Targeting proteins to the proteasome

GFP is widely used as a reporter in studies of gene expression and protein localization, and now in its most recent guise, as a reporter for cytosolic protein degradation. In the May issue of *Nature Biotechnology,* Dantuma *et al*. describe a fluorescence degradation assay in live cells for studying the proteolytic activities of the proteasome. They generated GFP-ubiquitin fusion proteins containing non-stable sequences that targeted the resulting protein for degradation by the proteasome. These ubiquitin-tagged GFPs are presented as a possible tool for high-throughput screening of novel protease inhibitors to identify those that interfere with specific functions of the proteasome.

Nature Biotech., **18,** 538–43 (2000)

Dendritic cells as cancer vaccines

In the May 15th issue of *Journal of Experimental Medicine,* Klein *et al*. show that dendritic cells engineered to express the tumor antigen MAGE-1 elicit anti-tumor effects when used to vaccinate mice with MAGE-1 tumors. Vaccination with these dendritic cells led to decreased metastases in a lung cancer model. In the case of a subcutaneous tumor model, the immunization led to prolonged survival and long-term cures. Further engineering of dendritic cells to also express cytokines such as GM-CSF, TNF-α or CD40L resulted in an even stronger therapeutic effect. In contrast, vaccination with MAGE-1–expressing tumor cells showed no therapeutic effect. The authors call for clinical trials using genetically modified dendritic cells.

J. Exp. Med., **191,** 1699–1708 (2000)

A role for Lck in thymocyte differentiation

In a recent issue of *Immunity*, Zamoyska *et al*. investigated the role of Lck, the T lymphocyte-specific tyrosine kinase, in thymocyte positive selection. *Lck* gene-targeted mice have an early block in thymocyte differentiation, resulting in dramatically reduced numbers of thymocytes. To test the role of Lck at various stages of thymocyte differentiation, the researchers established a tetracycline-inducible transgenic mouse model in which expression of Lck can be regulated in the thymocytes. This study illustrates the power of using an inducible expression system to achieve expression of a gene of interest in a time- and tissue-specific manner. Lck is central to the expansion of immature thymocytes, and is particularly important for positive selection in CD4, but not CD8, lineages.

Immunity, **12,** 537–46 (2000)

Concentrating on B cell and macrophage development

The transcription factor, PU.1, is required for the development of many lineages of the immune system. In a recent issue of *Science*, DeKoter and Singh show that differing concentrations of this protein regulate the development of B cells and macrophages. Retroviral transduction of *PU1* cDNA into hematopoietic progenitor cells reveals that a low concentration of the protein promotes B cell differentiation, whereas a high concentration induces macrophage differentiation and blocks B cell development. The authors speculate that graded expression of a transcription factor to specify distinct cell differentiation could turn out to determine the fate of many other lymphoid and myeloid cells.

Science, **288,**1439–41 (2000)

IL-6 and Crohn's disease

Changes in cytokine production by lamina propria macrophages and T cells may be involved in the pathogenesis of Crohn's disease. In the June issue of *Nature Medicine,* Atreya *et al.* investigate the role of the cytokine IL-6 in resistance of T cells to apoptosis in Crohn's disease. They found that Crohn's patients produced substantially more IL-6 than controls, and that the high IL-6 production was associated with increased production of the soluble IL-6 receptor. In animal models, a neutralizing antibody against IL-6R, or a blocking ligand of the sIL-6R, suppressed established experimental colitis by inducing apoptosis of mucosal T cells. Specific targeting of IL-6 signaling may be a therapeutic option for chronic intestinal inflammation.

Nature Med., **6,** 583–88 (2000)

NK receptor/MHC class I crystal complex

Boyington *et al*. report in *Nature* the crystal structure of a human NK cell receptor complexed to class I ligand HLA-Cw3. When an NK cell recognizes ligands on another cell, a signal is released which results in the death of that cell. To avoid killing cells that are normal and healthy, NK cells bind to MHC class I molecules and generate signals that inhibit killing. This NK receptor is part of the immunoglobulin family and consists of two globular immunoglobulin-like domains linked by a hinge region. The receptor binds the MHC molecule across the peptide groove. There are also direct interactions between the peptide and the receptor. The receptor-ligand structure indicates another binding site of the receptor to the MHC molecule, although the significance of this is yet to be established.

Nature, **405**, 537–543 (2000)

The strange life of chemokines

Chemokines are involved both in routine leukocyte trafficking and in the activation and recruitment of specific cells to sites of inflammation and infection. In the *Journal of Experimental Medicine*, Chvatchko *et al*. investigated the role of CCR4 by generating CCR4 gene targeted mice. These mice showed an unexpected resistance to the lethal effects of LPS in two models of LPS-induced endotoxic shock. In the December issue of *Immunity,* Cook *et al.* studied the function of CCR6, again using a gene targeting approach. The resultant mice have an impaired humoral response to orally administered antigen and the enteropathic rotavirus, and they show abnormalities in the distribution of cells in Peyer's patches. These findings illustrate the functional diversity of chemokines, from the inflammatory response to regulating immunity.

J.Exp.Med., **191,** 1755–63 (2000); *Immunity,* **12,** 495–503 (2000)