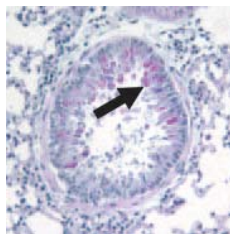


Under the Microscope

Research Highlights from the Ludwig Institute for Cancer Research Melbourne Tumour Biology Branch

Breathless without Lyn

Even though the incidence of asthma is increasing world-wide, the cellular and molecular mechanisms that cause this disease are still unclear. Defects in a subclass of T cells are thought to contribute to immune cell-mediated inflammation of the airways, which is a hallmark of asthma.



However, immune cells other than T cells are also commonly seen in asthmatic airways.

Members of the Signal Transduction Laboratory have used an experimental model of asthma in mice to show that a molecule called Lyn is important for normal lung function. Lyn is a tyrosine kinase that functions by transmitting specific signals inside cells and is present in all immune and blood cells except T cells. Mice that

were genetically engineered so that they did not have the Lyn gene had a much more severe and persistent form of asthma than normal mice, suggesting that Lyn normally switches off the molecular mechanisms that lead to asthma. The airways of these mice showed inflammation, infiltration with immune cells, overproduction of factors that stimulate asthma responses and increased mucus production, and they had poor lung function. The group also found that dendritic cells, a type of immune cell, taken from Lyn deficient mice could cause an asthma-like syndrome when transplanted into normal mice. Dendritic cells may therefore be the immune cells outside the T cell compartment that carry defects in molecules like Lyn that can affect the severity and persistence of asthma.

Beavitt, S.-J., Harder, K.W., Kemp, J.M., Jones, J., Quilici, C., Casagrande, F., Lam, E., Turner, D., Brennan, S., Sly, P.D., Tarlinton, D.M., Anderson, G.P. and Hibbs M.L. (2005). Lyn-deficient mice develop severe, persistent asthma: Lyn is a critical negative regulator of Th2 immunity. *J. Immunol.* **175**, 1867-1875.

Other highlights

The Angiogenesis Laboratory has demonstrated that VEGF-D, a growth factor that signals for the growth of lymphatic vessels, is not essential for development of the lymphatic system during embryogenesis in mice.

Baldwin, M.E., Halford, M.M., Roufail, S., Williams, R.A., Hibbs, M.L., Grail, D., Kubo, H., Stacker, S.A. and Achen, M.G. (2005). Vascular endothelial growth factor D is dispensable for development of the lymphatic system. *Mol. Cell Biol.* **25**, 2441-2449.

The Biological Production Facility at the Austin Campus has produced enough of the cancer antigen, NY-ESO-1, in a highly purified form and under code of Good Manufacturing Practice conditions for early stage human cancer vaccine trials in Australia and the USA.

Murphy, R., Green, S., Ritter, G., Cohen, L., Ryan, D., Woods, W., Rubira, M., Cebon, J., Davis, I.D., Sjolander, A., Kypridis, A., Kalnins, H., McNamara, M., Moloney, M.B., Ackland, J., Cartwright, G., Rood, J., Dumsday, G., Healey, K., Maher, D., Maraskovsky, E., Chen, Y.T., Hoffman, E.W., Old, L.J. and Scott, A.M. (2005). Recombinant NY-ESO-1 cancer antigen: production and purification under cGMP conditions. *Prep. Biochem. Biotechnol.* **35**, 119-134.

The Tumour Suppressor Laboratory has shown that FK228, a histone deacetylase inhibitor, blocks the activation of PAK1 in estrogen-dependent breast cancer cell lines, and can suppress the growth of both breast cancer and neurofibromatosis xenografts in mice.

Hirokawa, Y., Nakajima, H., Hanemann, C.O., Kurtz, A., Frahm, S., Mautner, V. and Maruta. (2005). Signal therapy of NF1-deficient tumor xenograft in mice by the anti-PAK drug FK228. *Cancer Biol. Therap.* **4**, 379-381. Hirokawa, Y., Arnold, M., Nakajima, H., Zalberg, J. and Maruta. (2005). Signal therapy of breast cancers by the HDAC inhibitor FK228 that blocks the activation of PAK1 and abrogates the tamoxifen-resistance. *Cancer Biol. Therap.* **4**.

Members of the Joint Proteomics Laboratory have demonstrated the utility of free-flow electrophoresis for the fractionation of human plasma to allow identification of low abundance plasma proteins by mass spectrometry.

Moritz, R.L., Clippingdale, A.B., Kapp, E.A., Eddes, J.S., Ji, H., Gilbert, S., Connolly, L.M. and Simpson, R.J. (2005). Application of 2-D free-flow electrophoresis/RP-HPLC for proteomic analysis of human plasma protein depleted of multi high-abundance proteins. *Proteomics.* **29**, 3402-3413.

Recent Research Publications

For a full listing of our research publications during the last 4 months, please see the publications database on our website at www.ludwig.edu.au/publications/pub_database.cfm

Smart chat between Smad and Stat

Cancers are characterised by the loss of regulation of growth and division of cells. To lessen the chances of cell growth getting out of control, many molecules in multiple cell signalling pathways are involved in keeping cell growth in check in normal cells. Sometimes, however, a change in a single molecule is enough to allow cancer to develop.

Members of the Colon Molecular and Cell Biology Laboratory and the Epithelial Biochemistry Laboratory found that this is the case in mice that were genetically engineered to have a change in a single amino acid in a cell-surface receptor molecule called gp130, which in turn leads to over-activation of a molecule inside all cells called STAT3 (see Under the Microscope, Number 12). Over-active STAT3 leads to stomach cancer in these mice, however mice that have both the alteration in gp130 and STAT3 activity that has been reduced back to a normal level do not develop stomach cancer.

The group reasoned that the alteration in gp130 must be affecting more than just the STAT3 signalling pathway to overcome the normal checks on growth of cells that line the stomach. They found that the TGFβ pathway, which normally keeps cell growth and division switched off, was under-active in mice with the altered gp130. They showed for the first time that the link between the two pathways was Smad7, a negative regulator of the TGFβ pathway that is switched on by STAT3. Importantly, the STAT and TGFβ pathways chatted to each other in human stomach cancer cells as well. A single molecular change in gp130 is therefore able to escalate into stomach cancer growth due to two unrelated signalling pathways talking to each other through Smad7.

Jenkins, B.J., Grail, D., Nheu, T., Najdovska, M., Wang, B., Waring, P., Inglese, M., McLoughlin, R.M., Jones, S.A., Topley, N., Baumann, H., Judd, L.M., Giraud, A.S., Boussioutas, A., Zhu, H.J. and Ernst, M. (2005). Hyperactivation of Stat3 in gp130 mutant mice promotes gastric proliferation and desensitises TGF-beta signalling. *Nature Med.* **11**, 845-852.

What's Happening?

- Associate Professor Andrew Scott was awarded a prestigious US National Institutes of Health \$US325,000 grant to conduct a clinical trial of a colon cancer therapy in an international collaboration between LICR's New York and Melbourne branches. The grant was announced at BIO2005 in Philadelphia by the Minister for Innovation, John Brumby, who said "This trial will be crucial in the effective treatment of colon cancer and reinforces the LICR's international standing as a world leader in cancer research". The trial combines radioimmunotherapy with a chemotherapy drug that is thought will further sensitise the cancer cells to the radioactivity, and was featured on the "7.30 Report" on ABC TV in July.

- A/Prof. Andrew Scott was also awarded an NH&MRC Development Grant to develop an antibody for treatment of rheumatoid arthritis.

- Also announced at BIO2005 was a study by LICR's Dr. Peter Gibbs which resulted in the State Government granting \$8 million to Cancer Trials Australia and Clinical Trials Victoria, and \$1.6 million to Bio21's molecular medicine informatics model. The Bioinformatics funding assisted researchers and doctors to markedly improve databases across several hospitals that collected information on patients with bowel cancer, including those with diabetes. Dr. Gibb's study of 1139 bowel cancer patients at the Royal Melbourne and Western Hospitals confirmed that patients with diabetes are more likely to develop cancer in the first part of the bowel and will allow better identification of who is at high risk for bowel cancer.

- In April, the Victorian Government awarded a \$7 million grant to a consortium that included the LICR Melbourne Branch to establish the Victorian Tissue Bank Initiative (VTBI). The VTBI is expected to provide tissue specimens to the LICR Human Colon Cancer Initiative and other cancer research organizations in Victoria.

- The Ludwig Institute participated in Medical Research Week with a display at Federation Square in June this year.

- Corwyn Willis, a UROP student in the Cytokine Biology Laboratory, was awarded a place on the University of Melbourne Faculty of Science Dean's Honours List for 2005.