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Enzymes involved in cancer and neurodegenerative diseases

My research focuses on the protein kinases and phosphatases involved in cancer formation and progression as well as neuronal cell death associated with Parkinson's disease.

Projects:

Deciphering the tumour suppression mechanism of CSK-homologous kinase (CHK) (with Prof. Harshal Nandurkar, St. Vincent's Hospital)

SFKs are protein products of the Src-family of oncogenes and proto-oncogenes. Constitutive activation of SFKs contributes to many forms of cancer. In normal cells, SFKs are kept in the inactive form by phosphorylation of the C-terminal regulatory tyrosyl residue (referred to as Y_T). CSK-homologous kinase (CHK) is one of the regulatory kinases that phosphorylate Y_T . In addition to Y_T phosphorylation, CHK employs a novel mechanism to inhibit SFKs – it binds directly to SFKs to form a stable protein complex. Since CHK constrains the oncogenic action of SFKs, it functions as a tumour suppressor in both solid tumours and leukaemia^{1,5,6,7}.

The first project focuses on deciphering (i) how CHK activity and expression are regulated in chronic myelogenous leukemia and acute myelogenous leukaemia and (ii) how expression of CHK induces apoptosis and growth arrest of the cancer cells. Students participating in this project will be co-supervised by me and Prof. Harshal Nandurkar³ of Department of Medicine, St. Vincent's Hospital.

Deciphering the role of Src-family kinase c-Src in excitotoxic neuronal death during ischemic stroke (With Dr. Carli Roulston and Prof Greg Dusting, Bernard O'Brien Institute of Microsurgery)

An ischemic stroke occurs when the one of the blood vessels (e.g. the middle cerebral artery) supplying the brain is blocked², leading to damage of the neurons nearby. The damaged neurons induce a second round of neuronal death by secreting an excessive quantity of the neurotransmitter glutamate. Over-stimulation of glutamate receptors in the neighbouring healthy neurons causes cell death – a process known as excitotoxicity. Exactly how over-stimulation of glutamate receptor induces neuronal death is poorly understood, but if we can block this process we might be able to rescue much more of the brain after stroke and accelerate recovery. Results of studies by us and others indicate that inhibitors of c-Src kinase are protectants, indicating that aberrant activation and/or subcellular localisation of c-Src contributes to excitotoxic neuronal death. We are using cultured mouse primary cortical neurons and a rat model of ischemic stroke to decipher how c-Src is aberrantly activated in neurons undergoing excitotoxic neuronal death, and how the activated c-Src induces premature death of neurons in culture and in live rats suffering from stroke. Students participating in this project will be co-supervised by Dr. Carli Roulston and Prof. Greg Dusting of the Bernard O'Brien Institute of Microsurgery at St Vincents Campus.

Protein kinases involved in the pathogenesis of Parkinson's disease (with Dr J Culvenor, Dept of Pathology and Dr. Kip Gabriel, Dept of Biochemistry, Monash University)

Parkinson's disease (PD) is a neurodegenerative disorder of movement known to result from the progressive, preferential loss of dopaminergic neurons from the substantia nigra of the mid-brain. However, the cause of such neuronal death in PD is not known. Recently the genes encoding PTEN-induced kinase 1 (PINK1) and leucine repeat-rich kinase 2 (LRRK2) were identified as PD-causative genes. The aim of this project is to identify the physiological substrates and define the regulatory properties of PINK1 and LRRK2.

Chemical Biology – development of chemosensor peptide substrates of protein kinases (Dr. Bim Graham, Faculty of Pharmaceutical Sciences, Monash University)

This project involves the development of peptide-based fluorescent chemosensors for the direct measurement of the activity of protein kinases SFK, PINK1 and LRRK2. The peptide chemosensor contains three modules:

1. The optimal phosphorylation sequence for a specific kinase
2. The chelation enhanced fluorophore
3. A β -turn to direct Mg^{++} binding between the fluorophore and the incipient phosphate.

The non-phosphorylated peptide chemosensor has a low level of fluorescence. However, upon phosphorylation of the optimal phosphorylation sequence by the protein kinase, Mg^{++} -chelation of the phosphate group significantly enhances the fluorescence of the fluorophore. The increase in fluorescence is therefore a measure of the protein kinase activity. This Honours project involves the chemical synthesis and biochemical characterization of the chemosensors⁸.

Recent publications:

1. Chong YP et al and Cheng H-C. (2006) 'C-terminal Src kinase-homologous kinase (CHK), a unique inhibitor inactivating multiple active conformations of Src family tyrosine kinases', *J Biol Chem*, 281:32988–32999.
2. Roulston CL, Callaway JK, Jarrott B, Woodman OL, Dusting GJ. (2008) "Using behaviour to predict stroke severity in conscious rats: post-stroke treatment with 3', 4'-dihydroxyflavonol improves recovery." *Eur J Pharmacol*. 584(1):100-110
3. Ruth N, MacKinnon, Carly Selan, Meaghan Wall, Elizabeth Baker, Harshal Nandurkar and Lynda J. Campbell. (2010) The Paradox of 20q11.21 Amplification in a Subset of Cases of Myeloid Malignancy with Chromosome 20 Deletion. *Genes Chromosomes and Cancer*. 49:998-1013
4. Mills RD, Sim CH, Mok SS, Mulhern TD, Culvenor JG, Cheng H-C. (2008) 'Biochemical basis of the neuroprotective mechanism of PTEN-induced kinase-1 (PINK1)', *J Neurochem*, 105, 18–33.
5. Zhu S, Bjorge JD, Cheng H-C, Fujita DJ. (2008) 'Decreased CHK protein levels are associated with Src activation in colon cancer cells' *Oncogene*, 27, 2027-2034.
6. Ia KK, et al, and Cheng H-C. (2010) 'Structural elements and allosteric mechanisms governing regulation, catalysis and substrate recognition of CSK-family kinases', *Growth Factors*, In Press.
7. Chan KC, et al Cheng H-C. (2010) 'Development of the Procedures for high yield expression and rapid purification of active recombinant Csk-homologous kinase (CHK) – Comparison of the catalytic activities of CHK and CSK', *Protein Exp. & Purif*, In Press.
8. Kamaruddin MA, Ung P, Hossain MI, Jarasrassamee B, O'Malley W, Thompson P, Scanlon D, Cheng HC, Graham B. (2011) "A facile, click chemistry-based approach to assembling fluorescent chemosensors for protein tyrosine kinases." *Bioorg Med Chem Lett*. 21(1):329-31.