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MAJOR RESEARCH INTERESTS

The research themes of this laboratory are translational in nature, and centre on gaining a better understanding of the basic pathophysiology of haematologic malignancies in order to improve the management and treatment of patients with these cancers. Several projects in the laboratory are guided by the overarching hypothesis that dysregulated mRNA translation is essential to cellular transformation. This hypothesis is supported by prior work from our group and others which have demonstrated that the aberrant activation of several signaling pathways associated with the oncogenic state (including MAPK and PI3K/Akt) impinge on the cellular machinery that regulates both cap-dependent and cap-independent mRNA translation. These observations suggest that dysregulated translation contributes to cellular transformation via altering the expression of genes that control cellular proliferation and/or death. Importantly, these data indicate that therapeutic targeting of dysregulated translation is a valid strategy to test in the cancer clinic.

Current projects in the laboratory include:

1. Investigating the role of cap-dependent and cap-independent translation in haematologic malignancies.
2. The identification and development of small molecules that can target aberrant mRNA translation in cancer.
3. Determining the identity of genes which are dysregulated at the level of translation in cancer.
4. Testing the feasibility and efficacy of targeting the mTOR kinase (a central regulator of eukaryotic mRNA translation) in patients with drug-resistant chronic myelogenous leukaemia.

RECENT PUBLICATIONS

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3. Peters UR, Hasse U, Oppliger E, Tschan M, Ong ST, Rassool FV, Borisch B, Tobler A, Fey MF. Aberrant FHIT mRNA transcripts are present in malignant and normal haematopoiesis, but absence of FHIT protein is restricted to leukaemia. *Oncogene*, 18(1):79-85, 1999.
4. Ong ST, Ly C, Nguyen M, Brightman K, Fan H. Expression profiling of a transformed thymocyte cell line undergoing maturation in vitro identifies multiple genes involved in positive selection. *Cellular Immunology*, 221, 64-79, 2003.
5. Ly C, Arechiga AF, Melo JV, Walsh CM, Ong ST. Bcr-Abl kinase modulates the translation regulators ribosomal protein S6 and 4E-BP1 in chronic myelogenous leukemia cells via mTOR. *Cancer Research*, 63: 5716-5722, 2003.
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7. A novel mechanism for Bcr-Abl action: Bcr-Abl-mediated induction of the eIF4F translation initiation complex and mRNA translation. Prabhu S, Saadat D, Zhang M, Halbur L, Fruehauf J, Ong ST. *Oncogene*, 26(8): 1188-1200, 2007.
8. Arechiga AF, Bell BD, Porter M, Wu Z, Kanno Y, Ramos J, Ong ST, Siegel RM, Walsh CM. A FADD/Caspase-8 signaling axis promotes S-phase entry and maintains S6 kinase activity. *Journal of Immunology*, 179(8):5291-300, 2007.
9. Inhibition of polysome assembly enhances imatinib activity against chronic myelogenous leukemia, and overcomes imatinib resistance. Zhang M, Fu W, Prabhu S, Trapp V, Ko J, Moore JM, Kim JW, Druker BJ, Fruehauf J, Gram H, Fan HY, Ong ST. *Molecular and Cellular Biology*, published on-line, 11th August 2008.