

The Molecular Pathology Research Laboratory

Prof Hamish S. Scott moved his laboratory from the Walter and Eliza Hall Institute in Melbourne to the IMVS at the beginning of 2008. He has an international reputation in the areas of genetics and genomics. While he has applied his skills to a broad range of subjects, he focuses on the study of transcriptional mechanisms (including epigenetics) and molecular pathogenesis in autoimmunity and haematological malignancies including identification of disease causing genes and mutations. Among the reasons for moving to the IMVS, was that as part of a pathology service, he now has outstanding access to patient samples.

The laboratory is situated in the Department of Molecular Pathology, in the [Centre for Cancer Biology](#) (a center of excellence in cancer research) of [SA Pathology](#) (formerly called the [Institute of Medical and Veterinary Science or the IMVS](#)).

PROJECTS

Researchers Name(s): Prof Hamish S Scott, Dr Chris N Hahn

Research area: Cancer genetics

Project title: Haematopoietic malignancy predisposition and progression

Project description (no more than 100 words)

Each year ~6460 Australian adults and children are diagnosed with leukaemia or other haematopoietic malignancy (HM), accounting for 15% of all cancers. We have accrued samples from over 60 families with predisposition to HM, which are invaluable resource for the identification of genetic and epigenetic changes leading to these and other cancers. Using candidate gene approaches, we have identified known causative genes in 11 of these families.

However, recently, with a combination of strategies including state-of-the-art exon capture and next generation sequencing, we have found 2 genes, not previously recognized in cancer, that segregate with diseased individuals in some of these families. Functional studies on one of these genes have exposed a possible mechanism for predisposition to acute myeloid leukaemia.

Work in our laboratory is at a very exciting stage of disease gene discovery and confirmation utilizing latest biological, technical and bioinformatics technologies.

Researchers Name(s): A/Prof Susan Branford, Prof Hamish S Scott

Research area: Mechanisms of cancer drug resistance and response

Project title: Examination of the BCR serine-threonine kinase domain for acquired mutations that may enhance BCR-ABL oncogenicity

Project description (no more than 100 words)

The pathogenesis of CML patients varies. While most respond to BCR-ABL inhibitor therapy, a minority rapidly progress to an acute leukaemia. A possible role of normal BCR in CML pathogenesis has been suggested. Normal BCR has serine/threonine kinase activity localised in its first exon, which has been shown by in vitro studies to down regulate BCR-ABL activity. However, BCR forms a heterotetramer structure with BCR-ABL leading to reduced serine/threonine activity and becomes an important facilitator of BCR-ABL induced leukaemia.

It has been reported that engineered point mutations within BCR that disrupt its kinase activity significantly enhance the oncogenic potency of BCR-ABL. This suggests another mechanism for increased oncogenicity in some CML patients. It is unknown whether kinase defective mutants are acquired within the first exon of normal BCR. This necessitates mutation analysis of the isolated BCR allele.

Researchers Name(s): Prof Hamish S Scott, Dr Brita Ardesjo Lundgren

Research area: Infection and autoimmunity

Project title: Autoimmune regulator (AIRE) gene defects and chronic mucocutaneous *candidiasis* susceptibility

Project description (no more than 100 words)

Autoimmune polyendocrine syndrome type 1 (APS-1) is a multiorgan autoimmune disease caused by mutations in the autoimmune regulator (AIRE) gene encoding a transcription factor. The majority of patients also have chronic mucocutaneous *candidiasis* (CMC), a form of oral (and elsewhere) yeast infection, but the cause(s) of this symptom is not known.

Aire regulates thymic expression of several APS-1 autoantigens and also the expression of several proteins expressed in neutrophils that are part of the defense against *Candida* infection. We are investigating if APS-1 patients and Aire^{-/-} mice show autoimmunity to these antigens and/or if autoimmunity to these antigens can be induced in Aire^{-/-} mice and if this is associated with increased susceptibility to *Candida* infection.