decided to marry education with culture and has put forward Viviane Reding, a former Luxembourg journalist, to head this new directorate. But Prodi plans to shift agricultural research into Busquin's directorate.

The new commission is being formed now because of the mass resignation last March of the previous incumbents in the wake of a scathing report by a European Parliament investigative panel that had alleged cronyism and mismanagement among Brussels officials, with Busquin's predecessor, Edith Cresson of France, one of the most heavily criticized (*Science*, 19 March, p.1827). Prodi called the new candidates "a top-quality team in which jobs have been allocated to match the proven abilities and experience of each commissioner." He said he would demand that the commissioners streamline the Brussels bureaucracy, live up to high ethical standards, and "give clear direction and leadership."

Busquin, 58, is known mainly as the leader of the Socialist Party in Belgium's French-speaking region. He received a physics degree from the Free University of Brussels in 1962 and was an assistant physics lecturer at the university's medical faculty from 1962 to 1977. He studied ecology and environmental issues at the Free University in 1976, and was chair of the board of directors of Belgium's Institute of Radioelements from 1978 to 1980. He entered local Belgian politics in 1977 and later held various national and regional ministerial posts until becoming vice president of the Socialist International, a federation of socialist parties, in 1992. He was elected as a member of the European Parliament last month.

–ROBERT KOENIG

HUMAN GENOME PROJECT

Commercial Firms Win U.S. Sequencing Funds

Several new groups are joining the government's human genome sequencing project this month, including—for the first time—two commercial firms. The National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, quietly awarded three yearlong grants totaling $15 million on 1 July. The winners can expect to be funded for at least two additional years at the current rate, NHGRI notices say. The objective is to scale up production of human DNA sequence and help deliver a 90% complete "working draft" of the human genome for public release next spring and a 99.99% finished version by 2003. NHGRI turned down some academic centers while funding commercial outfits, indicating that it is serious about rewarding efficiency.

The latest grants raise the total NHGRI kitty for human genome sequencing to nearly $100 million per year through 2002. The principal investigators (PIs) leading the newly funded teams are Maynard Olson at the University of Washington, Seattle ($7 million per year); Douglas Smith, co-director of the sequencing center at Genome Therapeutics Corp. of Waltham, Massachusetts, the first commercial firm to take part ($5 million); and Ronald Davis of Stanford University ($3 million). According to documents released by NHGRI, Olson expects to sign a contract with another company, Incyte Pharmaceuticals Inc. of Palo Alto, California, for about $3 million worth of DNA sequencing per year. NHGRI plans to continue funding these teams through 2002.

The newcomers join university-based groups that won larger NHGRI grants in March, including the Whitehead Institute/MIT Sequencing Center in Cambridge, Massachusetts, Washington University in St. Louis, and the Baylor College of Medicine in Houston, Texas (*Science*, 19 March, p. 1822). They are part of an international network that includes the U.S. Department of Energy's Joint Genome Institute in Walnut Creek, California, and the nonprofit Sanger Centre in Hinxton, U.K.

Smith says his group will work closely with the Sanger Centre, focusing mainly on sequencing chromosome 10. The Stanford group, says Davis's colleague Nancy Feldspiel, will contribute some DNA data but, more significantly, develop robotic instruments to make genome work more efficient. Olson will supervise a consortium that includes sequencers at Incyte focusing on chromosome 7 and on automated methods of finishing. All members of this network, including the companies, agree to release raw DNA data on a daily basis, refrain from patenting raw data, and publish finished data within 6 months of "validation."

Geneticist David Cox of Stanford University, whose lab did not get funded in this competition, says: "I think it's a great idea that we're looking for the most efficient ways to get high-quality sequence data."

–ELIOT MARSHALL

NEW RECRUITS

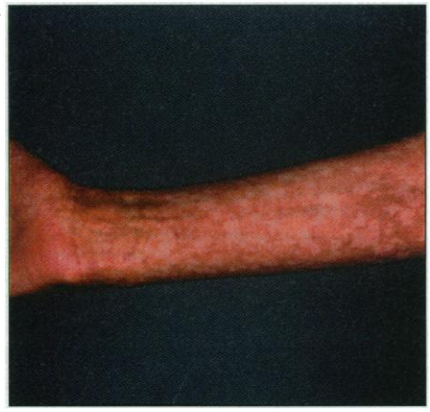
Institution and PI	Award
University of Washington, Maynard Olson	$7 million*
Genome Therapeutics Corp., Douglas Smith	$5 million
Stanford University, Ronald Davis	$3 million

* About $3 million will be subcontracted to Incyte Pharmaceuticals Inc.

IMMUNOLOGY

Keeping Bone Marrow Grafts in Check

Cancer patients who have received aggressive chemo- or radiotherapies often need bone marrow transplants, because the treatments wipe out their immune systems as well as their tumors. But bone marrow transplants (BMTs) often come at a price. Because the donor and recipient tissues usually differ genetically, about two out of three patients develop graft versus host disease (GVHD), in which donor T cells turn against their new host and wreak havoc in organs such as the skin, liver, and the intestines. Fever, rashes, and diarrhea ensue, and in severe cases GVHD can be lethal, making it the primary cause of death after BMTs.



Early warning. Rashes caused by donor T cells attacking and destroying skin cells of bone marrow transplant recipients are an early symptom of GVHD.

To curb GVHD, clinicians either sift out all the T cells from the donor marrow or treat recipients with powerful immunosuppressive drugs. Both approaches leave patients extremely vulnerable to infections, however. A report on page 412 now suggests another, and perhaps less dire, strategy. A team led by immunologist Stephen Emerson of the University of Pennsylvania School of Medicine in Philadelphia has found that GVHD can be suppressed in mice by inactivating the recipients' antigen-presenting cells, or APCs. APCs display snippets of foreign proteins to T cells, sparking an immune response. Suppressing these cells blindfolds the donor T cells toward host cells, the team found. In contrast, the T cells should still be capable of responding to viruses or other pathogens presented by donor APCs from the transplants.

The study "offers a new approach to tackle a problem that has pestered us for the last 25 years from an entirely different angle," says bone marrow transplant specialist Joseph

SOURCE: (LEFT) NHGRI; PHOTO: (TOP) BIOPHOTO ASSOCIATES/PHOTO RESEARCHERS

Antin of the Dana-Farber Cancer Institute in Boston. If it pans out in humans, Emerson adds, it may "improve the safety of bone marrow transplants so they could be used much more widely." They might, for instance, replace the faulty bone marrow in patients with sickle cell anemia or other blood diseases.

Emerson and his collaborator, Mark Shlomchik at Yale University School of Medicine, initially wondered whether GVHD is caused by donor APCs or by the recipient's own APCs, some of which survive the chemotherapy. To answer that question, the researchers created a new strain of mice whose bone marrow–derived cells no longer carried the proteins known as major histocompatibility complex (MHC) antigens. Because antigens must be displayed on MHC proteins, this rendered the APCs of the mouse strain incapable of presenting antigens to any T cells.

Emerson and his team then irradiated the altered mice, along with "normal" mice who were otherwise genetically identical, and performed BMTs on all the animals. For the transplants, the researchers used bone marrow from a strain of MHC-identical mice that differed only in minor surface markers —a match like the one doctors seek for human patients, says Emerson.

The team found that GVHD occurred less often and in a milder form in mice whose APCs had been crippled by their lack of MHC molecules. These animals lost about 46% less weight due to GVHD-induced diarrhea, and only two out of 16 died, compared to 14 out of 16 in the control strain. This indicates, says Emerson, that "the great majority of the APCs that trigger GVHD are host-derived rather than donor-derived."

Of course, it is impossible to use the same APC-inactivating strategy on human cancer patients, but other work by Emerson and his colleagues suggests that host APCs can be inactivated with antibodies. The researchers irradiated mice and then injected them with an antibody that binds to the cell surface of APCs. When they dissected the animals' lymph nodes and spleens, organs where APCs abound, they found that "the antibody had covered all the [APCs] present," says Emerson. If the antibody were coupled with a toxin, he adds, it might be able to eliminate the remaining host APCs and thus prevent GVHD.

The study is a "proof of principle; it shows that host APCs play a major role" in GVHD, says Voravit Ratanatharathorn, a BMT specialist at the University of Michigan, Ann Arbor. But he cautions that "how to block the APCs in [patients] is yet another problem." So far, he notes, the Emerson team has not shown that anti-APC antibodies work in mice, let alone humans.

He and others point out that after a BMT, the donor immune cells also play a role in keeping some cancers, such as leukemias, from recurring. If so, then inactivating the patients' APCs may lessen this protective effect. As immunologist Jonathan Sprent of The Scripps Research Institute in La Jolla, California, asks, "If the [donor] T cells never see [host] APCs, are they ever going to be activated" against leukemic cells if the cancer were to recur after the BMT?

But others think that the strategy of inactivating recipient APCs is worth exploring, as the alternative often involves eliminating the T cells from the graft. Compared to recipients of complete bone marrow, "the engraftment of T cell–depleted bone marrow is much worse, and the relapse rate in leukemia patients is much higher," says immunologist H. Joachim Deeg of the Fred Hutchinson Cancer Research Center in Seattle.

–MICHAEL HAGMANN

IMAGING

A Microscope With An Eye for Detail

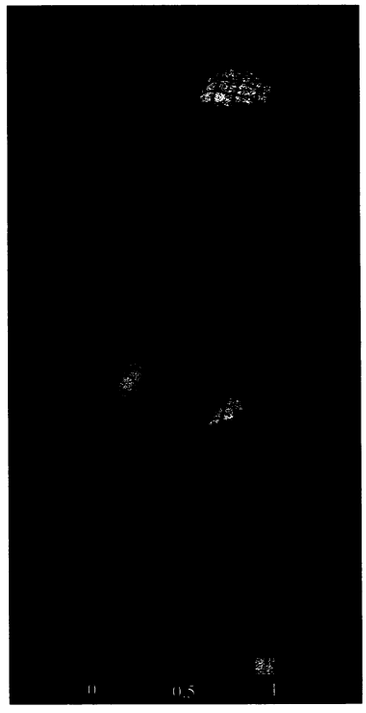
Once, it was a microscope's optical precision that limited the detail it could see. Today microscope design has reached the point where the limits of resolution are set by the laws of physics. But even basic laws can sometimes be flouted with creative thinking. In the 15 July issue of *Optics Letters*, researchers describe a principle they say can dramatically improve the resolution of fluorescence microscopes, which have traditionally been constrained by the so-called diffraction limit.

Diffraction limits resolution because light waves passing through any aperture, such as a lens, spread out slightly, countering the focusing effect of the lens and making it impossible to focus the light to an arbitrarily small point. "For decades most people had accepted the diffraction limit," says Min Gu, a physicist at Victoria University of Technology in Australia, "but it can be overcome." Stefan Hell, a physicist at the Max Planck Institute of Biophysical Chemistry in Göttingen, Germany, and his colleagues have now shown as much with a clever combination of two laser beams. One illuminates and images the sample, while the second sculpts the first to reduce the effects of diffraction.

Because of diffraction, most microscopes using light have a resolution no smaller than about 200 nanometers (nm), about the size of a large virus. Electron microscopes can do better, and light microscopes can also beat the diffraction limit by simply omitting the lens. The scanning near-field optical microscope (SNOM), for example, images objects with a resolution as fine as 80 nm or so by squeezing light through a tiny opening in a fiber and scanning the fiber tip across the object, collecting reflected light.

But nothing can quite replace an optical microscope based on focusing lenses. Cells have to be killed and dehydrated to be viewed with an electron microscope, and SNOMs construct an image slowly. And neither kind of microscope can image structures in the interior of a cell, as an optical microscope can when proteins or other cellular components are tagged with dyes that light up when photons from a laser excite them.

Diffraction prevents the laser beam—and hence the spot of fluorescence—from being focused to a spot any smaller than about 200 nm. So any two features closer than 200 nm apart will fluoresce together and be mistaken for one. But Hell thought that if he could suppress the fluorescence from part of the beam, objects closer together than 200 nm could be illuminated and detected separately.



Making distinctions. A fluorescence image made with a sculpted laser beam reveals three dye particles (bottom), which blur in a conventional image.

CREDIT: T. A. KLAR, M. DYBA, AND S. W. HELL

A few years ago, he had shown that theoretically, a second beam of laser light that partially overlapped the first one could force the excited dye molecules to take another path down to their ground state, in a process known as stimulated emission. They would give off light at a different wavelength, reducing the size of the fluorescent patch. "If you look down from the lens, the spot [of light] is round, like a hamburger," says Hell. "Now imagine taking a bite off the outer part of the hamburger." The sculpted beam could be scanned across the sample, lighting up features smaller than the diffraction limit one by one.

Hell and his colleagues have now dem-