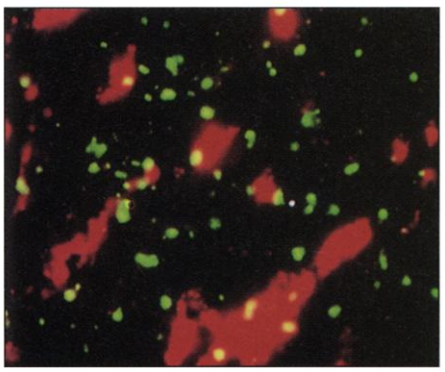
ANGIOGENESIS RESEARCH

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.

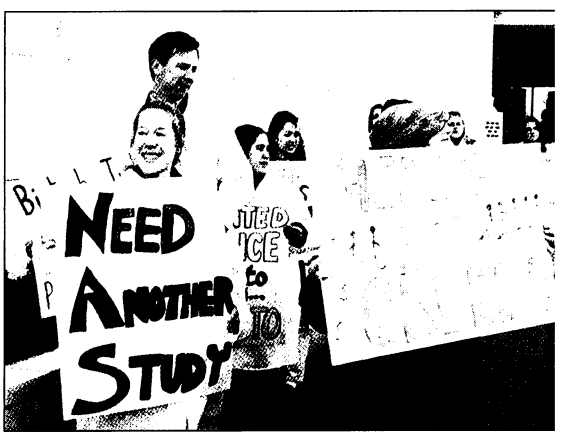
But Kerbel and Folkman caution that oncologists should not put patients who have other options on metronomic therapy unless clinical trials prove it to be effective in humans. Even if clinical studies do show benefit, they expect the approach will be less successful in humans than in mice, given experience 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

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