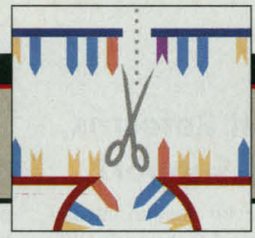
2436
Lava fountain on Io

LEAD STORY 2438
Storm warnings in space



2441
Turning off genes with DNA

asked NIH in August to "withdraw" the draft guidelines, saying they were "illegal" and would make it difficult for his company to work with NIH grantees. Haseltine declined to comment on the final text.

Richard Burgoon, vice president and general counsel of Arena Pharmaceuticals in San Diego, says many executives may not want to comment publicly on NIH's guidelines because they don't want to cause offense. Although he fears that some will not want to share new technology with NIH grantees without assurances that they can retain control, he remains "optimistic … that NIH will make a good-faith effort" to remain flexible.

–ELIOT MARSHALL

CANCER RESEARCH

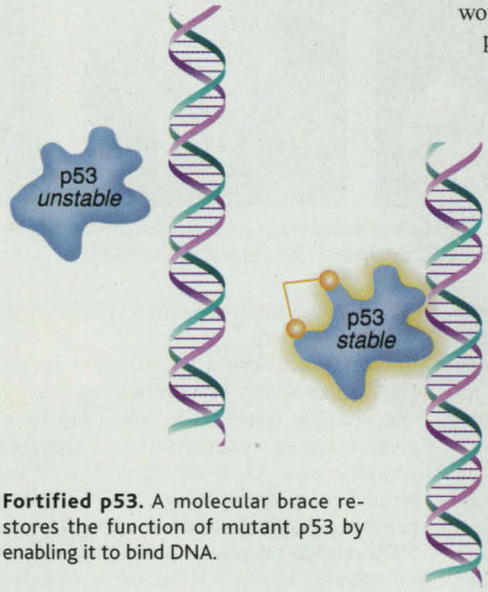
Bracing p53 for the War on Cancer

Sometimes called the "guardian of the genome," the tumor suppressor protein p53 responds to DNA damage by either shutting down cell division or causing the cell to commit suicide. Either way, p53's action helps short-circuit tumor formation by preventing cells that have suffered malignant mutations from continuing to grow. Yet the *p53* gene itself is susceptible to damage, which is thought to contribute to the development of half of all cancers, including common ones such as skin, breast, and colon cancers. Now, researchers have identified a drug that may be able to restore the normal function of some mutated p53 proteins and might therefore point the way to a new kind of cancer therapy.

To halt cell division or trigger cell suicide, p53 needs to regulate the activity of various genes, which requires that it first bind to the DNA of the genes' regulatory sequences. And researchers have found that many of the mutations that disable p53 cause the protein to misfold, thereby producing a molecule without the rigid three-dimensional conformation it needs for this binding. In the new work, which is described on page 2507, cancer biologist Farzan Rastinejad and his colleagues at Pfizer Central Research in Groton, Connecticut, have come up with a molecular prosthesis that enables mutant p53 to fold correctly. With its proper posture restored, the aberrant p53 can put the brakes on cell division in both lab cultures and in tumors growing in mice, the researchers report.

ILLUSTRATION: C. CAIN, SOURCE: F. RASTINEJAD

Their results are just a first step on the long road toward making a drug that can be used in humans. Nevertheless, they represent "an exciting proof of principle of what promises to be a new form of therapy," says Bert Vogelstein, a cancer biologist at The Johns Hopkins University School of Medicine in Baltimore, Maryland. What's more, Rastinejad adds, because misfolded proteins are implicated in other disorders, including Alzheimer's, cystic fibrosis, and the brain diseases thought to be caused by infectious proteins called prions, "this approach may pertain to a lot of diseases."



Fortified p53. A molecular brace restores the function of mutant p53 by enabling it to bind DNA.

Before searching for a molecule capable of bracing an aberrant p53 in the correct position to attach to DNA, Rastinejad and Pfizer cancer biologist Barbara Foster needed a quick way to tell whether a compound was working. They hit on the idea of using a well-known antibody that recognizes a part of p53 that is exposed only when the protein is in the right conformation. Ultimately, Rastinejad and Foster screened more than 100,000 compounds with the antibody, first identifying compounds that could increase its binding to normal p53, then testing the successful compounds on mutant p53 in the test tube. The compounds that passed that test then went on to the next phase, in which the Pfizer team looked to see which ones could correct a mutant p53 protein in cultured tumor cells.

The researchers found that a few did work in this assay, causing a fivefold increase in the amount of properly folded p53. The compounds also restored the ability of mutant p53 protein to activate genes. To monitor p53 activity, the researchers equipped the cells with the gene for luciferase, an enzyme that can make cells luminescent, linked to control sequences that would cause the gene to be turned on by p53. The p53-restoring compounds, they found, produced a 10-fold increase in the intensity of the luminescence. Because it takes about 5 hours to see these effects, Rastinejad thinks that the compounds aren't fixing existing p53 but rather are ensuring that new p53, which the cells constantly produce in high quantities, maintains its correct fold.

However they work, the booster molecules curbed cancer growth in mice. In animals that received daily injections of the best of these compounds for a week, tumors caused by injecting mice with human skin cancer cells that have mutant *p53* genes grew to only half the expected size, and twice-a-day treatments reduced tumor growth even more—by 75%. Twice-daily treatment also completely prevented tumors from appearing in mice that had first been injected with human colon cancer cells. "These researchers seem to have hit on a way of making mutant p53 act like a normal protein," notes Karen Vousden, a molecular biologist at the National Cancer Institute laboratory in Frederick, Maryland.

Vogelstein cautions that the doses required are too high for the compounds to be practical at this point. Still, Rastinejad says, these results suggest ways to make better compounds. He notes that the 300 compounds that worked have common features—a hydrophobic, or water-hating, end, which likely fits into a hydrophobic pocket in p53, and a positive charge at the other end, which likely attaches to a negatively charged spot on p53. "You [also] have to have just the right distance between the two ends of the molecule" for the molecular brace to fit right, Rastinejad adds. By designing new compounds with similar characteristics, he says, researchers can find molecules several orders of magnitude better at putting the guardian of the genome back on duty.

–ELIZABETH PENNISI