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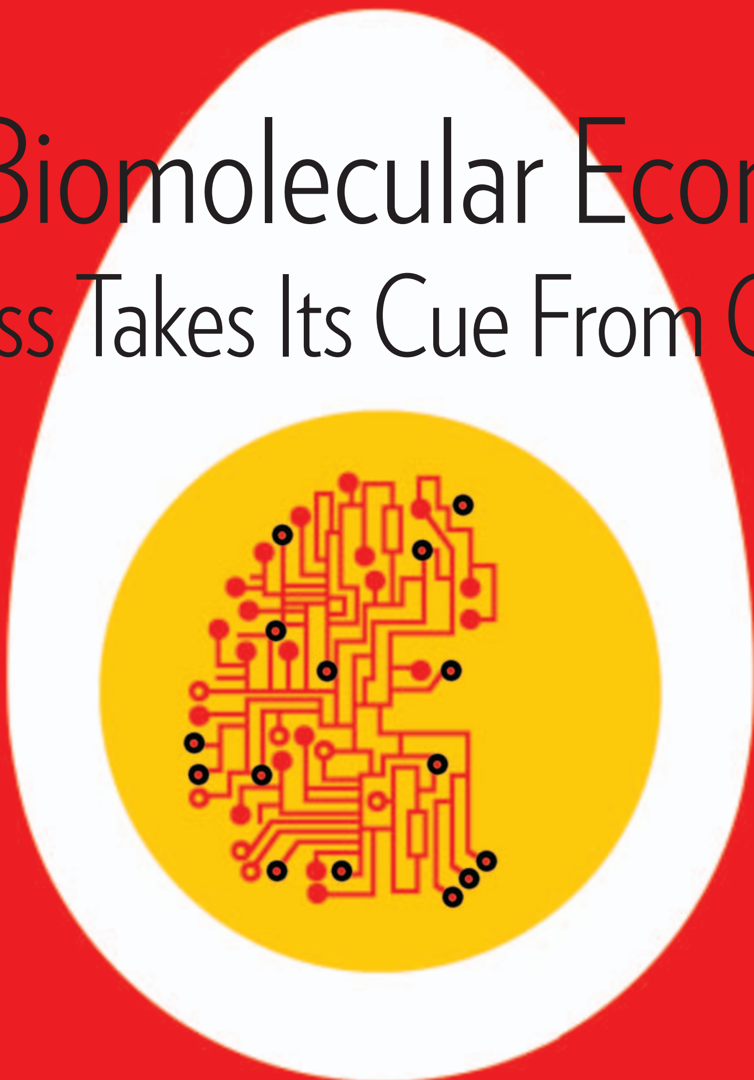


An Injection of Hope

A vaccine in tests for a rare form of cancer has patients living more than twice as long as those treated by radiation and chemotherapy. Could it serve as a model for other types of cancer?

By Bruce Goldman

Amy Pomykal admits to feeling a bit tired right now, and you can't blame her. She is, after all, both a flight attendant for American Airlines and the mother of a little boy who just celebrated his 1st birthday. "Right now his molars are coming in. That'll get your attention," she says. The busy 34-year-old former Mrs. Dallas County also jogs three or four times a week, or tries to. "I have great intentions!" she says in a soft drawl betraying no hint that she needs the interruption of this phone interview like a hole in her head.

Actually, as she puts it, there already *is* a hole in her head—in her brain, to be exact—where a tumor the size of a large grape was surgically removed five years ago. Not long afterward, she enrolled in a clinical trial of an immunotherapeutic vaccine—one given after someone becomes ill, instead of before—aimed at treating glioblastoma, a highly aggressive form of brain cancer.

Glioblastoma is a relatively low-frequency illness—about 10,000 patients get diagnosed with it annually in the United States—but a nasty one. Only about 50 percent of patients live a full year after their diagnoses, even when the tumors have been surgically excised. Half the time, the tumor is back six months after removal, but Amy Pomykal's latest MRI scan—she gets them every four months—showed virtually no trace of abnormality, just a hole where a tumor used to be.

The vaccine—since tweaked to make it far simpler to administer—is now being tested in a rigorous multi-center study. Although it's not being touted as a cure-all, results to date consistently show patients not only surviving more than twice as long as those treated by radiation and chemotherapy, but surviving without the debilitating side effects associated with these more conventional treatments.

"No randomized trial to date has shown effectiveness for any cancer vaccine in humans," says Jeffrey Weber, an oncologist at H. Lee Moffitt Cancer Center in Tampa, Florida. If the glioblastoma vaccine succeeds where many other candidates have failed—and Pomykal is not the only long-term survivor from the trial so far—it may serve as a template for cancer immunologists looking to extend the immunotherapeutic principle to other indications.

That would be a welcome development. The century-long history of cancer vaccinology is largely a tale of fallen candidates, many of which showed potential in the early stages but burned out in large-scale, randomized Phase III trials. Just this year, the U.S. Food and Drug Administration (FDA) rejected an application for approval of Provenge, a widely touted prostate-cancer vaccine, when that product failed to meet its stated objective—tumor shrinkage—although it did seem to prolong patients' lives by a few months; another once-promising melanoma vaccine, Canvaxin, not only failed to enhance melanoma patients' survival, but may possibly have shortened their lives relative to other patients who received a placebo instead. "The data were pretty scary," says Weber, who in June 2007 was a discussant in a panel session after the announcement of the Canvaxin results at an annual meeting of the American Society for Clinical Oncology (ASCO).

That cancer can outwit a vaccine should surprise no one. Indeed, every tumor represents a failure of the immune system. Roving cellular cops called T-cells routinely identify and kill cells

PETE LACKER

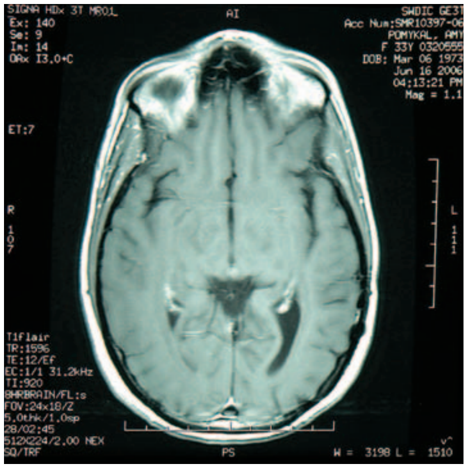
After treatment with an immunotheraputetic vaccine, Amy Pomykal's MRI scans show virtually no trace of glioblastoma, a highly aggressive form of brain cancer.

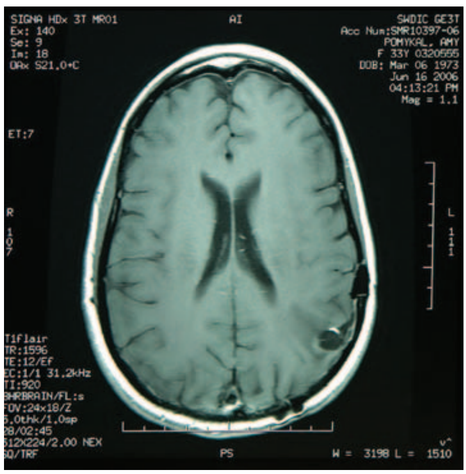
The dearth of effective treatments for glioblastoma means the vaccine can be given on an experimental basis to newly diagnosed patients, whose immune systems haven't yet been ravaged by successive courses of radiation and chemotherapy.

whose surface markers—or *antigens*—appear either suspiciously altered or altogether foreign to the body. This is so mutant cells continuously cropping up in healthy people's bodies don't propagate and blossom into full-fledged tumors. Left to their own devices, cancer cells simply refuse to stop dividing. Those that stumble on ways of evading immune detection survive to divide again, and thus certain tumor types have evolved numerous defense mechanisms that enable them to, effectively, put the immune system to sleep.

Is there any way to wake the immune system up? Researchers hope to make vaccines, renowned for shining a flashlight on intruding infectious agents, do the same thing to cancer cells hiding out in the body. We commonly think of vaccines as preventing infectious disease by giving the immune system early exposure to some component of an infectious organism—like stuffing a bloodhound's nose into a suspect's shoe—so that when a bacterium or virus does try to infect, the immune system is prepared to pounce immediately. In theory, there's no reason a vaccine couldn't be used therapeutically (after the fact) to encourage an immune assault on an individual's own cells when they exhibit suspect antigens.

In practice, though, this kind of vaccine has to climb a steep, rocky slope. The major difference between a preventive vaccine and a therapeutic vaccine is, of course, that the latter application assumes the patient's previous exposure to the antigens. There may already have been an initial immune response, and it may even have been partially effective. But if a patient has been diagnosed with cancer, clearly that response was inadequate. "In fact, often the immune system is defeated and rendered tolerant to the antigens the vaccine is targeting," says Johns Hopkins University oncologist Hy Levitsky. Without immune tolerance—the shrugging off of familiar antigens—healthy tissues would be sitting ducks for autoimmune disease. Tolerance to a malignant tumor, however, is lethal.

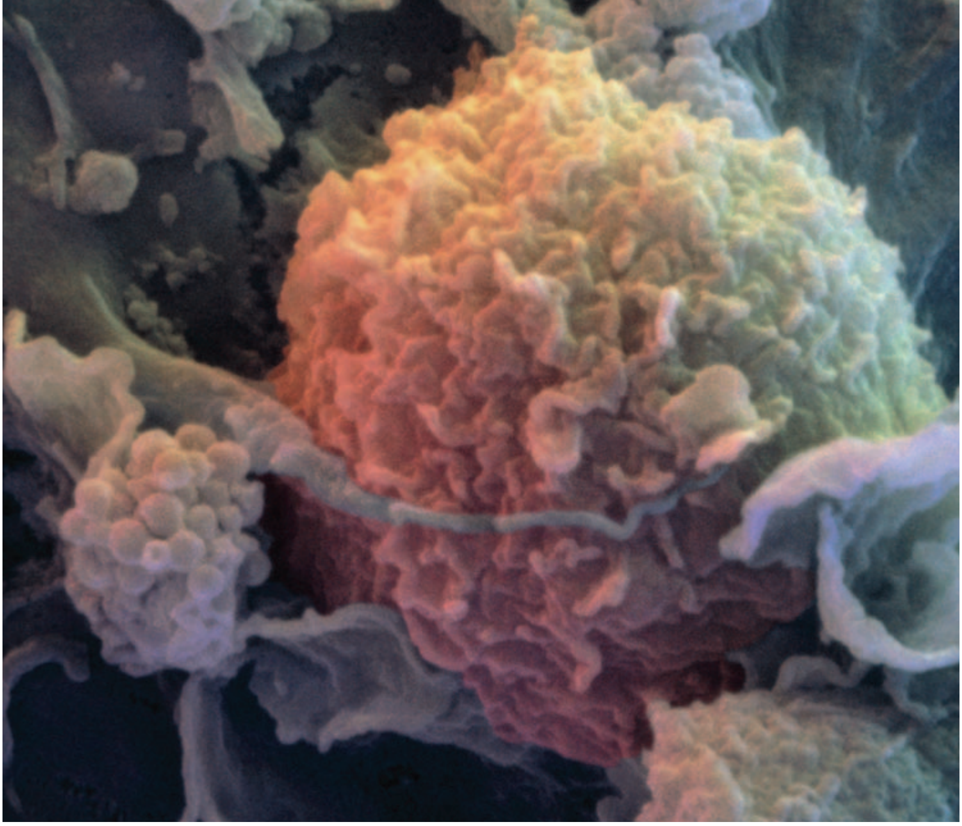




An MRI of Pomykal's brain shows no signs of cancer. The bottom scan shows the hole where the tumor was removed near the outer edge of the right hemisphere.

To make things even more difficult, most cancer antigens aren't unique to tumors. Many are simply normal proteins that are overexpressed or inappropriately expressed on malignant cells. With these tumor-associated antigens, it's the devil or the deep blue sea: Tolerance to them can be broken, but only at the cost of toxicity to healthy cells unfortunate enough to harbor, however legitimately, the same chemical barcode.

A vaccine that targets a tumor-specific antigen—one expressed by every cancer cell, and never by normal cells in the body—would spare normal cells, thus causing mild side



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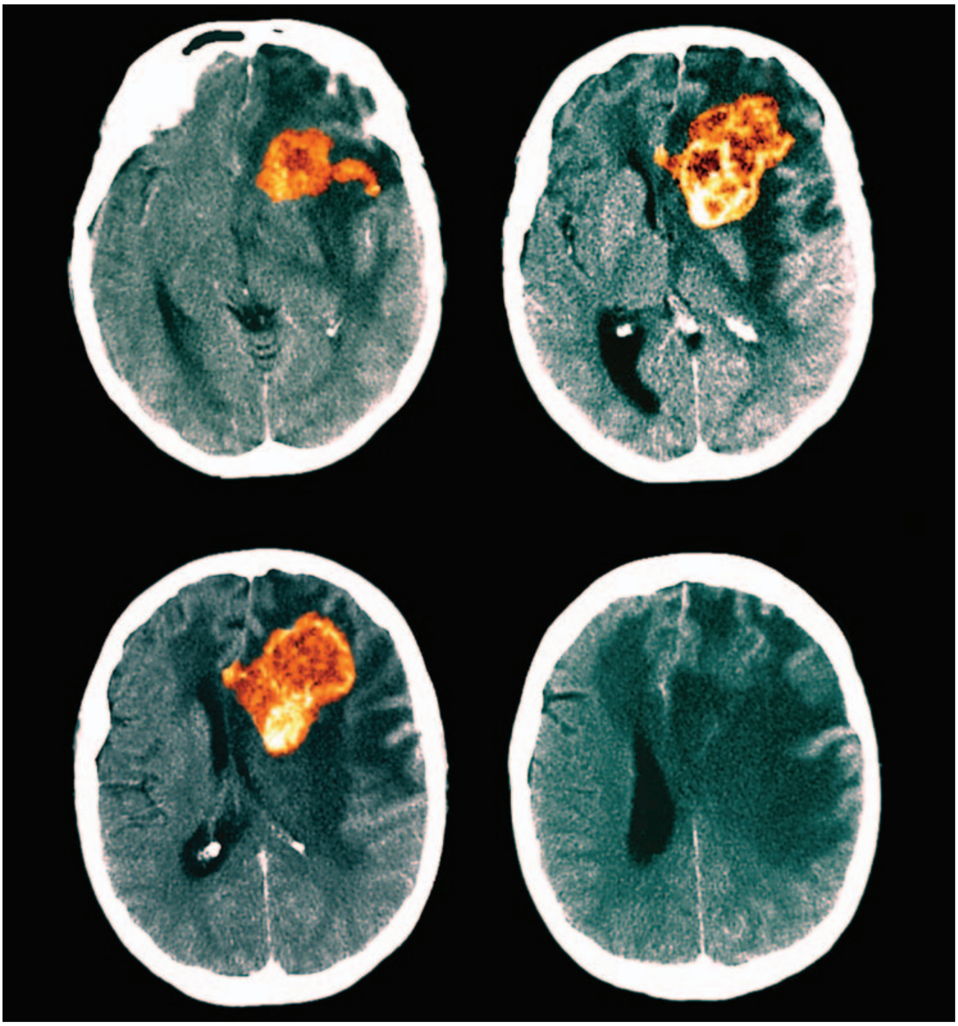
effects compared to those associated with the shotgun approaches of chemotherapy and radiation. And theoretically, says Moffitt Cancer Center's Weber, because it would not be a "self" antigen, the patient's immune system would not be tolerant to it. But trying to identify these random products in an individual patient is like looking for a needle in a haystack. "You can discover any number of mutated antigens that are tumor-specific," Weber says, "but mutated antigens tend to be highly patient-specific."

Now and then, the haystack is made out of needles. Three biotechnology companies are developing vaccines for B-cell lymphoma, which arises from the unremitting proliferation of what started as a single antibody-producing B-cell. By dint of their common ancestry, a patient's malignant B-cells (and only those cells) all harbor the same antibody on their surfaces, making it an easily identified, tumor-specific antigen. Immunologists have purified or synthesized large amounts of the distinctive tip of the telltale antibody and formulated vaccines from it. Favrille (San Diego), Genitope Corporation (Redwood City, California), and Biovest International (Worcester, Massachusetts) are currently conducting Phase III trials along broadly similar lines in this arena, with results expected in the next year or two.

Lacking solid tumors' structural defenses, and thus more accessible to the immune system, blood-borne cancers are promising vaccine targets. Still, each B-cell lymphoma patient's vaccine uses a different antigen and must be custom-made, torpedoing the efficiencies inherent in a mass-produced vaccine's manufacture as well as raising thorny regulatory conundrums. (For example, must each individual's vaccine be analyzed separately for safety and efficacy? If so, how?)

The antigen employed in the new glioblastoma vaccine represents the best of both worlds: tumor-specific, but not patient-specific. At least one-third of all glioblastomas—including Pomykal's—contain cells with an altered cell-surface protein created by a mutation in the gene encoding a workhorse cell-surface pro-

A colored electron micrograph of two types of protective cells of the human immune system. A T-cell (yellow) is attached to a large dendritic cells in the background.



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Colored axial CT scan of a patient with glioblastoma which shows up in orange in the left hemisphere of the brain.

tein: the epithelial growth-factor receptor, or EGFR. The mutant protein, called EGFRvIII, is locked in a permanent "on" position. It fires continuous bursts of chemical signals, driving cells to divide at a breakneck pace—and making EGFRvIII the ideal tumor-specific vaccine target. Any EGFRvIII-positive cell is guaranteed to be malignant; no cell carrying such a mutation could behave normally.

The vaccine's defining antigen—a simple 13-amino-acid-long protein fragment, or peptide, from EGFRvIII's mutated region—is easily synthesized, compounding the economies of scale accruing from the frequency of EGFRvIII's occurrence. Another advantage: The dearth of effective treatments for glioblastoma means the vaccine can be given on an experimental basis to newly diagnosed patients, whose immune systems haven't yet been ravaged by successive courses of radiation and chemotherapy. Moreover, these tumors haven't been subjected to the evolutionary pressure—and thus they have not become the moving targets—such treatments generate.

Finally, these patients have what oncologists call minimal residual disease, meaning that surgical resection has left only traces of the tumor in situ. Even after careful surgery, a glioblastoma almost always re-emerges—it's really been there all along, at a volume too small to detect. By guiding T-cells to root out these microscopic pockets of malignant cells, might a cancer vaccine succeed in converting a remission into a cure?

In the case of the EGFRvIII-targeting vaccine, there's no reason to presume so, because glioblastomas tend to be highly heterogeneous: Some tumor cells carry the mutation, others don't. Those that don't should go unscathed.

But EGFRvIII-positive cells seem to be more aggressive, and may be egging on other cancer cells via some kind of yet-unknown chemical signal. Maybe, researchers have opined, taking out EGFRvIII-positive cells would at least slow or halt tumor growth.

Pomykal participated in the first 20-patient clinical trial of the peptide vaccine, conducted at Duke University by neuro-oncologist John Sampson. Dendritic cells—front-line sentinels of the immune-system with an unrivaled ability to bring antigens to the attention of T-cells—were harvested from her bloodstream and cultured for six weeks with the EGFRvIII peptide, then returned to her blood in three biweekly injections. Sampson says patients' overall survival averaged close to 30 months, compared to an expectation of about 12 months in historically matched, untreated controls.

Success for the glioblastoma vaccine could spur rapid progress in some other cancer indications.

So Sampson launched a second, two-center trial in collaboration with his former post-doctoral student Amy Heimberger, now at M.D. Anderson Cancer Center in Houston. The investigators recruited 23 newly diagnosed patients whose EGFRvIII-positive glioblastomas were surgically removed and who were then treated with a round of radiation and chemotherapy with the cytotoxic drug temozolomide. Judging the dendritic-cell approach costly and cumbersome, the two researchers modified the regimen by directly injecting patients with the mutant peptide, chemically linked to a molecule of an adjuvant—a substance that generally arouses patients' immune systems, fueling an attack on the peptide. A third vaccine component, a synthetic version of a natural immune secretion, promotes immune-cell proliferation.

Patients received three biweekly vaccine injections followed by monthly booster shots. While the treatment phase is complete, final results aren't in yet, happily, because some patients are still alive. But preliminary findings once again indicate, with a very high degree of statistical significance, that the median time until tumor recurrence is greater than 15 months, more than double than that for historically matched controls. Median patient survival is just under 29 months, versus about a year for patients treated with temozolomide.

After that two-center trial got underway, another large-scale study showed that giving patients not just one but several successive rounds of temozolomide added 2.5 months to median survival, increasing it to a bit over 14 months. This was deemed sufficient evidence of efficacy to get the drug approved by the FDA for front-line treatment of glioblastoma. Temozolomide is now typically given to patients on five consecutive days during each of several 28-day cycles.

To test the vaccine's capacity to function in combination with the now-standard new temozolomide regimen, Sampson and Heimberger have started yet another trial in which the vaccine is given on Day 21 of each cycle (Day 1 representing the first of the five days of temozolomide infusion). The study is still in progress, with more than a dozen patients recruited so far. So far, none has had any tumor recurrence, and preliminary observations show a paradoxical synergy between the temozolomide and vaccine regimens.

Conventional wisdom among immunologists holds that, by destroying immune cells as well as cancer cells, chemotherapeutics such as temozolomide seriously impair the capability of a vaccine, which relies on a functioning immune system. The trial results so far are turning that conventional wisdom on its head. Data reported by Sampson and Heimberger at the June 2007 ASCO meeting strongly suggest that, far from interfering with the vaccine's effectiveness, temozolomide enhances it. "Temozolomide wipes out your T-cells, but it doesn't wipe them out forever," says Sampson. "They recover, and during that recovery phase they have a lower threshold for activation. If you vaccinate at the right time—we think around Day 21—you have a captive audience for the antigen in your vaccine."

And vice versa. Some veteran researchers suspect that the vaccine may enhance the effectiveness of chemotherapy. Tumor biologist Web Cavenee, who heads the Ludwig Institute in San Diego, thinks EGFRvIII's incessant signaling may boost the entire tumor's chemoresistance. Paul Mischel, a UCLA professor of pathology, laboratory medicine, and molecular and medical pharmacology who has also studied EGFRvIII at length, says, "It's not just what the EGFRvIII cells themselves are, but what they do to the rest of the tumor. It seems clear that having EGFRvIII-positive cells in there does something to the tumors

PETE LACKER

Mommy time: Pomykal and her one-year-old son Weston.

that makes them more aggressive." Elimination of those EGFRvIII-positive cells may explain why Pomykal and some other patients' cancers haven't recurred as might be expected, given their tumors' heterogeneity.

None of the glioblastoma-vaccine trials has been controlled, so their results should be viewed with caution. It's always possible that patients who enroll in clinical trials are in better shape than those who don't, so have better prospects to begin with. But a definitive trial is now in progress. Celldex Therapeutics (www.celldextherapeutics.com), a Phillipsburg, New Jersey-based Medarex spin-off that holds the license to CDX-110 (the company's name for the vaccine) has initiated a multi-center Phase II trial whose overall design is almost identical to the latest Duke/Anderson trial. Some 90 newly diagnosed EGFRvIII-positive glioblastoma patients at more than 20 centers (six have opened so far) are, in addition to receiving several temozolomide cycles, being randomly assigned on a two-to-one basis to vaccine or placebo, then evaluated for time to recurrence. If this trial, whose results are likely to be available by year's end, yields the same kinds of results as those achieved in the earlier ones, the study will be scaled up to a full-blown 360-patient Phase III trial with overall survival as its primary endpoint.

If there's any upside to the swift progress of a disease like glioblastoma, it is how rapidly a prospective treatment's efficacy can be judged. B-cell lymphoma patients often survive for much longer than 10 years, even without therapy. Other cancer types have protracted timelines, as well. "When prostate or kidney cancer patients have surgery, the interval preceding relapse is measured in many years," says Levitsky. "So, with a randomized study where your endpoint is time to progression—the time it takes before you see evidence of recurrence—the first challenge is that some of the patients were cured by the surgery to begin with and will never relapse, even if you didn't vaccinate them. The second challenge is that even among those who are going to relapse, it takes a very long time." Levitsky thinks one of the main reasons that no FDA-approved cancer vaccine is currently available is that, in the very setting where it's likely to work best—minimal residual disease—the development pathway is the hardest. "Many small biotechs that are funding the development of this work don't have the financial resources to survive such a study," he laments.

Success for the glioblastoma vaccine could spur rapid progress in some other cancer indications, because EGFRvIII is also found at high rates in head-and-neck cancers, and on upwards of five percent of the most common form of lung tumor—a small percentage of a very large number. Studies suggest that it appears in breast, ovarian, colon, and prostate tumors, as well.

Participating in a cancer trial is a daring proposition, which suits Pomykal's style. When she doesn't have a plane to catch, she's hopping on freaky rollercoaster rides with her older sister, Teri, at the Texas state fair. "We laugh our heads off," she says. TJOLS

Bruce Goldman is a San Francisco-based author of over 200 articles aboutscience, biotech, and medicine. He is co-author of 2020 Visions: Long View of a Changing World.