

# Taming a Mutinous Mutant: An Errant Receptor Becomes a Prime Cancer Target

By Bruce Goldman

Vaccines typically are given to prevent disease, but in theory there's no reason they couldn't be used to nudge the immune system into fighting a disease someone already has. In practice, it's a different story. Researchers have been trying for years to come up with therapeutic vaccines to fight established cancer and other diseases, with little success.

Now a vaccine for a nasty brain cancer is showing early promise. It will soon be tested in a multicenter phase II trial just getting under way for patients with glioblastoma, the most common adult brain cancer, and it may eventually see duty in other cancer types.

About 10,000 patients will be diagnosed with glioblastoma this year in the United States; only about half of them will survive 1 year. A mere 2.5-month median survival increase, in a study reported in the *New England Journal of Medicine* in March 2005, sufficed for FDA approval of the addition of repeated cycles of the chemotherapeutic drug temozolomide to an initial round of radiotherapy. This new regimen is now the accepted standard of care for glioblastoma.

But further improvement might be possible. In a recently completed phase II trial conducted by John Sampson, M.D., Ph.D., at Duke University, and Amy Heimberger, M.D., at the University of Texas M. D. Anderson Cancer Center, 23 newly diagnosed glioblastoma patients with a median age of 52 years were injected three times in 2 weeks and then monthly with a vaccine containing a small sliver of a mutant form of the epidermal growth factor receptor protein, called EGFRvIII, that occurs in upwards of one-third of glioblastoma tumors. These patients had tumors testing positive for EGFRvIII and, before getting vaccinated, had had all but microscopic traces of their tumors removed by surgery. They also received radiation therapy and the chemotherapy drug temozolomide.

Half of the patients were still alive 30 months or more after their diagnosis.

On average, patients in the vaccine trial remained tumor free for about 12 months versus about 7 months in patients on either temozolomide regimen. About two-thirds were still alive 2 years after diagnosis, versus 5% of unvaccinated patients with EGFRvIII-positive glioblastomas.

While there is reason to be optimistic, the Duke-M. D. Anderson trial was tiny and not randomized so it must be evaluated cautiously. And the glioblastoma vaccine is not a cure. The cancer always recurs because glioblastomas are highly heterogeneous cancers—they comprise many clusters of cells with different features—and the vaccine-primed immune system spares those tumor cells that are devoid of EGFRvIII. Still, in each of nine recurrent tumors examined for its presence, none of the mutant protein remained, Heimberger says, suggesting the vaccine is performing as designed.

But why does this one work when so many previous attempts have failed? First, these were newly diagnosed patients, in better shape than patients who have failed prior therapies, Heimberger says. Second, only residual traces of the tumor remained after surgery, disabling the myriad decoys and traps solid tumors evolve to deflect immune responses.

Finally, EGFRvIII is an ideal immunological target because it's a mutant version of an important protein that straddles the cell surface. Epidermal growth factor receptor (EGFR) responds to the docking of circulating EGF in its customized binding site outside the cell by signaling internally, generating a cascade of activity that fosters rapid cell division. Absolutely necessary for tissues with high turnover rates, such as skin or intestinal linings, EGFR at hyperactive levels pushes cell division to reckless levels.

## Discovering Mutant EGFR

The discovery, about 20 years ago, that EGFR was massively overexpressed in perhaps half of all glioblastoma tumors drew neurooncologists' attention. Not long afterward, several investigators independently discovered that about one-third of all glioblastomas harbored a mutant EGFR that was missing a sizable chunk from the part that protrudes from the cell surface. As a consequence, the mutant receptor—designated EGFRvIII because it was the third of about a dozen altered EGFR variants isolated in glioblastomas—can no longer bind EGF. But it doesn't need to. EGFRvIII never stops signaling, which drives relentless cell multiplication. "It's like a leaky faucet," says Web Cavenee, Ph.D., director of the Ludwig Institute for Cancer Research in San Diego and a veteran tumor biologist whose group, then in Montreal, did substantial work characterizing EGFRvIII's genetics and activity in the late 1980s.

Many tumors host overabundant but otherwise normal proteins. But because these proteins also appear on healthy tissues, the immune system is trained not to attack them. "That's why we don't have autoimmunity," says Albert Wong, M.D., director of the brain tumor research laboratories at Stanford University. Wong played a key role in the EGFRvIII vaccine's development, first as a researcher in Bert Vogelstein's lab at Johns Hopkins University and then as a faculty member at Thomas Jefferson University. EGFRvIII, though, is tumor specific—no cell harboring a molecule like EGFRvIII on its surface could ever remain "normal." The vaccine's EGFRvIII-specific component is



Web Cavenee, Ph.D.

a 14-amino-acid snippet that precisely mimics the sequence created by the EGFR sections flanking the mutant's missing chunk.

Sampson and Heimberger are now conducting another randomized phase II trial incorporating the now-standard several-cycle temozolomide regimen into both its treatment and control arms. "Our preliminary human data, and certainly our laboratory data, would strongly suggest that temozolomide is actually very beneficial" when used with the vaccine, Sampson said.

Chemotherapy works by killing off rapidly dividing cells—a category that includes not only cancer cells but also immune cells. However, Heimberger says, the immune system does recover fairly quickly after chemotherapy, so a vaccine given at day 21 of the temozolomide cycle, when immune cell counts have been restored, encounters enough immune cells to stimulate a reaction. Moreover, EGFRvIII's incessant signaling may enhance a tumor cell's ability to withstand chemotherapeutic assault, so the vaccine's assault would come at a good time. Cavenee says that when his group

impaired EGFRvIII signaling with a small molecule in a mouse model and in human tumor cells in culture, the tumors' growth slowed and they became susceptible to chemotherapeutic drugs that had previously failed. Knocking out the mutant receptor with a vaccine may well have the same effect.

The vaccine's success also suggests that the blood-brain barrier may not be the obstacle to immunotherapy that it once seemed. Even the noncancerous brain isn't fully insulated from immune patrol, and lesions from the tumors themselves and brain surgery further ease access.

New Jersey-based Celldex Therapeutics has licensed the vaccine, which it is calling CDX-110, and is launching a randomized phase II trial that closely follows the latest Duke-M. D. Anderson study's protocol. Starting in March, 90 glioblastoma patients will be recruited to a phase II at several centers throughout the country. Celldex hopes to have 20 centers aboard nationwide by year end, says chief medical officer Tom Davis, M.D. If the vaccine is shown to delay tumor recurrence, the trial will escalate to full-blown

phase III status with an anticipated 375 patients, and the primary emphasis will shift from disease-free survival to overall survival, Davis says.

### Outside the Brain

There's reason to believe the vaccine or a similar one could be useful in other cancers. EGFRvIII has turned up in 42% of samples from head and neck tumors and about 5% of squamous-cell lung carcinomas (the most common type of lung cancer worldwide). Breast, colon, ovarian, and prostate tumors all often overexpress EGFR, which may render them more likely to produce the mutant receptor variety and thus expose them to attack by the vaccine. Drugs targeting normal EGFR—such as erlotinib, gefitinib, and monoclonal antibodies such as cetuximab and, now, panitumumab—have proved ineffective for nearly all patients with these cancers, and they haven't worked at all in glioblastoma. But, investigators speculate, defanging EGFRvIII with a vaccine may render some tumors more vulnerable to their effects.

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