



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

The Promise of Cancer Research

IN RECENT YEARS, I HAVE HEARD THE ARGUMENT THAT WE ALREADY KNOW ENOUGH about fundamental biological mechanisms to cure cancer, and that the best way to improve cancer outcomes would be to focus nearly all of our cancer research resources on applying what we know to develop therapies. This would be a mistake. To make my point, I describe two of many examples where a much deeper understanding of fundamental mechanisms seems almost certain to improve cancer treatments. Of necessity, I omit many other promising ways of attacking this disease.

Cancer arises when the descendants of just one of our more than ten thousand billion cells proliferate out of control, eventually interfering with normal body functions. Since so many cells are at risk, the most amazing thing about cancer to me is how many years it usually takes to develop the disease. One major obstruction to the proliferation of cancerous cells is the phenomenon of apoptosis, which causes nearly all of our cells to kill themselves whenever they start to behave aberrantly.

A complicated cellular signaling network determines the balance between the pro-apoptotic and anti-apoptotic proteins inside animal cells. Each of our many cells is constantly sensing its external and internal environment and will sacrifice itself (for our own good) if it is either not correctly located or not behaving normally. Without mechanisms of this type, the evolution of large complex organisms such as ourselves would probably not have been possible, because the tumors caused by cancerlike diseases would have overtaken us early in life.

Tumors arise after a long process of random mutation followed by multiple rounds of selection for those cells able to proliferate best. One change selected for is in apoptotic mechanisms, which will be altered in different ways in different tumors. Imagine that we could determine why the cells in an individual's tumor incorrectly compute that they need not kill themselves, as normal cells would do in their condition. If we understood the fundamental mechanisms by which cells make these decisions, we would stand an excellent chance of creating a tailored mixture of drugs that causes the tumor cells to compute differently, so that they commit suicide without harming normal cells.

Another promising strategy takes advantage of the fact that essentially all cancer cells have acquired a defect in some aspect of their "DNA metabolism," often some aspect of DNA repair that causes them to become highly mutable. This genetic instability of cancer cells is selected for early in tumor development, because only such cells can evolve the multiple additional changes, including defects in apoptosis, that are necessary for most cell types to become malignant.

Cells that are too genetically unstable will die. Therefore, a treatment that blocks a particular DNA repair process can be lethal for a cancer cell, while sparing normal cells. If we could determine why the cells in a particular individual tumor are genetically unstable (for example, which DNA repair protein has been altered during the evolution of that tumor), we might be able to design drugs that kill the cells in that cancer highly selectively, with little harm to normal cells.

These examples of rational approaches to cancer therapy were only a dream until recently. But by targeting these types of alterations in cancer cells, researchers have made impressive progress and are thus much closer to being able to design highly selective therapies based on the critical molecular defects in an individual tumor. But for most tumors, this type of approach is still hit or miss, because oncologists are severely hampered by an inadequate understanding of the fundamental processes that are altered in a particular tumor. My conclusion: If I were the czar of cancer research, I would give a higher priority to recruiting more of our best young scientists to decipher the detailed mechanisms of both apoptosis and DNA repair, and I would give them the resources to do so.

– Bruce Alberts

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