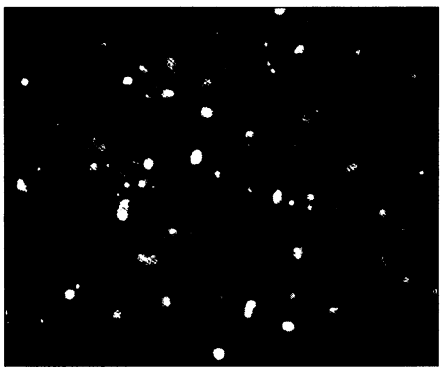
ANGIOGENESIS RESEARCH

Cancer Drugs Found to Work in New Way

When it comes to treating cancer with drugs, the dogma is "no pain, no gain." Patients are hit with doses that may take them within an inch of their lives, then allowed to recover for several weeks before being blasted again. Occasionally, when patients can't tolerate or have already failed to respond to high-dose chemotherapy, oncologists try a gentler chemotherapy regimen: low oral doses taken continuously. Although this approach minimizes side effects and sometimes even shrinks tumors, it does not work well enough to be widely used. Nor has anyone understood its mode of action, especially when it slows down tumors that have already developed resistance to the drug. Now answers are emerging from two new studies in mice, and the information may enable clinicians to improve the effectiveness of this type of therapy.



Double targets. In this mouse tumor, both endothelial cells (yellow nuclei) in the microvessels (red) and tumor cells (green-stained nuclei) are dying as a result of metronomic therapy.

The studies come from Timothy Browder, Judah Folkman, and colleagues at Harvard Medical School in Boston, who describe their results in the 1 April issue of *Cancer Research*, and from another team, led by Giannoula Klement and Robert Kerbel of the University of Toronto, who presented their findings last week at the annual meeting of the American Association for Cancer Research (AACR) in San Francisco. (Most of what they reported appears in the 15 April issue of the *Journal of Clinical Investigation*.) Both teams show that this gentler form of chemotherapy, recently dubbed "metronomic" therapy because it never misses a beat, may work by blocking angiogenesis—the sprouting of new blood vessels that feed growing tumors. What's more, both groups show that the effectiveness of metronomic therapy is enhanced when it is used in combination with drugs that specifically inhibit angiogenesis.

Folkman and Browder set out 5 years ago to find out why standard chemotherapy, which kills dividing cells, doesn't block angiogenesis by killing the endothelial cells that divide to form new blood vessels. If chemotherapy did target those endothelial cells, then it should kill even drug-resistant tumors by blocking their blood supply. Working in mice with tumors, Browder figured out why that doesn't happen: With standard intermittent chemotherapy, the endothelial cells recover during the rest periods and restore the tumor's blood supply.

In the current work, both the Harvard and Toronto teams report that if they eliminate the rest periods, they can prevent this from happening. The two teams inoculated mice with tumors, including some that were highly resistant to the chemotherapy drugs they were using—cyclophosphamide in the Harvard group's experiments, and vinblastine in the Toronto group's. Both found that continuous treatment with relatively low and easily tolerated doses of the drugs caused the tumors to shrink or slowed their growth. "That suggests we are having an effect on some other [nontumor] cell type," says Kerbel. Indeed, Browder's work confirmed that the treatment kills endothelial cells and blocks angiogenesis.

The tumors eventually regrew. But when the teams added a known antiangiogenic drug to the mix—the Harvard team used a drug called TNP-470, and the Canadians used an antibody that blocks the receptor through which vascular endothelial growth factor, VEGF, exerts its effects—the tumors did not return, even when treatment was discontinued.

Not only does this suggest that the treatments cured the mice, says Kerbel, but his team saw "no overt toxicity" in the treated animals. The Harvard mice also fared well, losing only 5% of their body weight—compared to 20% on standard chemotherapy—and living out their full life-spans. "I'm very excited" about the promise of combining antiangiogenesis drugs with metronomic therapy, says cancer biologist Douglas Hanahan of the University of California, San Francisco, who wrote a commentary on the Kerbel team's paper. "There could be some real benefits there."

The extent of benefit for humans remains to be seen, but some cancer researchers have been sufficiently optimistic to undertake clinical trials. A team at the European Institute of Oncology in Milan has begun a study of metronomic chemotherapy, using the drugs Cytoxan and methotrexate, in patients with breast or colon cancer. At the AACR meeting, team member Filippo de Braud reported that some patients are showing tumor shrinkage. He also said the team plans to combine the therapy with an antiangiogenesis drug.

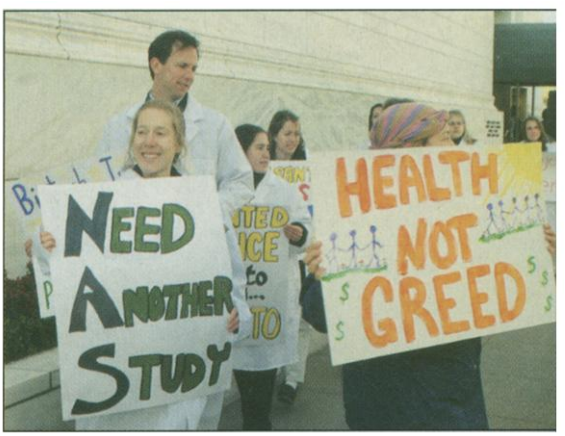
But Kerbel and Folkman caution that oncologists should not put patients who have other options on metronomic therapy unless clinical trials prove it to be effective in humans. Even if clinical studies do show benefit, they expect the approach will be less successful in humans than in mice, given experience with other cancer drugs. But, Kerbel adds, if the work leads to a new cancer therapy that "prolongs survival in a subset of cancer patients, with minimal or no toxicity, that will be a very significant advance."

–MARCIA BARINAGA

BIOTECHNOLOGY

Transgenic Crops Report Fuels Debate

Wading into one of today's most politically charged scientific issues, a National Academy of Sciences panel* last week called for tightening the regulation of plants genetically modified to repel pests. Transgenic crops have generally been adequately tested for health and environmental effects, but agencies should collect more data and coordinate their reviews, concluded the panel. In keeping with the drama that accompanies anything about genetically modified organisms (GMOs), industry groups immediately trumpeted the report's conclusion that biotech foods on the market are safe, while environmentalists dismissed the report as "tainted" by industry ties.



Bitter harvest. Activists protest the academy's report on transgenic crops.

The long-awaited study is the first academy report in more than 10 years on biotech crops, which are flooding the market. Indeed, more than one-fifth of all corn and cotton crops planted in the United States last year contained a bacterial gene for a pest-

* Genetically Modified Pest-Protected Plants: Science and Regulation, National Academy Press, books.nap.edu/catalog/9795.html

CREDITS: (LEFT TO RIGHT) T. BROWDER *ET AL.*, *CANCER RESEARCH* (1 APRIL 2000); BILL FREESE/FENTON COMMUNICATIONS

killing toxin called Bt. Many activists and some scientists have argued that the health and ecological risks of these plants haven't been adequately assessed (*Science*, 26 November 1999, p. 1662). On the flip side, a number of scientists have voiced concerns about overregulation. A coalition of 11 scientific societies has been lobbying the Environmental Protection Agency (EPA) to scrap a 1994 proposed rule that regulates transgenic "pesticidal plants," arguing that it is unscientific to regulate the process, genetic engineering, as that could encompass features as innocuous as pest-repelling hairs on a plant's leaves (*Science*, 9 April 1999, p. 249). Instead, the societies argued that EPA should regulate the plant's products, such as expressed proteins that might be toxic.

The academy panel, chaired by Perry Adkisson, an entomologist and chancellor emeritus at Texas A&M University in College Station, was formed a year ago partly to address scientists' concerns about the EPA rule. Looking only at what it termed "transgenic pest-protected plants," the panel endorsed their use, saying they could help to reduce the amount of chemical insecticides applied. The panel also dismissed health concerns: "The committee is not aware of any evidence that foods on the market today are unsafe to eat as a result of genetic modification." But it urged more research on, for instance, the flow of genes from crops to weedy relatives, long-term ecological effects of transgenic crops, and potential health effects, monitored through long-term animal feeding studies.

As for EPA's proposed regulations, the panel came down firmly on the side of keeping—indeed strengthening—them. It recommended scrapping two EPA exemptions that assume certain plants are safe: those made by adding viral coat proteins (because the virus could spread to weeds), and those made by inserting a gene from a plant similar enough to interbreed. And it suggested that regulatory agencies add a few requirements—for example, tests for protein allergenicity—and share their data with the public.

The panel's report is "schizophrenic," says R. James Cook, a plant scientist at Washington State University in Pullman and spokesperson for the 11 scientific societies. Cook wonders why the panel endorses a different type of regulation for transgenic crops while concluding that they are not inherently more risky than traditional crops. The answer is simple and pragmatic, says panelist Fred Gould, an entomologist at North Carolina State University in Raleigh: "If you got rid of that rule, public confidence would be down the toilet."

Even so, public confidence could still use some shoring up. Although the Biotechnology Industry Organization (BIO) was delighted with the report—it issued a press release proclaiming that transgenic foods "are thoroughly tested and safe"—many activists weren't. Before the report was released, protesters gathered in front of the academy with Representative Dennis Kucinich (D–OH). He urged the academy to "scrap the study" because the panel was "tainted by pervasive conflicts of interest," including the departure of the study's original director, Michael Phillips, last July for a job with BIO. The academy concedes that two panel members—an attorney and an industry consultant—did have conflicts of interest, but, according to executive officer William Colglazier, "we felt their regulatory expertise was needed." An internal investigation determined that the report was not biased by Phillips's involvement, he says. The one activist on the panel, ecologist Rebecca Goldburg of Environmental Defense, concurs. "Obviously, I think the panel had enough to offer that I stuck with it." **–JOCELYN KAISER**

ARCHAEOLOGY

'Pre-Clovis' Site Fights For Recognition

One of the fiercest battles in paleoanthropology concerns the peopling of the Americas: Were the first Americans so-called Clovis hunters who crossed from Asia about 12,000 years ago, or did others get here first, perhaps crossing the Pacific or the Atlantic? At the annual meeting of the Society for American Archaeology, held last week in Philadelphia, a team of researchers presented evidence that humans camped many times on a site in Virginia dated to 18,000 years ago. Distinctive stone tools, found at a site called Cactus Hill, lie below artifacts typical of the Clovis people, who take their name from an 11,500-year-old site in Clovis, New Mexico. Many researchers are wary of the dates, but others say the results are a strike against the Clovis-first theory. "It's step one of accepting it as pre-Clovis," says Dennis Stanford of the Smithsonian Institution's National Museum of Natural History.

How old? Humans may have camped here at Cactus Hill as many as 18,000 years ago.

CREDIT: KENNETH GARRETT/NATIONAL GEOGRAPHIC SOCIETY

At one level in the Virginia site—a large, sandy hill some 70 kilometers south of Richmond—the team found classic Clovis blades dated to about 10,000 years ago, says Joseph McAvoy of Nottoway River Survey, a private archaeological consulting firm. Some 15 centimeters below, they uncovered subtriangular projectile points that were clearly not like Clovis artifacts. Radiocarbon dates from associated charcoal suggested that the tools were 5000 years older than the Clovis points above, as documented in an extensive 1997 report. But many archaeologists worried that the unusual artifacts might have fallen from above and been mixed in the sand by plant roots or burrowing animals.

McAvoy marshaled an interdisciplinary team of 15 researchers to find out. Lucinda McWeeney of Yale University's Peabody Museum of Natural History found a much higher concentration of silica remains from plants at tool-bearing levels. She says that's consistent with the idea that people were camping and bringing in plant materials, although others point out that this may be due to ecological succession. She also noticed matching peaks of phosphates, perhaps from urine or excrement.

Meanwhile, Daniel Bush and James Feathers of the University of Washington, Seattle, dated the sand samples with a process called optically stimulated luminescence, which measures the time elapsed since grains were exposed to light. This backed up the radiocarbon dates. Moreover, five samples showed virtually no vertical mixing of grains, McAvoy adds. "There's still some uncertainty about the absolute age of the pre-Clovis deposits, but the relative sequence looks very good," says David Meltzer of Southern Methodist University in Dallas.

Meltzer and others caution that the artifacts may not be the same age as nearby 18,000-year-old charcoal, because particles are often transported inside sand deposits. The team did get a wide range of radiocarbon dates—both pre- and post-Clovis—on charcoal associated with the pre-Clovis tools. McAvoy's team dismisses the younger dates as due to contamination. But others aren't so sure. "If there's no consistent pattern [in the dates], then there may be a problem with mixing" of charcoal from different levels, Meltzer says.

Still, the fact that the tools are roughly similar to those of another possible pre-Clovis site in Pennsylvania, called Meadowcroft, is good news. "These are not isolated things that we can't make sense of," Meltzer says. "The point forms bear some resemblance to each other. We're starting to see commonalties, and that's heartening."

–ERIK STOKSTAD