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The *ASCB Newsletter* is published twelve times per year by The American Society for Cell Biology.

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Deadlines for submission of articles and advertising materials:

Issue	Deadline
January 2008	December 1
February	January 1
March	February 1

ASCB Newsletter
ISSN 1060-8982
Volume 30, Number 11
November 2007

Postmaster: Send change of address to
ASCB Newsletter
The American Society for Cell Biology
8120 Woodmont Avenue, Suite 750
Bethesda, MD 20814-2762

PRESIDENT'S Column

How Might the NIH Fund the Best Possible Research Relevant to Human Health?

Two of my previous articles in this series have been entitled "Why Basic Research in Cell Biology Is Still Critical for Human Health" (*ASCB Newsletter,* June 2007) and "Peer-Review Processes at the National Institutes of Health" (*ASCB Newsletter,* February 2007). In this article, I will further explore this question: How might we optimize the synergies between basic and medically focused science, so as to fund the best possible research relevant to the long-term health of the U.S. and the world? For this purpose, I return to the massive reorganization of the study sections that the NIH completed in early 2002. The reorganization, undertaken in response to the report of the Panel on Boundaries for Scientific Review (PBSR) that I chaired, was intended to increase the above synergies. Is it serving its intended purpose?

Bruce Alberts

Some Thoughts on Cancer Research

To begin to explore this question, consider the case of cancer research. This is an area that I find fascinating, a fascination stimulated by teaching medical students at the University of California, San Francisco, and by my involvement in five editions of the textbook, *Molecular Biology of the Cell.* In recent years, we have heard statements that we already know enough to cure cancer, and that now is the time to focus nearly all of our resources on developing therapies. There have even been occasional claims that researchers working to understand the molecular basis of cancer are "satisfying their curiosity at the expense of the taxpayer." What we now know about Cell Biology and cancer causes me to reject such ideas completely.

Experts believe that human cancer should be considered to be hundreds of different diseases, depending on the cell of origin and on the pattern of specific changes acquired during the process of tumor progression.[1] We can certainly hope to be able to cure some specific types of cancers by direct approaches that focus on inhibiting specific oncogenic protein kinases—for example, by using drugs such as Gleevec® in combination with other inhibitors.[2] However, I believe that the strategies that could permit a major breakthrough are different.

Two broad strategies that could lead to cures for many different cancers seem particularly attractive, and each is based on an important area of Cell Biology where much more high-quality research is needed. Perhaps the most obvious of these anti-cancer strategies would have the goal of understanding the complicated signaling network inside the cell that determines the balance between the pro-apoptotic BH123 and BH3 proteins, and the anti-apoptotic Bcl-2 proteins, which in turn determine whether a cell kills itself by apoptosis.[3] This balance needs to be perturbed by either mutation or epigenetic changes for cancer cells to proliferate despite their many abnormalities. Suppose that we had a way of determining exactly why the cells in a particular individual tumor incorrectly compute (through a process that I like to refer to as "cell thinking") that they need not kill themselves as normal cells would do in their condition. If we understood enough about how cells make such decisions, we could then add a tailored mixture of drugs to cause them to "think" differently, in a manner that causes the cancer cells to kill themselves without harming normal cells.

A second broad strategy that promises to allow the highly selective killing of tumor cells takes advantage of the fact that essentially all cancer cells have acquired a defect in some aspect of what might be called "DNA metabolism"—often some aspect of DNA repair that causes them to become highly mutable.[4] This genetic instability was selected for early in tumor progression, because only cells with this property were able to acquire the 10 or so additional

changes that seem to be needed for most cell types to become malignant.[5]

Fortunately, cells that are too genetically unstable will die, and thus cancer cells should be inherently susceptible to treatments that increase their instability in ways that might not be a problem for normal cells. The DNA repair pathways in normal cells are very complex and partially redundant in ways that increase the probability of success in this type of anti-cancer approach.[6] If we had a method that was capable of determining exactly why the cells in a particular individual tumor are genetically unstable (for example, exactly which repair pathway is defective), we might be able to add a drug that kills them highly selectively, without harm to normal cells. This type of approach was only a dream until recently. But the impressive selective killing of BRCA1 and BRCA2 deficient cells with Parp inhibitors,[7, 8] a treatment now in Phase 2 trials in humans, encourages the belief that much more can be done along these lines.

How might we optimize the synergies between basic and medically focused science, so as to fund the best possible research relevant to the long-term health of the U.S. and the world?

Assessing Peer Review

Studies with yeasts have proven to provide a powerful short cut to our understanding of human DNA repair systems of all kinds.[9] Are some of the leading researchers unraveling the mechanisms of yeast and human DNA repair pathways being reviewed in tumor biology study sections, or are they all competing with basic researchers in a small number of study sections flooded with high quality competitors whose work has little relevance to cancer? Likewise, are many of the grants of researchers exploring new approaches to understanding the normal signaling system for apoptosis being reviewed in tumor biology study sections, as I believe they should be, or are they directly competing with all other basic research on signaling systems?

It is, of course, impossible for any peer-review process to do a perfect job of funding the biomedical sciences. But in an area where new techniques, approaches, and knowledge are being generated at a tremendous pace, the NIH needs to subject itself to frequent, continuous improvement cycles that are based on thoughtful, unbiased analyses of how well it is currently functioning. I am pleased to announce that the ASCB has just begun a new study, in collaboration with the American Society of Biochemistry and Molecular Biology (ASBMB), to help the NIH with such an analysis. This effort is being led by our Public Policy Committee Chair Tom Pollard and overseen by a committee consisting of Michael Caplan, Beth McNally, and Peter Sorger from the ASCB, plus Sally Kornbluth, John Kyriakis, and Linda Van Aelst from the ASBMB. It is meant to generate meaningful data concerning study section organization, composition, and function that will be provided to one or more of the "Open Houses" being organized by the NIH's Center for Scientific Review headed by Tony Scarpa (see http://cms.csr.nih.gov).[10] The ASCB-ASBMB Committee will lead an effort in which its members—and other members of our two scientific societies—carry out a detailed analysis of a sample of study sections; in this process; they will be aided by ASCB staff member Kevin Wilson and professional policy analyst Kathy Hanna—whom the ASCB and ASBMB have recently hired as a consultant.

The manner in which the two cancer research areas briefly outlined above are currently reviewed at the NIH might provide one test-case for examining the extent to which the vision underlying the PBSR report is being achieved. Briefly stated, a critical part of the original plan was to improve the quality of both basic and medically focused research by forming new study sections that contain a balanced mix of researchers focusing on a human disease or organ system with researchers focused on unraveling the fundamental mechanisms required to understand that disease or organ system (the latter group would often be appropriately focused on model organisms such as yeasts, worms, and flies). To what extent did this happen?

All those with suggestions or comments for the new ASCB-ASBMB Committee are encouraged to email Kevin Wilson at kwilson@ascb.org. ■

Comments about this column are welcome and should be sent to president@ascb.org.

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