nature biotechnology
VOLUME 16 OCTOBER 1998

War on cancer II?

On a day that saw her husband's dream of recreating Camelot become the nightmare of Nixon redux, Hillary Rodham Clinton turned the collective media attention of the world, at least for a few minutes, to the US government's latest effort in the ongoing war on cancer—a war first declared, ironically enough, by the same Richard Milhous Nixon when he was immersed in a number of battles of his own.

Unlike viruses, the centerpiece of the first US National Institutes of Health (NIH) offensive, which aimed at identifying what it hoped would be a tractable number of direct cancer causing genes, this newest assault is focused on a specific target, colorectal cancer, with a rather specific tactic—to encourage increased use of a worthwhile, if slightly uncomfortable, diagnostic procedure in people over 50 years old.

As Mrs. Clinton described in detail the various ways this public service message was to be disseminated, and who its principal sponsors, apart from the US Department of Health and Human Services, were to be, the focus of her speech began to shift from the hospital clinic to academic and biotechnology research laboratories. In announcing the award of an $8 million grant to the Fred Hutchison Cancer Research Center to investigate the causes, prevention, and detection of colorectal and pancreatic cancers, she argued eloquently for the Congress to quickly approve appropriations for additional NIH research funding, saying that we were on the verge of important breakthroughs in understanding and diagnosing cancer. We could not agree more.

The emergence of extremely powerful new genomics' tools, such as serial analysis of gene expression, coupled with the growing and welcome second influx of mathematically trained scientists into molecular biology, promises to reinvigorate a field which, since the 1970s, has been dominated by a qualitative theory based on specific mutations, whose major public health contribution has been in describing genetic markers that are linked to the likelihood of developing one or another cancer.

We all recognize, however, that the differentiated phenotype of a human cell cannot be the result of the function of one or a few genes, and that current genetic explanations of cancer are limited in the results they can realistically achieve. But just as increased sophistication in our knowledge of complicated, interacting biological systems at the enzyme level allowed the development of metabolic flux analysis—a rigorous, quantitative approach that replaced the idea of the "rate-limiting enzyme" with the much more useful one of "distributed control"—the real revolutionary advances that are being made almost daily in our ability to collect, compare, organize, and manipulate sequence and kinetic data, will allow us to understand, and consequently treat, cancer at the genetic level as the "statistical mechanical" phenomenon it is. Such an understanding, a worthy enough goal on the edge of the century, seems imminently achievable.

So while we join with the First Lady in urging the Congress to spend more funds on cancer research, we also urge it and the NIH to earmark a substantial portion of any such money for projects that are devoted to using the enormous power of genomics to do more than look for new cancer-related genes.

Pharmacogenomics at work

On a related note, the approval of Herceptin by the US Food and Drug Administration's (FDA's) Oncologic Drugs Advisory Committee, and its likely approval by the FDA itself for commercialization later this fall, is a window on the opportunities that will be afforded by pharmacogenomic approaches to drug discovery and delivery.

Herceptin is Genentech's monoclonal antibody against late-stage breast cancer, a drug that inhibits the action of the *HER2* gene. Some 25–30% of all breast cancer patients overexpress *HER2;* these are the women who will benefit from treatment with the drug. Genentech has already announced a deal with Denmark's DAKO to develop *HER2* diagnostic screening, and other companies are gearing up to jump into the diagnostic fray.

Pushed forward by public advocacy, the Herceptin story is nonetheless a striking example of how identifying patient population subsets can bring a new measure of safety and efficacy in its wake: It takes us out of the days of poisoning the patient and hoping that the tumor dies first and moves us into a time when tumor targeting could truly be effected without debilitating, or even life-threatening, side effects.

Would that Tamoxifen, a breast cancer drug that is now up for approval as a prophylactic measure for women at high risk of developing the disease, came with such clearly delimited patient borders. As it is, women must assess, along with their physicians, based on family history and clinical trial statistics, whether they are at a high enough level of risk of developing the disease to chance the further risk of undergoing treatment. Bringing decisions like these out of the realm of descriptive natural history and into the realm of individual genetic biology is part of pharmacogenomics' promise.