01 are associated with severe skin reactions caused by certain antiepileptic drugs, but little is known about the underlying mechanisms of these associations. Recent research has demonstrated that direct binding of the drug to the HLA molecule led to changes in the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and driving T-cell activation. This project aims to find out whether this mechanism also applies to the case of the interactions between antiepileptic drugs and these HLA alleles.

202. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effect - also offered as MBiomedSc
Supervisors: Dr. Marian Todaro, Dr Slave Petrovski, Prof Terence O’Brien, Prof Patrick Kwan
Project Site: The Comprehensive Epilepsy Program, Department of Neurology, The Royal Melbourne Hospital.
Contact: Dr Marian Todaro T: 9342 7500 E: Marian.Todaro@mh.org.au; Dr Slave Petrovski E: slavep@unimelb.edu.au; Professor Terence O’Brien T: 8344 5479 E: obrienti@unimelb.edu.au

Project Description: This study aims to investigate the individual responses of patients who developed a rash or drug-induced hepatitis due to an anti-epileptic drug (AED), and link this information to the genetic profile of each patient – in particular that for the human leukocyte antigens (HLA). The results will help to identify genetic markers that could predict when a patient is at risk of having side effects with a particular medication.

Previous experience has shown that individuals vary greatly in their responses to drugs. Although medication is effective and well tolerated in most patients side-effects can necessitate treatment changes. One of the most common, and potential serious, types of side effects to anti-epileptic drugs is hypersensitivity reactions - including generalised skin rashes, Steven Johnson Syndrome (SJS), and drug-induced hepatitis. It has been shown that genetic factors play an important role in determining an individual’s response to medication. Recently, the occurrence of SJS in Asian patients taking carbamazepine has been repeatedly associated with the carriage of a particular HLA antigen, HLA-B*1502. However, this association does not persist in non-Asian populations and HLA associations in other populations, or with other types of AED-induced hypersensitive reactions, have not yet been identified. Understanding why responses vary has the potential to improve the safety and effectiveness of medical treatment for various conditions.

This project will utilize an international unique cohort of more than 400 patients who have been prospectively enrolled and followed following starting treatment with an AED for the first time. The HLA profiles of patients who developed hypersensitivity reactions will be compared with those who took the same drug but did not develop any such reactions. The goal of this research is to eventually allow the choice of medication to be tailored to an individual’s specific genetic profile.
203.  **Pharmacogenetics: do mutations in CYP 2C19 alter the clinical effectiveness of clopidogrel in patients with cerebrovascular disease? - also offered as MBiomedSc**

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**Supervisors:** A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
**Location:** Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
**Contact:** A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital,  
T: +61 3 9349 2477 / F: +61 3 9349 4489, Email: bernard.yan@mh.org.au  
**Project Description:** Stroke is the third leading cause of death in Australia. The prevention of recurrent strokes is an important strategy to improve health and reduce medical costs. Globally, anti-platelet agents (aspirin, clopidogrel, prasugrel etc) are the first-line treatment to prevent further ischaemic events (i.e. strokes). Anti-platelets work by inhibiting platelet aggregation with consequent reduced risk of artery blockages. However, up to 30% of patients are “resistant” to clopidogrel treatment. Of note, activity of clopidogrel is critically dependent on its conversion from the pro-drug to its active form by a member of the P 450 family of enzymes (CYP 2C19). A genetic mutation, e.g. CYP 2C19*2, predicts lower levels of the active form clopidogrel leading to failure of platelet inhibition. We hypothesize that patients with genetic mutations of CYP 2C19 (e.g. CYP2C19*2) will demonstrate clopidogrel failure and increased risk of stroke.  
The results will have the potential to change clinical practice in the prescription of clopidogrel.

**Research Plan:** Our project is part of a large pharmacogenomics project led by Professor Patrick Kwan’s research group. Our research arm focuses on CYP 2C19 genetic mutation and its clinical consequences. Human ethics committee approval has been obtained to test anti-platelet resistance. Inclusions criteria: patients previously exposed to clopidogrel or with plans to start clopidogrel (e.g. aneurysm coiling, pipeline flow diversion device implantation etc). Methods: all patients will be tested for CYP2C19 genetic status by PCR and a novel DNA amplification technique. The patients will be followed clinically and by neuroimaging to identify recurrent cerebral ischaemic events.

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Skills to be learned: Human genomics, immunogenetics, bioinformatics, clinical phenotyping, multivariate statistics.

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204. **A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy - also offered as MBiomedSc**

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**Supervisors:** Professor Terence O’Brien, Professor Frank Vajda and Dr Slave Petrovski - Epilepsy and Neuropharmacology Group, The Department of Medicine: The Royal Melbourne Hospital  
**Project Site:** The Department of Medicine (RMH)  
**Contacts:** Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au; Frank Vajda E: vajda@netspace.net.au; Slave Petrovski E: slavep@unimelb.edu.au  
**Project Description:** Valproate is the most widely prescribed AED for children and adults with epilepsy. Despite the increased risk associated with taking AED in pregnancy, most women with epilepsy who become pregnant, or plan to do so in the near future, cannot simply cease the drugs because of the risk to the health and safety of the mother and child of uncontrolled seizures. The development of methods that would allow the prediction that a specific drug would be associated with a higher risk of a birth defect in a particular woman would be of great potential benefit. There is evidence from family and twin studies that genetic factors may play a role in determining predisposing an individual to having a child with an AED associated birth defect. The Australian Register of Anti-epileptic Drugs in Pregnancy has been established in an attempt to obtain more accurate information about the risks of specific AEDs. This is a prospective, voluntary, telephone interview based study that enrolls pregnant women with epilepsy, prior to the outcome of the pregnancy being known, and follows the outcomes of their pregnancies. The study has been running since July 1999, and to date has enrolled more than 1600 pregnant women.

This study will attempt to identify genetic markers that predict the risk of valproate-induced birth defects. Participants will be identified through the Australian Registry of Anti-epileptic drugs in pregnancy. Women with epilepsy who were taking an AED in the first trimester, and their partners, will be offered enrollment. Two types of genetic tests will be performed:

- **A case-control genetic association** studies comparing genetic information from mothers and infants taking a valproate AED during the first trimester with those who were taking the same valproate but did not have a child with a birth defect
- **A transmission disequilibrium test (TDT),** design will be also be employed. This test looks for significant disequilibrium in the transmission of the allele of interest in the patient with a characteristic of interest. It therefore eliminates any potential sources of bias between the affected patients and non-affected controls, which may occur in case-control association studies. Blood for genetic analysis would be taken from the mother, father and child.
**POPULATION HEALTH**

205. **Life-long Lifestyle Factors for Healthy Ageing – also offered as MBiomedSc**

**Supervisor:** A/Professor Cassandra Szoeke  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic 3052. Women’s Healthy Ageing Project (WHAP)  
**Contact:** A/Professor Cassandra Szoeke T: 61 3 8344 1835  
E: cszoeke@unimelb.edu.au  

**Project Description:** Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. For example, smoking, alcohol consumption and a lack of physical activity have been linked to an increased rate of cognitive impairment and cardiovascular diseases. Studies investigating lifestyle factors have been limited by cohort sampling bias, cross sectional designs, short follow-ups and small sample sizes. Furthermore, the frequency and intensity of lifestyle alteration is still not defined. In this project we examine a 20 year longitudinal dataset to determine the influence of lifestyle (i.e. alcohol consumption, smoking, diet and physical activity) on cognitive performance and health.

This project will involve direct hands-on participant evaluation. You will also have the opportunity to work with a rich database with lifestyle data that spans over 20 years. As well as an opportunity for publication.

206. **Iron and Fatigue – also offered as MBiomedSc**

**Supervisors:** A/Professor Cassandra Szoeke  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic, 3052.  
**Contact:** A/Professor Cassandra Szoeke T: 61 3 8344 1835 F: 61 3 9387 9384  
E: cszoeke@unimelb.edu.au  

**Project Description:** Iron deficiency is prevalent in ageing women. Studies have shown that iron deficiency results in fatigue, reduced physical performance and impaired cognition. These symptoms are commonly reported in ageing populations. The Women’s Health Ageing Project is an epidemiological sampled longitudinal prospective study that contains 20 years’ worth of data on a number of measures including blood, cognition, diet and lifestyle, mood and wellbeing, hormones, illnesses, bone, and genes among others. This unique resource will therefore have the potential to identify new preventive health interventions and address issues relating to social determinants of health and health inequalities through social epidemiology across two decades. Over a hundred papers on this study have been published in peer reviewed journals. The results of this study have been internationally recognised and contributed significantly to the understanding of healthy ageing.

207. **Vitamin D deficiency and balance - also offered as MBiomedSc**

**Supervisors:** A/Professor Cassandra Szoeke, Professor Meg Morris  
**Project Site:** Dept of Medicine, UoM, Parkville, Vic 3052.  
**Contact:** A/Professor Cassandra Szoeke T: 61 3 8344 1835  
E: cszoeke@unimelb.edu.au  

**Project Description:** Vitamin D is made in the skin, a process that requires sun exposure, ingestion in the diet or being taken as a nutritional supplement. Adequate levels of vitamin D are essential for healthy bones and muscle function, and research has only recently started to associate low levels of vitamin D to depression and other mood related disorders. The effects of mild to moderate deficiency are less clear-cut, but symptoms may include muscle pain, weak bones, low energy, fatigue, lowered immunity, and symptoms of depression; moods swings, and sleep irregularities. In Australia, mild to moderate vitamin D deficiency is relatively common in the adult population, but the health consequences of this deficiency in apparently healthy adults are poorly understood. It is also not clear below which level in the blood, vitamin D level mood disorders may arise. The purpose of this project is to investigate the consequences of mild to moderate vitamin D deficiency (blood already collected) on mood including depression, anxiety, and wellbeing (measures already collected) in healthy women from the internationally re-known Women’s Healthy Ageing Project (WHAP).

**Opportunities:** You will have the opportunity to work with an internationally re-known cohort and research team each with international recognition. (Prof L Dennerstein, Prof D Ames, Dr C Szoeke)  
The study has data over 20 years already collected.  
There is opportunity for publication within one year.  
This project will suit a candidate with an interest in media or commercialisation.

208. **An epidemiological exploration of the HIV cascade in Victoria**

**Supervisors:** A Prof Mark Stoove  
**Project Site:** Burnet Institute  
**Contact:** E: stoove@burnet.edu.au
Project description: In Australia, more than three quarters of new HIV diagnoses are made among men who have sex with men (MSM), with annual diagnoses continuing to increase. Our understanding of HIV prevention has increased substantially over recent years, with prevention increasingly focused on timely diagnosis and the early initiation of HIV therapy. To assess the success of Australia’s HIV prevention strategies, it is therefore vital to be able to monitor effectively the “HIV Cascade” – the proportion of people with HIV who are diagnosed, the proportion of those diagnosed who are receiving HIV treatment and the proportion of people on treatment who are virally suppressed.

Burnet Institute (in collaboration with the Kirby Institute in at the University of NSW and the Alfred Hospital) is developing a new and innovative linked surveillance system to monitor the progress of individuals through the HIV Cascade. An opportunity exists for students interested in the epidemiology and prevention of HIV to work with this novel data. Outcomes will explore the system’s effectiveness in monitoring the trajectories of individuals through the HIV Cascade and the extent to which HIV transmissions in Australia are influenced by the timing of diagnoses and entry into care and treatment.

This project will involve working with both cross-sectional and prospectively linked clinical and behavioural data from the HIV Cascade Sentinel Surveillance System. Training in the management of complex epidemiological datasets will occur alongside the analysis and interpretation of time varying prospective data.

209. Sexting, porn, and Tinder. An investigation of education and health promotion needs and evidence
Supervisors: Dr Megan Lim
Project Site: Burnet Institute
Contact: E: lim@burnet.edu.au
Project description: Access to new technologies could present novel risks to young people’s sexual health. The emerging popularity of sexting, online pornography use, and dating apps has been linked in some studies to sexual risk behaviours (e.g. not using condoms). There is very little known about how to educate young people about these topics. Many previous programs have taken a fear-based approach which tends to exaggerate the risks of these behaviours and promote abstinence as the only option. This project will investigate previous campaigns, survey the opinions and needs of young people, schools, parents, and health promotion practitioners, and provide recommendations for future campaigns. A mixed methods approach will involve content analysis and review of existing health promotion, online surveys, interviews, and focus group discussions.

210. Sex, drugs and rock’n’roll: Young people and risk behaviours
Supervisors: Dr Megan Lim
Project Site: Burnet Institute
Contact: E: lim@burnet.edu.au
Project description: Sexually transmitted infections (STI) are on the rise among young Victorians. Since 2005, we have surveyed over 9,000 people aged between 16 and 29 years of age at Melbourne’s Big Day Out about sexual risk behaviour and drug use. From 2015, we have moved the survey to an online form. Questions have covered participant’s sexual histories, condom use, knowledge and perceptions of STIs, and STI testing histories. We ask about alcohol and other drug use, and other risks and behaviours such as gambling, diet and exercise, contact with police, mental health, and smoking. There is also a series of questions concerning media use, e.g. pornography, sexting, social media and smartphones, online gambling. The student project could focus on one of these issues or a range of themes. These findings, in the context of current public health measures, will be used to advise on the design of future sexual health promotion campaigns. In this project the student will use the data collected to investigate patterns of sexual risk behaviours, knowledge, and attitudes. This will involve quantitative analysis of the relationship between variables such as condom use, number of sexual partners, drug and alcohol use, and perceptions of risk. The project could also involve in-depth qualitative data collection via focus group discussions or interviews.

211. Agents of YEAH Needs Assessment
Supervisors: Dr Megan Lim
Project Site: Burnet Institute
Contact: E: lim@burnet.edu.au
Project description: Agents of YEAH is a HIV and sexual health peer education and leadership program run by YEAH (Youth Empowerment Against HIV/AIDS). Through the Agents of YEAH program, young people aged 15-29 are trained to run HIV and sexual health workshops and events in their local communities.

The Agents of YEAH program is designed to improve the active participation of young people in delivering positive and reliable information on sexual health to other young people in their local communities and in doing so improve access to youth friendly sexual health information and services.
Volunteer led Agents of YEAH teams are located in Melbourne, Adelaide, Brisbane, Darwin and Perth.

The First Agents of YEAH Needs Assessment was delivered in late 2013 as a monitoring and evaluation tool designed to better understand the experiences of our volunteers and to identify the strengths and weaknesses of the Agents of YEAH program.

The key purpose of this project is to create and deliver the third Agents of YEAH Needs Assessment to all Agents of YEAH enrolled in the program in 2016 across YEAH’s five locations.

212. **Trends in STI testing and positivity in priority populations in Australia**  
*Supervisors: Caroline van Gemert, Carol El Hayek*  
*Project Site: Burnet Institute*  
*Contact: E: carolinevg@burnet.edu.au*

**Project description:** In the last decade, communicable disease notification systems have seen a dramatic increase in the number of notifications for chlamydia and several other STIs. Higher prevalence is commonly seen in populations that have higher sexual risk practices (such as men who have sex with men, Aboriginal and Torres Strait Islander People, Sex Workers). It is important to monitor rates of STI testing and positivity in these priority populations, as well as the general population, in order to identify emerging patterns and trends in STI epidemiology.

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmitted Infections and Blood Borne Viruses (ACCESS) project is a sentinel surveillance system that monitors STI testing and positivity in a range of priority populations. This project will use existing data collected in the ACCESS project to explore STI testing and positivity in priority population and identify factors which are associated with both testing and positivity.

This project will involve quantitative data analysis of data collected through the ACCESS project. Data analysis will involve analysis of data collected through either laboratories or general practices and family planning clinics, and supplemented with behavioural data collected in the Victorian Primary Care Network for Sentinel Surveillance of STIs. Data analysis will involve calculation of testing and positivity rates for a range of STIs and factors associated with these (such as age, gender and other relevant characteristics) in priority populations (including men who have sex with men, Aboriginal and Torres Strait Islander People, Sex Workers).

213. **Understanding risky single occasion drinking and links to harms in a cohort of young Melburnians – also offered as MBiomedSc**  
*Supervisor: Paul Dietze, Michael Livingston, Sarah Callinan*  
*Project Site: Burnet Institute*  
*Contact: E: pauld@burnet.edu.au  Telephone: 9282 2134*

**Project description:** Young Australians frequently engage in Risky single occasion drinking (RSOD). This drinking pattern is associated with a variety of harms including increased risk of accidents, exposure to violence and risky sex. Most research on RSOD has focused on normative drinking behaviours within the past year rather than on the specific circumstances of RSOD. The aim of this study is to examine specific occasions of RSOD by young people to understand the specifics of drinking contexts and links to harms.

The proposed study involves analysis of quantitative data collected through the Young Risky Drinkers (YRD) study. The YRD is a representative sample of 802 young high-risk drinkers recruited across metropolitan Melbourne using Computer Assisted Telephone Interviewing (CATI) during 2012. Specific questions were asked about their most recent episode of high risk drinking. The cohort is being followed up in 2013 with a similar questionnaire. Analysis will be undertaken to characterize risky drinking occasions and use findings from these analyses at baseline to examine whether these predict subsequent experiences of harm. Findings from the project will present a unique picture of RSOD.

214. **Modeling the syphilis epidemic in Victoria – also offered as MBiomedSc**  
*Supervisor: Ms Carol El Hayek, Dr Emma McBryde*  
*Project Site: Burnet Institute*  
*Contact: E: carol@burnet.edu.au  Telephone: 8506 2303*

**Project description** In Victoria 80% of infectious syphilis cases are in men who have sex with men (MSM). Mathematical modeling of syphilis transmission in Australian MSM suggests an effective way to reduce syphilis is to increase the frequency of testing and treatment of MSM.

In recent years, we have seen a sustained increase in routine syphilis testing among MSM at high caseload clinics alongside a decline in infectious syphilis incidence.
How much testing needs to occur in Victoria’s MSM community to eradicate infectious syphilis? This project will involve the design of a syphilis transmission schema and model for mathematically predicting infection rates. Running the model will require defining input parameters which should be based on an extensive literature review.

215. **Low income as a barrier to opioid substitution therapy** - *also offered as MBiomedSc*

*Supervisor:* Dr Peter Higgs, Co-Head, Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute

*Project site:* Burnet Institute

*Email:* peterh@burnet.edu.au

*Project description:* People who inject drugs (PWID) often report low levels of income, with many reporting weekly incomes of less than $250. PWID on opioid substation therapy (OST) commonly describe an adverse impact from pharmacy dispensing fees for accessing OST. These fees are typically around $5 per dose, or $35 per week – for many a significant proportion of weekly income, especially after necessary expenditures (rent, food, etc.) are deducted.

This project would involve analysis of data from the Suboxone (a national year-long examination of a particular OST formulation, with a number of cross-sectional arms investigating the health domains of PWID and practices of prescribing pharmacists) and MIX studies (a Melbourne-based prospective cohort study running since 2008 with over 700 PWID as participants), examining the dispensing practice/cost for differing pharmacies, and personal in-depth interviews with PWID to further illicit the impact of dispensing costs and the extent that low income is a barrier to substitution therapy.

**PREGNANCY RESEARCH**

216. **Understanding changes in haemostasis during pregnancy and pregnancy complications** – *also offered as MBiomedSc*

*Supervisors:* A/Prof Joanne Said and Dr Briony Cutts

*Project Site:* Melbourne Medical School, Sunshine Hospital, St Albans.

*Contact:* E: jsaid@unimelb.edu.au or briony.cutts@thewomens.org.au

*Project description:* Haemostasis in humans represents a complex balance between prothrombotic and anticoagulant proteins. During pregnancy, this balance is shifted in favour of a prothrombotic state such that pregnant women have an increased risk of developing deep vein thrombosis. This disturbance in coagulation is even more pronounced in a range of pregnancy complications. The aim of this study is to investigate the changes that occur during pregnancy, and in various adverse pregnancy conditions, using the calibrated automated thrombinoscope. This modern technology allows a global assessment of haemostasis rather than investigating individual factors. The project will be conducted in the brand new laboratories at the Centre for Health Research and Education based at Sunshine Hospital. Sunshine Hospital is the second largest maternity unit in Victoria and thus there is an ample population of pregnant women available to participate in this study. Techniques: Recruitment of patients, sample collection, thrombin generation assays.

217. **Stem cells and their Potential to Treat Clinically Important Disorders of Pregnancy** - *also offered as MBiomedSc*

*Supervisors:* Dr Bill Kalionis

*Project Site:* Pregnancy Research Centre, Royal Women’s Hospital

*Contact:* Dr Bill Kalionis T: 8345 3748 E: bill.kalionis@thewomens.org.au

*Project Description:* We are interested in the potential for manipulating gene expression in decidual mesenchymal stem cells as for the treatment for clinically important pregnancy disorders such as preeclampsia. The latter stages of preeclampsia are characterised by an environment of high oxidative stress in the decidua. We have shown that decidual MSCs are abnormal in their response to oxidative stress in preeclampsia. The aim of the project is to use human cell culture models to test strategies for restoring normal oxidative stress response to abnormal, preeclampsia-affected decidual MSCs (PE-DMSCs). For example, we have shown that aldehyde dehydrogenase expression, which is required for MSCs to resist oxidative stress, is abnormally low in PE-DMSCs. We will increase expression of aldehyde dehydrogenase in PE-DMSCs using plasmid-based expression vectors and test whether resistance to oxidative stress in PE-DMSCs is restored.

*Techniques:* stem cell preparation and characterisation by immunocytochemistry and FACS, RNA/DNA extraction methods, real-time PCR, siRNA and gene overexpression analysis and immunohistochemistry. Functional analyses will include proliferation, migration and differentiation assays.
218. Stem Cell Microvesicle Repair of the Damaged Endothelium in Preeclampsia. - also offered as MBiomedSc  
Supervisors: Dr Bill Kalionis  
Project Site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Bill Kalionis T: 8345 3748 E: bill.kalionis@thewomens.org.au  

**Project Description:** Preeclampsia is the most significant clinical disorder of pregnancy, affecting 5% of all pregnancies. Preeclampsia is a significant cause of maternal morbidity as well as fetal morbidity and mortality. Currently, there are no early diagnostic tests or effective treatments for preeclampsia. We are interested in the potential for subcellular microvesicles shed from mesenchymal stem cells to treat the symptoms of preeclampsia. In preeclampsia, the endothelial cells lining the vessel walls become damaged. Systemic vascular damage contributes significantly to the symptoms of preeclampsia. Microvesicles shed from stem cells contain a variety of beneficial growth factors, cytokines and microRNAs that can be delivered to damaged cells, which prevent cell apoptosis, promote cell proliferation and differentiation, and thereby assist cells in recovering from damage. The aim of the project is to identify the growth factors, cytokines and microRNAs produced by microvesicles derived from placental mesenchymal stem cells.  
**Techniques:** Stem cell preparation and characterisation by immunocytochemistry, flow cytometry and differentiation assays, microvesicle preparation from stem cells, ultracentrifugation, microvesicle characterisation and fluorescence labelling, screening assays for microRNA, growth factors and cytokines.

219. How do hormones work: investigating new steroid receptors  
Supervisors: Dr. Penelope Sheehan  
Project Site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Penelope Sheehan E: penny.sheehan@thewomens.org.au  

**Project Description:** Progesterone is known to be a key hormone in human pregnancy and is particularly thought to play a role in maintaining myometrial quiescence throughout gestation, allowing the fetus to grow. Antiprogestins, such as mifepristone (RU 486), are known to contribute to parturition. Yet, in humans, maternal serum progesterone concentrations do not significantly decrease at labour onset, suggesting a change at the receptor level. However detailed knowledge of intracellular and molecular mechanisms are unknown. We have identified two new receptors capable of binding progesterone which may help improve our understanding of progesterone action. The pregnane X receptor (PXR) is a nuclear receptor which is able to regulate gene transcription. The endogenous ligand with the highest affinity for the PXR is the progesterone metabolite, 5βDHP. Progesterone receptor membrane components 1 and 2 (PGRMC1, PGRMC2) are also putative progesterone receptors. Detailed study of the pathways affected by these receptors using myometrial explant cultures and gene silencing techniques may provide new therapeutic targets for treatment of preterm birth and also for induction of labour in postdates pregnancy.  
This project will build on previous Pregnancy Research Centre findings identifying changes in expression of these two new receptors in association with human labour at term in myometrium. The methodologies are established within our laboratories at The Royal Women’s Hospital.  
**Techniques:** Tissue culture, siRNA gene silencing, Real-time RT-PCR, western immunoblotting, microarray.

220. Can dietary phytophenols prevent the development of diabetes in pregnancy? - also offered as MBiomedSc  
Supervisors: Associate Professor Martha Lappas  
Project site: Department of Obstetrics & Gynaecology, University of Melbourne located at the Mercy Hospital for Women  
Contact: T: 8458 4370 E: mllappas@unimelb.edu.au  

**Project description:** Gestational diabetes mellitus (GDM) affects up to 20% of all pregnancies. It has an impact that extends well beyond pregnancy and childbirth, with the potential for lifelong morbidity or mortality for both mother and baby. Despite the enormous health-impact of this condition, little progress has been made with interventions aimed at prevention; rates of GDM are increasing in parallel with the obesity epidemic. A safe and effective intervention that can reduce the burden of GDM would be a major public health initiative. Of promise, however, is the increasing volume and quality of evidence that high fruit and vegetable intake in pregnancy is associated with a decreased risk of adverse pregnancy outcomes. Many of the beneficial effects are due to phytophenols which are natural products found in fruits and vegetables and beverages derived from plants. Thus, in this study, we will use a mouse model to determine if phytophenols can prevent the development of GDM.  
**Techniques:** Animal work, PCR-based analysis, Western blotting and ELISA
221. Can dietary phytophenols stop preterm birth? - also offered as MBiomedSc
Supervisors: Associate Professor Martha Lappas
Project site: Department of Obstetrics & Gynaecology, University of Melbourne located at the Mercy Hospital for Women
Contact: T: 8458 4370 E: mlappas@unimelb.edu.au

Project description: The single most important complication contributing to poor pregnancy and neonatal outcome is preterm birth. Of the 130 million babies born each year, 8 million die before their first birthday. Up to 2.7 million of these deaths are attributable to being born too early. Bacterial infection is the most common trigger for preterm birth. It activates inflammation in placenta which can trigger the processes that lead to preterm birth. In our in vitro studies, we have shown that natural plants chemicals (i.e. phytophenols), such as luteolin which is found in celery, can reduce inflammation in the placenta. Although this data is very promising, in vivo studies are needed to determine if these plant chemicals will be useful as therapeutics to prevent preterm birth. In this project, we will induce preterm birth in mice (using bacterial infection). We will then determine if phytochemicals can prevent infection induced preterm birth. The possibility of phytophenols as therapeutic agents offers an exciting step forward into the management of a condition responsible for unequalled morbidity and mortality in infants.

Techniques: Animal work, PCR-based analysis, Western blotting and ELISA

SPINAL CORD INJURY

222. Acute management of traumatic central cord syndrome
Supervisors: Dr Peter Batchelor, Dr Camila Battistuzzo
Project Site: Department of Medicine (RMH)
Contact: Dr Peter Batchelor: peter.batch@unimelb.edu.au
Dr Camila Battistuzzo: camilab@unimelb.edu.au

Project description: Acute traumatic central cord syndrome (TCCS) is the most common type of incomplete cervical spinal cord injury. TCCS is usually the result of a hyperextension injury in a patient with pre-existing narrowing of the spinal canal and can result in paralysis and permanent functional deficits. At present there is no standardized treatment for this condition, although early surgery to relieve spinal cord compression may improve neurological recovery. The aim of this project is to map the process of care of people with TCCS to determine the timing of spinal decompression surgery and factors that influence surgical decisions.

This project is part of the Immediate Cooling and Emergency Decompression (ICED) trial. You will have access to our database and opportunity to work with our national and international collaborators. We have already obtained Human Ethics Committee approval. There is opportunity for publication within one year. This project would suit a candidate with an interest in trauma, spinal surgery and acute medicine.
2015/16 KEY DATES

Aug-November 2015: Contact potential supervisors to discuss Honours projects (Step 1)
28 August 2015: Open date to register online application
7 September 2015: Open date to lodge project preferences through HATS
13 November 2015: Closing date to register online application (Step 2)
27 November 2015: Closing date to lodge project preferences through HATS (Step 3)
3rd wk December 2015: First round of offer letters from 18 December sent to students
4 January 2016: Closing date for acceptance/rejection by students of First Round offers
8 January 2016: Second round of selection and mailing of offer letters begins
25 January 2016: Deadline for Late Applications
15 February 2016: RMH Honours 2016 Program commences / RMH Student Orientation.

HONOURS ENTRY REQUIREMENTS

To be eligible to enter the Bachelor of Biomedicine (Honours) or the Bachelor of Science (Honours), applicants must satisfy both:
• the Faculty of Medicine, Dentistry and Health Sciences or Faculty of Science entry requirements;
• and the requirements of the department offering the Honours program.

Please note: The minimum entry requirement is 65 (WAM). Students who meet the minimum entry requirements for entry to MDHS Honours does not guarantee a place in the Honours program. All successful applicants will also need to be selected for admission by the department.

For further details see the Department of Medicine Honours Website:
http://honoursrmh.unimelb.edu.au/

Faculty of Medicine, Dentistry & Health Sciences website:
http://sc.mdhs.unimelb.edu.au/honours
http://sc.mdhs.unimelb.edu.au/entry-requirements

HONOURS COURSEWORK

BIOM40001 – Introduction to Biomedical Research (12.5%) – Semester 1
This core subject contributes 12.5% to the total mark of the Honours year and is administered through the Faculty of Medicine, Dentistry & Health Sciences.

Structure: Series of 10 x 2 hr tutorials to introduce students to processes and strategies at the core of modern biomedical research.

Assessment: Semester 1: 2 written reports (each not exceeding 3000 words).

For further details on course work please see the RMH Academic Centre Honours Program Course Structure website:
http://honoursrmh.unimelb.edu.au/Applications/CourseDetails.html

MEDI40004 – Advanced Coursework (12.5%) – Semester 1
This subject contributes 12.5% to the total mark of the Honours year.

Structure: Semester 1: Attend Seminars in Translational Medicine - thematic topics of approximately 20 lectures (1 hour each).
Semester 1 & 2: Attend Weekly Research Seminars. Attendance is compulsory from March to October but not assessed.

Assessment: Semester 1: Multiple Choice Question examination covering examinable topics from the Seminars in Translational Medicine.

MEDI40003 & MEDI40012 – Research Project (75%) – Semester 1 & 2
The written thesis together with an Oral Presentation constitutes the Research Project for Semester 1 & 2 and contributes 75% to the total mark of the Honours Year.

Structure: Research Project (Thesis)

Assessment: Semester 1: Oral Presentation on project outline. Feedback only - not assessed.
Semester 2: Written research report (thesis) to be submitted. 80% Formal Thesis Oral presentation. 20%
HOW TO APPLY - HONOURS

Course Codes:
Bachelor of Biomedicine (Honours) – BH-BMED
Bachelor of Science (Honours) – BH-SCI
RMH Enrolling Department is: MEDICINE RMH

2015 APPLICATIONS

If you wish to be considered for Honours in 2016, and you would like to undertake your project and coursework with Department of Medicine at RMH, Faculty of Medicine and Dentistry Sciences or affiliated institute (enrolling unit: Department of Medicine (RMH)), you will need to carry out a THREE STEP PROCESS:

STEP 1: Contact Potential Supervisor
You will need to decide which Department or Institute(s), Supervisor(s) and Project(s) that you wish to apply for. To do this, you must speak to potential supervisors. Please see our Honours project book and Department of Medicine (RMH) website to review our projects available for 2015. http://honoursrmh.unimelb.edu.au/

STEP 2: Lodge an online application
Lodge an online application between Friday 28 August to Friday 13 November 2015: http://sc.mdhs.unimelb.edu.au/how-apply

Applications for Honours are lodged to MDHS via one of the following processes:

a) Current and previous University of Melbourne applicants (local and international) apply online and select the ‘RETURN APPLICANTS, CURRENT STUDENTS or PREVIOUS STUDENTS” option.

b) Non-University of Melbourne applicants apply online and select the ‘FIRST TIME APPLICANTS” option.

All previous and current University of Melbourne applicants please note the following:
Students who have an existing Student ID number in the university of Melbourne system but who apply as “First Time Applicants” will have their records data matched and merged. This will delay the processing of their application.

All non-University of Melbourne applicants please note the following:
Please provide an original or certified copy of your complete official Academic Transcript to the Honours Admissions Team as part of your application and ensure that you include your University of Melbourne applicant or student number.

Documents should be sent to the address below. (Please include your Applicant / Student ID in all correspondence with the University)

Attention : Honours Admissions Team
Learning and Teaching Unit,
Level 1, Brownless Biomedical Library
The University of Melbourne, Victoria, 3010. Australia

It is essential you carry out Step 2 BEFORE you carry out Step 3. Note the closing date for Step 2 is 13 November 2015.

STEP 3: Honours Application and Tracking System (HATS)
Once you have contacted the potential research supervisors (Step 1) and submitted your online application (Step 2), you will be issued with a password for the Honours Application and Tracking System (HATS). This system allows you to submit up to ten (10) research project preferences online.

HATS usernames/passwords are issued once a week (usually on a Monday) to applicants whose applications are submitted properly in the previous week.

Please note that HATS is ONLY available to On-Time applicants for Start Year entry.

HATS will open 7 September 2015 and will close at 5pm on Friday 27 November 2015.

If you have lodged your online application for Honours, you will receive an email with your HATS password so you can lodge your project preferences.

Please note that you must ONLY list project preferences for which you have already made contact with the supervisor.
**LATE APPLICANTS**  ie those applying after the Application Closing Date in mid November must complete Step 3 by submitting a hard copy “Late Application – Project Preference Form”.  Late applications will be assessed in January as part of the Round 2 selection process. The “Late Application – Project Preference Form” will be made available on the MDHS Honours “How to Apply” web page after the Application Closing Date, but only allows applicants to list a maximum of three (3) project preferences.  [http://sc.mdhs.unimelb.edu.au/how-apply](http://sc.mdhs.unimelb.edu.au/how-apply)

To carry out STEP 3 in HATS you will need to:

A. **Enter your Application ID into HATS**

B. **Enter your HATS password**
   HATS passwords are issued once a week. Your HATS password will be emailed to you on the Monday following the date you completed Step 2.

C. **Click on Preferences then Search Projects**
   Use this search to make sure that the project(s) you wish to apply for are present in HATS. If you cannot find the project you are interested in, you should contact the supervisor of these projects, who will be able to take steps to have the project details entered into HATS.

D. **Click on Preferences then Lodge/Update Preferences to lodge your project preferences with HATS.**
   You can update/change your preferences as many times as you wish. However, you must ensure that your final preference list (in order of 1-10; you must enter at least 1 preference, and you can enter up to 10) is lodged by Friday 27 November 2015. This list will be supplied to Departments to allow them to carry out their selection process in early December 2015.

You will receive a round one offer letter for the highest preference project you have been offered by mail before Christmas.  You can choose to accept the offer or not.  If you choose not to accept, you will be considered for selection by Departments for the second round of selection in mid January.

**Note:**  The Department of Medicine (RMH) is the enrolling unit for RMH Departments of Medicine, Radiology, Surgery, Psychiatry, Obstetrics & Gynaecology RWH and affiliated institutions.

**For further details on ‘How to Apply’ please refer to the following websites:**

Department of Medicine Honours: [http://honoursrmh.unimelb.edu.au/](http://honoursrmh.unimelb.edu.au/)

Faculty of Medicine, Dentistry and Health Sciences Honours: [http://sc.mdhs.unimelb.edu.au/why-honours](http://sc.mdhs.unimelb.edu.au/why-honours)

Faculty of Medicine, Dentistry and Health Sciences Application Process: [http://www.mdhs.unimelb.edu.au/future_students/honours/application_process](http://www.mdhs.unimelb.edu.au/future_students/honours/application_process)

**IMPORTANT NOTE:**
Please note that the above process is for applications to the Biomedical and Health Sciences Departments ONLY. Students interested in submitting preferences for projects in Genetics, the Melbourne School of Psychological Sciences, Optometry and Vision Sciences, Veterinary Science or Zoology, must contact those departments directly.

**STEP 3: Offers**
Round 1 offer letters are sent to applicants via post and email around the 3rd week of December. Students MUST accept their offer by the Offer Lapse Date noted in their offer letter.

It is the responsibility of applicants to ensure their contact details and mailing address are correct and up to date, as offer packs will be sent to the address provided in the original course application, unless other arrangements have been made in advance.

Students who meet the minimum entry requirements for entry to MDHS Honours but do not receive an offer in Round 1 will be considered for a place in Round 2, along with Late Applicants.

Students who do not meet the entry requirements or are not successful in obtaining a place in the course will be advised in writing by the end of January.

**Please note:** Not all students who meet the minimum entry requirements and make contact with supervisors will be offered a place in a MDHS Honours course. Entry is conditional upon selection by the Departmental Selection Committee and is academically competitive.

**MID-YEAR ENTRY**
Students applying for Mid Year entry must contact potential supervisors to confirm if the department is offering mid-year entry (Step 1). Submit an online application for entry to the course (Step 2) and submit a hard copy “Mid Year Project Preference Form”. Mid-Year coursework will commence from 1-10 July 2016. Application details will be available on the website from April 2015. [http://sc.mdhs.unimelb.edu.au/how-apply](http://sc.mdhs.unimelb.edu.au/how-apply)
MASTER OF BIOMEDICAL SCIENCE - COURSEWORK
Previously Master of Science (Biomedical and Health Sciences)

The Master Biomedical Science is one of the research training streams of the Master of Science. The research training streams give students the opportunity to undertake a substantive research project in a field of choice as well as a broad range of coursework subjects including a professional tools component, as a pathway to PhD study or to the workforce. The MSc is a two year course that can be taken in place of Honours.

Students must complete 200 points comprising of:

Major Research Project (Literature Review, Thesis, & Ora Presentations) 125 points
Core Discipline subject (Introduction to Biomedical Research BIOM40001) 12.5
Discipline Subjects 37.5 points
Professional Skills 25 points

MAJOR RESEARCH PROJECT: 125 points.

• A literature review of up to 6,000 words. Due end of 2nd semester Year 1. Assessment hurdle – marked satisfactory/unsatisfactory.
• Two 20 minute oral presentations. Due end of 2nd semester Year 1 and final semester Year 2.
• Major research report of up to 20,000 words. Due end of final semester Year 2.

As this project is a larger body of research work than an Honours research project (75pts) the expectation about the extent of work undertaken is adjusted and more research output is expected to be achieved. More supervisor input is required but this is over the 2 year duration.

Available Projects:
For MBiomedSc projects available with the Royal Melbourne Hospital please see projects listed as available for MBiomedSc in the 2016 Honours / Master of Biomedical Science Project List Handbook: For further details on the project please contact the supervisor listed in the handbook.

HOW TO APPLY - MBIOMEDSC

Course Code MC-BMEDSC

1. Applications for the Master of Biomedical Science are made directly via the University online application system. Late applications can be considered for admission (but may not be eligible for competitive fee places or bursaries).
2. Talk with academic staff offering projects you are interested in. Find out what is involved. Talk to the students in the labs. Talk with the Department Masters Coordinator if you have questions about the overall course structure.
3. When you are ready to make a formal application, lodge an online – see links below on how to apply: http://medicine.unimelb.edu.au/study-here/postgraduate_coursecwork_programs/master_of_biomedical_science

You will be required to nominate a Department, Supervisor and Project, and have your prospective supervisor provide you with evidence (ie a letter or email) of their potential willingness to supervise your project. You will be required to submit this information as part of your course application.

Domestic Applications:
Closing date: 27 November 2015
Offer date: 14 December 2015
Semester 1 start: 15 February 2016
http://futurestudents.unimelb.edu.au/admissions/applications/grad-dom

International Applications:
Closing date: 30 October 2015
Offer date: 20 November 2015
Semester 1 start: 15 February 2016
http://futurestudents.unimelb.edu.au/admissions/applications/grad-int

4. Wait for your letter of offer in the mail early-mid December. If you do not receive an offer for one, you will be assessed for any other applications made.
5. Complete the Faculty acceptance form and follow enrolment instructions for 2015.
As for Honours, Commonwealth supported places (CSP) are competitively available for eligible Masters students and HECS funding arrangements for fees apply. Overseas and Australian Fee places are also offered (and Fee Help support is available for local students). Students entering the Masters program need to check the banding classification of specific subjects to determine overall fees payable as some selected Discipline and Professional Skills subjects may be in fee bands which are different (possibly lower) than fee bands which apply to natural and physical sciences, mathematics and statistics fee band subjects. Some students may qualify for scholarship funding.
http://www.futurestudents.unimelb.edu.au/admissions/fees

Local students applying for the Masters may be eligible for financial support

ENQUIRIES

Email: biomedsci-gradstudent@unimelb.edu.au

Melbourne Medical School Masters Coordinator
Prof Lea Delbridge
Department of Physiology
lmd@unimelb.edu.au

Melbourne Academic Centre Honours/MBiomedSc Coordinators:
− Dr Chris French E: frenchc@unimelb.edu.au,
− A/Professor Caroline Marshall E: Caroline.Marshall@mh.org.au
Melbourne Academic Centre (RMH) Honours/MBSc Administrator: Mary Ljubanovic E: mlju@unimelb.edu.au

RMH DEPARTMENT LINKS:

Department of Medicine (Royal Melbourne Hospital)
http://www.medrmhwh.unimelb.edu.au/

Department of Surgery (Royal Melbourne Hospital)
http://www.surgeryrmh.unimelb.edu.au/

Department of Psychiatry (Royal Melbourne Hospital)
http://www.psychiatry.unimelb.edu.au/

Department of Radiology (Royal Melbourne Hospital)
http://www.melbourne-radiology.org/Staff.html

Obstetrics & Gynaecology (Royal Women’s Hospital)
http://www.obsgyn.unimelb.edu.au/