Occlusion of the blood vessels supplying the brain leads to ischemic stroke and infarction—irreversible death of brain tissue. Risk factors causing stroke, especially those involving lipid metabolism, form the basis of current therapies to reduce stroke risk. However, although decades of research have increased our understanding of the molecular events occurring during infarction, the translation of these discoveries to “druggable” targets to treat stroke outcome (death of brain tissue) has been disappointing. Novel approaches will be required to identify new and more physiologically relevant targets.

The scientific rationale of our work is that naturally-occurring allelic (DNA sequence) variations underlie the profound differences in individual stroke outcomes that are observed clinically, and that these neuroprotective gene variants would provide a powerful path towards the identification and development of novel drug targets for stroke treatment. However, conventional genetic mapping approaches in the human (e.g., genome wide association studies - GWAS - of infarct volume as a quantitative trait among ischemic stroke patients) are intrinsically problematic for stroke due to uncontrollable variation in the extent and location of the occluded vessel, strong environmental variables (diet, smoking, etc.), and especially, variation in the critical time between first recognized symptoms of stroke and medical intervention. Unsurprisingly, despite an explosion of human GWAS for disease phenotypes, to date we can find no published GWAS for infarct volume in ischemic stroke. All are instead studies on stroke risk.

We have taken an alternative, forward genetic (phenotype-driven) approach to discover novel genes modulating infarction. We have surgically occluded the distal middle cerebral artery (MCAO) in over 32 commonly used inbred mouse strains and found that infarct volume differs more than 50-fold. These robust and highly reproducible differences in infarct size are at least 10-fold larger than in any “engineered” knockout or transgenic mouse lines but, importantly, are instead caused by natural allelic variation in the mouse genome. We have mapped several of these genetic loci and through a combination of genetics and genomics, have identified some of these genes. Two different physiological mechanisms have been uncovered that seem to span the effects of these loci/genes. These data will be presented in this seminar.