Affirmation of suppression

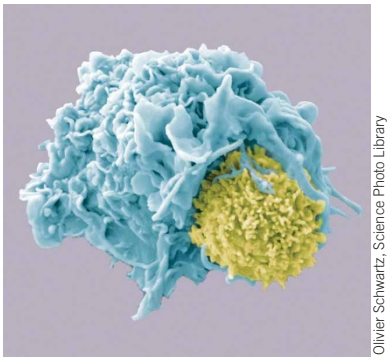
In the mid-1990s, 'suppressor T cell' was a dirty word among most immunologists: evidence for the existence of such an immune-suppressing T-cell population was spotty and hard to verify.

All that began to change in 1995. Shimon Sakaguchi *et al.* identified a population of T cells with specific molecular markers that protected against various autoimmune symptoms in mice, such as those directed at the thyroid and the joints (*J. Immunol.* **155**, 1151–1164; 1995). The clincher came when researchers identified a transcription factor, foxp3, necessary for the development of these cells—now generally called 'regulatory T cells' (*Science* **299**, 1057–1061; *Nat. Immunol.* **4**, 330–336; 2003). Mice or humans deficient in foxp3 die at a young age from uncontrolled autoimmunity (*Nat. Genet.* **27**, 18–20, 20–21; 2001).

Since the 1995 discovery, experiments in mice have implicated regulatory T cells in a variety of diseases, including inflammatory bowel disease, diabetes and leishmania. More recent studies, many this year, have provided parallel findings in humans for diseases ranging from multiple sclerosis and HIV to rheumatoid arthritis and asthma.

Therapeutically, the new knowledge has found the most promise so far in cancer and transplantation. Depletion of regulatory T cells can help fight tumors in mice—in line with findings that regulatory T cells also counteract tumor growth in humans. Injection of regulatory T cells from the donor into mice with bone marrow transplants can control graft-versus-host disease. But the ability to strike the balance between too little and too much immune suppression remains the key to ultimate success. —*CS*

Kiss of death



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A dendritic cell and a T cell interacting.

Three groups found in 1998 what it takes to activate a cytotoxic T cell, prompting it to kill targets such as virally infected cells. Previous work had shown that this conversion required an encounter of the cytotoxic T cell with an antigen on the surface of an antigen-presenting cell, often with an added boost from a T helper cell. Those findings led to the idea that the T helper cell and the cytotoxic T cell had to recognize the same antigen-presenting cell simultaneously. But the likelihood of such a ménage à trois is extremely low, and the new discovery provided a simpler solution (*Nature* **393**, 474–478, 478–480, 480–483; 1998). The T helper cell activates an antigen-presenting dendritic cell after antigen recognition through an interaction between CD40 and CD40 ligand. This 'licensed' dendritic cell in turn can stimulate a killer T cell in a subsequent encounter. The researchers found that an antibody specific for CD40 activated the dendritic cell directly, removing the need for T cell help—a trick since used experimentally in strategies to induce immune responses to tumor antigens. —*AF*

Written by Alison Farrell, Clare Thomas and Charlotte Schubert in consultation with experts in the field.

Trends in transplantation

During the last ten years, transplantation biologists edged closer to their ultimate aim—to transplant an organ without life-long immunosuppression, or without increased risk of cancer or infection.

Christian Larsen *et al.* made a splash in 1996 by simultaneously blocking two different signaling pathways in mice required for activation of T cells, thereby preventing rejection of skin grafts. (*Nature* **381**, 434–438; 1996). The approach supported the development of costimulation blockade as a regimen to induce transplant tolerance. In 1999, Allan Kirk *et al.* extended these findings by showing that blocking just one of the pathways prevented rejection of kidney allografts in monkeys without the need for additional immunosuppression (*Nat. Med.* **5**, 686–693; 1999). But clinical experiments have tempered enthusiasm for the approach, which is hampered by side effects related to blood clotting. Other strategies gaining favor include establishing allogeneic chimerism—in which the recipient of a solid organ also receives bone marrow cells from the donor to facilitate graft tolerance (*Transplantation* **68**, 480–484; 1999). More recent findings suggest that regulatory T cells hold clues to the induction of tolerance.

Meanwhile, pigs continue to be explored as alternate sources of tissue grafts. Two groups (*Science* **295**, 1089-1092; *Nat. Biotechnol.* **20**, 251–260; 2002) created pigs that lacked one copy of a gene that causes rejection of human organs. The gene encodes an enzyme that makes a sugar molecule on the surface of pig cells. Complete knockouts have since been generated, but pig retroviruses could hold back the technology (*Nat. Med.* **3**; 282–286; 1997). —*AF*

Monoclonal mania

Monoclonal antibodies were first harnessed for therapy in the 1980s, but the approach reached full swing in the 1990s. In the last ten years, the US Food and Drug Administration approved more than 12 monoclonal antibodies. Examples include antibodies against TNF-α for rheumatoid arthritis and inflammatory bowel disease and antibodies against the growth factor receptor Her2, which can shrink tumors in some advanced breast cancers (*J. Clin. Oncol.* **14**, 737–744; 1996). An antibody against CD20, a transmembrane protein expressed on B cells is effective against non-Hodgkin lymphoma and other conditions (*Blood* **84**, 2457–2466; 1994 and *J. Clin. Oncol.* **16**, 2825–2833; 1998). Innovations include linking antibodies to toxins or radionuclides. There are now over 400 monoclonal antibodies in clinical trials. —*CS*

Killing naturally

Natural killer T (NKT) cells are a strange breed. They share killing mechanisms in common with conventional T cells and natural killer cells, which recognize target cells in a non-specific manner. Crucial aspects of how NKT cells function were obscure until 1995, when Albert Bendelac *et al.* revealed how NKT cells recognize the cells they eliminate (*Science* **268**, 863–865; 1995).

Like conventional T cells, the repertoire of NKT cells is selected in the thymus during development. During T-cell development, this selection is controlled by the interaction of the T cell receptor with the MHC class I–peptide complex on antigen-presenting cells. But the NKT cell receptor does not recognize MHC I. Bendelac *et al.* discovered that NKT cells instead recognize the cell-surface molecule CD1. And instead of presenting peptides, CD1 molecules present lipids to NKT cells.

Recognition by CD1 prompts release of cytokines. NKT cells therefore not only kill cells directly, but modulate the immune system in other ways to affect the response to certain infections, and during autoimmunity and allergy. —*CT*