

Sharon Begley

This Is No Way To Cure Cancer

WHEN THE GOVERNMENT DANGLES \$1.5 BILLION IN front of scientists, they rarely say, oh no, please, keep it, there are better ways to spend the money. But as the biomedical establishment gears up for yet another megaproject, some leading scientists are doing exactly that, making the heretical suggestion that this latest extravaganza is poor science and bad policy.

Called the Cancer Genome Atlas, it aims to identify mutations in tumor cells from the 50 most common kinds of human cancer. (A genome is the full set of genetic information in, in this case, all the malignant cells in these 50 cancers.) You can think of the mutations as misspellings in the cells' DNA; the hope is that designer drugs tailored to a patient's mutations will cure the cancer just as spellcheck cures typos. Now beginning a three-year, \$100 million pilot phase, the atlas threatens to suck up ever-dwindling resources at a time of budget carnage at the National Institutes of Health, which funds it. But there's a bigger problem: the atlas's very premise may be fatally flawed.

"From a clinical and drug perspective, the cancer-genome project is so shallow it's worthless," says George Gabor Miklos, who has served as a consultant on genome projects, the holy grails of biology for a decade. NIH, he says, has "made an enormous mistake that will cost the taxpayer billions." Scientists from top institutions including the Mayo Clinic, the University of Chicago and Harvard Medical School are weighing in to denounce the project as "high-cost, low-efficiency," "not informative" and "naïve."

To understand their concern, it helps to know some basics about how cancer kills and, paradoxically, how relatively unimportant the actual tumor is. The cancer atlas will catalog mutations in primary tumors—those solid masses in lung, breast, prostate and other tissues. But what kills an estimated 90 percent of cancer patients is not the primary tumor (you can live without a prostate). It is metastases. These are malignant cells that spread to a vital organ like the brain. "What matters for survival is not the primary tumor but the rare

mutations that cause or sustain a tumor but also those that are innocent bystanders. How many of the latter do tumors have? Malignant cells accumulate mutations 200 times faster than normal cells, Lawrence Loeb of the University of Washington School of Medicine finds in a recent study. That works out to about 1 billion mutations in a single tumor. Scientists hope they can separate cancer-causing mutations from innocuous ones.

It gets worse. Different parts of a tumor can have completely different mutations. Biopsies usually sample one or two spots. Even if the research does lead to new drug cocktails, a doctor will logically choose drugs that target mutations he or she knows are there—that is, in the biopsied part of a tumor—leaving the very different mutations in nonsampled areas free to proliferate.

Proponents of the cancer atlas argue that it is already discovering new mutations. A 2006 study, led by scientists at Johns Hopkins University, found that breast and colon tumors harbor 191 important mutations in numerous genes, for instance. But even they admit the genetic dragnet hauls in mutations that are merely along for the ride. And while it's all well and good to identify prevalent mutations and hope you can craft drugs that target them, the malignant cells may hang on just fine by relying on their rarer mutations. This seems to be why the much-hyped new "targeted" drugs hardly extend survival; they block one pathway that cancer cells use to grow and lay



The latest genome project, to identify mutations in 50 kinds of tumors, is sucking up resources at a time of budget carnage.

cells—1 in 50,000—in it that give rise to metastases," says Miklos. Identifying all the mutations in a tumor is overkill, especially since the atlas will not zero in on mutations that underlie metastasis.

The atlas may miss such mutations entirely. Metastatic cells often emigrate early in a tumor's life, points out cancer geneticist Christoph Klein of the University of Regensburg, Germany. But many mutations arise only when a tumor is larger than an inch, which is when biopsies tend to be done. "By this time, cells that give rise to metastasis have already left," says Klein. Mutations in primary tumors, which the atlas will identify, may therefore not provide good drug targets. As Miklos says, "Most of the millions of mutations in the tumor will be clinically irrelevant."

The dragnet will sweep up not only

down supply lines, so the cells take a biological detour to achieve the same end.

No wonder experts are pleading for "a note of caution" on the cancer atlas, as Klein puts it. Even Dennis Slamon of UCLA, whose work on breast cancer led to the highly successful drug Herceptin and who served on the panel that crafted the cancer-atlas project, has doubts. "It's a reasonable approach but certainly expensive, and based on a premise that might or might not bear fruit," he says. "At the end of the day, you still have to prove that the mutations you find are playing a role."

Cancer is poised to supplant heart disease as the nation's leading killer. Patients are understandably desperate for cures, and the genome establishments for projects that keep it funded. Neither motive produces good science.



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