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

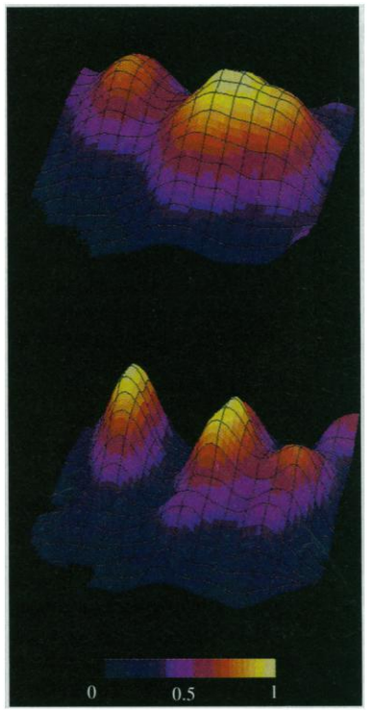
Once, it was a microscope's optical precision that limited the detail it could see. Today microscope design has reached the point where the limits of resolution are set by the laws of physics. But even basic laws can sometimes be flouted with creative thinking. In the 15 July issue of *Optics Letters*, 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-

onstrated this technique in the laboratory with a test sample consisting of scattered nanocrystals of a fluorescent compound, pyridine. With a burst of an ultraviolet laser, they sparked fluorescence in the crystals. They then sent in the second laser pulse, known as the stimulated emission depletion (STED) pulse, to take a bite out of the first one. The result was dramatic: Where two pyridine molecules appeared as a single blur without the STED beam, they could be distinctly resolved once the STED beam was turned on.

Gu says he is impressed by the 30% improvement in resolution, which allowed the STED microscope to distinguish crystals as little as 100 nm apart. Peter So, a mechanical engineer at the Massachusetts Institute of Technology in Cambridge, thinks the resolution could eventually reach 30 nm, fine enough to distinguish structure in individual DNA molecules. Advances like Hell's are a sign, So believes, "that we are in the midst of a renaissance in optical microscopy."

–MEHER ANTIA

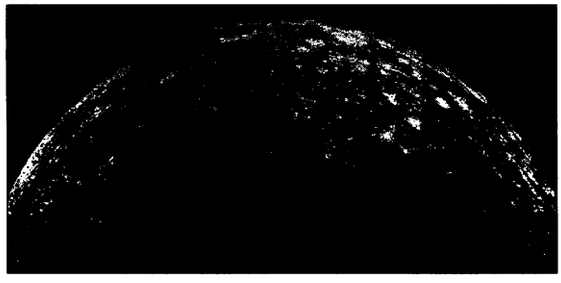
Meher Antia is a writer in Vancouver.

SPACE SCIENCE

NASA Plans Close-Ups Of Mercury and a Comet

NASA last week selected two spectacular shows as part of its Discovery program of quick and cheap space missions. In 2008 and 2009, a spacecraft will scrutinize Mercury, and in 2005, another mission will shoot a massive copper cannonball into a comet to learn more about its innards. The scheduled date for the cometary fireworks, which space enthusiasts can watch from Earth: 4 July.

The spacecraft Messenger, to be launched in spring 2004, will orbit Mercury for 1 year after two brief flybys. Loaded with cameras to map the planet's surface and spectrometers to analyze its crust and tenuous atmosphere, Messenger will transmit the first close-ups of Mercury since the Mariner 10 mission in 1974–75. Messenger should shed light on how planets form and why some, like Mercury and Earth, have retained their magnetic fields while others, like Mars, have shed theirs, says planetary scientist Sean Solomon of the Carnegie Institution of Washington's Department of Terrestrial Magnetism, who leads the $286 million mission.



Pockmarked planet. Messenger will take the first close-ups of Mercury since 1975.

The extremely dense planet consists mainly of a large metal core, says planetary geophysicist Raymond Jeanloz of the University of California, Berkeley. A giant impact, much like the one that chipped off Earth's moon, may have splashed off most of Mercury's mantle, he says. Messenger's gravity mapping studies will probe for evidence of crust-busting impact sites. The mission should also reveal whether volcanoes have shaped Mercury's surface and if ice exists in the shadows of its polar craters, says planetary scientist Faith Vilas of the Johnson Space Center in Houston.

In January 2004, a $240 million mission called "Deep Impact" will take off for comet Tempel 1, which circles the solar system every 5.5 years. When it arrives a year and a half later, an observation module will release an "impactor"—essentially a 500-kilogram copper bullet—which will slam into the comet's surface at a speed of 10 kilometers per second. A camera onboard the bullet will transmit images as it hurtles toward its target; the hovering observer module will record both the crash and the size and shape of the resulting crater, and analyze solid and gaseous material released by the blast.

The crash may help answer questions about the composition of comets and their chemical histories, says Lucy McFadden of the University of Maryland, College Park, one of the project's scientists. Comets formed from primordial material condensing at the edge of the solar system, but their interiors may have heated and undergone chemical changes during their tours through the solar system. So far, scientists have only been able to model these processes and simulate comets' internal properties. "This is an in situ experiment that will constrain these theories," says McFadden. Indeed, Deep Impact marks planetary science's graduation from classic, observational studies to active experimentation, notes Alan Stern of the Southwest Research Institute's Department of Space Studies in Boulder, Colorado.

Smash hit. Deep Impact will fire a copper cannonball into comet Tempel 1.

The approval of Deep Impact follows close on the heels of a NASA decision to scrap a mission, called Champollion, that would have attempted a soft landing on Tempel 1. The lander would have drilled into the comet's surface and analyzed core samples at different depths. Although its estimated cost was roughly the same as that of Deep Impact, Champollion fell within NASA's New Millennium Program and was competing for scarcer funds than the Discovery Program missions.

Deep Impact should entertain the Earthbound as well as further space science: If skies are clear, the celestial collision will be visible with a pair of ordinary binoculars. But don't expect too much: The comet will look like a small smudge, and the impact will show up as a mere pinpoint of bright light.

–LAURA HELMUTH

YOUNG FACULTY AWARDS

Keck Helps Five Careers With $1 Million Grants

All spring Yale University biophysicist Mark Gerstein had been on tenterhooks. As one of 10 finalists in the W. M. Keck Foundation's new Distinguished Young Scholars in Medical Research program, Gerstein was on the verge of getting a flexible, $1 million grant—a significant bounty for a researcher of his age (33). But after making his pitch in April, Gerstein's phone went silent—until last week, when he learned that he was one of five junior faculty members in the United States to make the final cut. "I was ecstatic," he says. "But I'm also relieved—that's a lot of grant applications that I won't have to write for a few years." Gerstein's $1 million award will support his research in genomics and bioinformatics.

The Los Angeles–based foundation,

CREDITS: (TOP) BALL AEROSPACE; (BOTTOM) NASA