



Bruce Alberts is Editor-in-Chief of *Science*.

## Redefining Cancer Research

SENATOR TED KENNEDY'S RECENT DEATH FROM MALIGNANT GLIOMA, AN INCURABLE BRAIN TUMOR, reminds us of the terrible toll that cancer takes on humanity. The United States alone experiences nearly 1.5 million new cases of cancer each year, resulting in more than 500,000 annual deaths, and about one-fourth of us will die in this way. Jim Watson, of DNA double-helix fame, argues that because of our new profound understandings of the molecular mechanisms underlying the disease, it's finally time to launch a real war on cancer.\* I agree. But for success in such a project, we will need to expand the scope of "cancer research" funding, so as to include far more than work with cancer cells themselves.

Cancer is a disease of cell biology. The human body is a cooperative of some 80 trillion cells, any one of which can cause cancer if it behaves selfishly and proliferates at the expense of the other cells around it. Our bodies function because each cell receives signals from its neighbors to tell it how to behave. Most often, these signals tell the cell to rest without dividing. But on occasion, as for example near a wound, the signals instruct cells to grow and divide, to create the new cells needed for healing. Each cell knows precisely what to do because it contains a specific program, based on the instructions carried in its DNA. But instructions in DNA invariably accumulate small accidental errors as we age. We now know that cancer arises only when a large number—perhaps 10 to 20—of these errors occur, overriding the many layers of fail-safe controls that normally prevent the inappropriate proliferation of our cells.

Moreover, a defect in the maintenance of DNA sequences, which is different for individual tumors, causes the cells in cancers to be accident-prone, often having mutation rates that can be hundreds of times greater than normal. This defect presumably arose early in the growth of the tumor, because a high rate of accidents was essential to allow the cells to escape from multiple layers of fail-safe controls.

Thus, we can expect all cancer cells to be defective in some aspect of DNA repair that makes them unusually mutable. In principle, this weakness can be exploited by finding a drug that makes the original defect lethal to the cancerous cell instead of just destabilizing it, without causing harm to normal cells. The recent discovery of the strong therapeutic benefit of so-called PARP inhibitors, when used on tumors with defects in one type of DNA repair pathway,† provides a proof of principle for organizing a major new attack on cancer.

There are at least 150 different proteins that catalyze DNA repair in human cells, forming many different overlapping repair pathways. To seed new therapies, geneticists and molecular biologists are needed to explore the detailed consequences of an alteration in each of these repair pathways—not only in human cells, but also in more accessible model organisms such as bacteria, yeast, worms, flies, fish, and mice. Biochemists and chemists are required to screen for the inhibitors that can serve as new drugs. And experts in genomic and proteomic technologies are needed to design inexpensive tests for screening a patient's tumor for the specific defect that makes it highly mutable, so that, as for the PARP inhibitors, a designer drug that specifically blocks a parallel repair pathway can be used to kill the cancer cells. In the current funding structure, there is far too little emphasis on such investigations.

In cancer treatment, as in many other areas, translational medicine needs to cast a much broader net. Major funding agencies such as the U.S. National Cancer Institute should enlarge their view of what constitutes cancer research, recognizing that often the discoveries that have the most profound impact on cancer treatments emanate from basic research on model organisms, rather than from studies of highly complex human tumors.

– Bruce Alberts

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\*]. D. Watson, *The New York Times*, 6 August 2009, p. A29. †P. C. Fong et al., *N. Engl. J. Med.* **361**,123 (2009).

