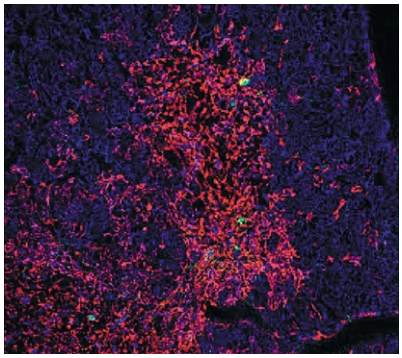
Stem-cell answer to immunosupression?

Researchers from Monash University (Victoria, Australia) have achieved a world first by identifying thymus stem cells and using them to grow a functional organ. Research on the thymus, which is critical in generating T cells, has until now been hampered by an inability to identify the cells that give rise to a complete thymus. This new finding is likely to have widespread implications for immunocompromised patients, such as those with AIDS, diabetes or patients with cancer who have received chemotherapy.

Haemopoetic stem cells have long been known to differentiate into lymphocytes, but until recently very little was known about epithelial stem cells and how to isolate them. The epithelium is an integral part of the thymus, which is vital to the immune response because it converts haemopoetic stem cells to T cells, controls the ability of T cells to recognise foreign invaders, and helps prevent them from attacking body tissues.

The research, published in *Nature Immunology* (2002; **3:** 635–42) involved the development of an antibody that recognises the MTS24+ cell-surface glycoprotein, which was used to identify mouse-embryo cells that were the likely precursors of the adult thymus. Cells expressing this marker were then isolated, cultured, and implanted into mice at a different location in the body; the cells subsequently reformed into a thymus.



Courtesy of J Gill

MTS24+ labelling of thymic epithelial cells.

Lead investigator Jason Gill said: "We hope that our findings will eventually lead towards methods of manipulating thymus cells to increase T-cell production and thereby alleviate disease progression." Next, the Monash team plan to pursue a human analogue of the MTS24+ glycoprotein and develop methods of stimulating the thymic epithelium in mice.

Gill expects this work to have a significant effect on medical oncology in the future. "At present, it may take up to 3 or 4 years for a cancer patient's immune system to regain normal amounts of T-cells following chemotherapy. The option of giving them a post-treatment therapy that stimulates the thymus and restores the immune system would greatly enhance their recovery by reducing complications."

Although this finding is the culmination of more than 15 years of research by the Monash team, Gill foresees rapid translation into the clinic. "Because there is such a great clinical need, we hope to see therapies that stimulate T-cell production in the clinic within 3 years."

Gill speculated that the research may also have implications for cancer prevention. "Our immune systems start to senesce from a young age and we become more susceptible to disease as we get older. In theory, restoring thymic function could help prevent many diseases including cancer, that are more common in old age."

Brad Timms

New drug blocks acute myeloid leukaemia gene mutation

Acute myeloid leukemia (AML) may have a new enemy. A study in *Blood* (2002; **99:** 3885–91) reports that CEP-701, a drug that interrupts leukaemic cell proliferation and survival, could help about one third of patients with AML—ie, those with a mutation in the gene encoding the FLT3 receptor.

Donald Small (Johns Hopkins University, MD, USA), lead study author and consultant to Cephalon Inc, a partial funder of the research, says, "right now patients with FLT3 mutations have a poor chance of survival. Over time, we hope this mutation will actually be encouraging, because we'll have an increased chance for cure in these patients."

Small's team tested CEP-701, a tyrosine kinase inhibitor which blocks signaling through the FLT3 protein, using cultured cells, in vivo mouse models, and cells from patients with AML. "Their study clearly shows that leukaemic cells exposed to the drug stop proliferating and die," states Bob Löwenberg (Erasmus University, Rotterdam, Netherlands), "[but] these cell lines are not always we see in the clinic."

In further tests, CEP-701 killed leukaemia cells harvested from primary human samples containing mutated FLT3. In addition, mice injected with leukaemic cells had improved survival when treated with CEP-701. "It's too early to predict whether clinical leukaemia will be sufficiently responsive to in vivo use of the drug or whether it will be possible to define a [regimen in which] patients will receive sufficient [drug] to eradicate leukaemic cells," Löwenberg adds.

"Recent data have suggested that FLT3 mutations may be secondary events in the process of leukaemogenesis, so therapy with an inhibitor as a single agent may be inadequate," says Panagiotis Kottaridis (Royal Free and University College London Medical School, UK). "Nevertheless, patients with FLT3 mutations carry an increased relapse risk and therefore inhibitor combination with cytotoxic drugs may maximise its benefit and prolong the disease-free survival."

Small concludes: "We hope combining CEP-701 with chemotherapy is where we'll see a big impact in killing these cells." A clinical trial with CEP-701 has now started in adults with AML and the FLT3 mutation.

Kathleen Nelson