VIEWPOINT

Ensuring an Innovative and Productive Future for the Next Generation of Scientists

The 2016 Lasker-Koshland Special Achievement Award in Medical Science

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Viewpoints

Supplemental content

The 2016 Lasker-Koshland Special Achievement Award in Medical Science has been presented to Bruce Alberts for fundamental discoveries in DNA replication and protein biochemistry, for visionary leadership in directing national and international scientific organizations to better people's lives, and for passionate dedication to improving education in science and mathematics.

The highly distributive, cooperative global system that is called science has proven to be an immensely powerful human invention, repeatedly producing amazing new breakthroughs. Thus, tremendous advances have been made in knowledge of the fundamental chemistry of living organisms over the past 3 to 4 decades. In particular, it is now increasingly appreciated that life is made possible by incredibly complicated, highly interactive networks of chemical reactions, catalyzed by elaborate complexes of macromolecules that function as "protein machines."[1] In fact, the chemistry of life is by far the most sophisticated chemistry known, and this fact has critical implications both for medicine and for biomedical research.

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My nearly 40 years of research and teaching has convinced me that there is still a long way to go before science can claim to truly understand even the simplest living cell. As just one piece of evidence, consider a recent attempt to define the minimum set of gene products required to maintain a cell. Beginning with a tiny bacterium with an unusually small genome, *Mycoplasma mycoides*, and using powerful synthetic genome synthesis technologies, scientists were able to create a stripped-down bacterium with only 473 genes that divides once every 3 hours. This "minimal cell" contains 149 genes that have unknown biological functions: unexpectedly, what nearly one-third of the genetic instructions do for the simplest known cell remains a complete mystery.[2]

Hundreds of talented young scientists should be leaping to fill this huge gap in understanding of fundamental biological mechanisms, perhaps earning several Nobel Prizes along the way. Over the long term, such results are certain to lead to powerful new approaches for improving human health and welfare. However, the specific route is unknowable. An extensive analysis of 20 past breakthroughs shows that completely unpredictable combinations of new knowledge form the path from research to human benefit.[3]

Humans contain roughly 50 times as many genes as the minimal cell just described, and the lack of understanding about what these gene products do is correspondingly substantially greater. A still bigger mystery is how the thousands of billions of human cells cooperate to form and maintain the tissues and organs that keep individuals healthy. When teaching medical students at the University of California, San Francisco, I would always emphasize how astonishing it is that most humans do not get cancer at a very early age. The known spontaneous mutation rate, when combined with the enormous number of cells at risk, should make a failure of cell cooperation highly likely somewhere in the human body, creating a selfish cell lineage that multiplies to cause death. Research on model organisms, like the fruit fly *Drosophila*, provides a shortcut to understanding how human cells cooperate so astoundingly well; as for the *Mycoplasma* mystery described earlier, new fundamental principles are certain to emerge from such studies—along with yet more Nobel Prizes.

Those who teach biology can do a much better job of imparting such critical areas of ignorance to students. But textbooks and professors quite naturally focus on conveying what is known, leaving most students with the impression that 90% of what needs to be known is already known about any topic. After all, it is possible to rapidly determine the complete DNA sequences of genomes and use powerful mass spectroscopy methods to follow all of a cell's proteins. But vast troves of such data are far from enough; in fact, data collection is not understanding, and accumulating too much data can even distract from a focus on central unsolved issues. For this reason, the authors of the *Molecular Biology of the Cell* have appended a special "What We Don't Know" section at the end of each chapter in the sixth edition.[4] As proof of the importance of model organisms for generating vital understandings, this book's chapter on the development of tissues contains approximately 50 references to impor-

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tant research findings in *Drosophila*, 4 times more than for the next most-cited organism, the mouse.

The public and its political representatives cannot appreciate that the ignorance about biological processes is so profound. Based on news media reports, many well-meaning advocates for more government funding for the biological sciences sense that enough is known to focus the limited resources on particular diseases, some even claiming that scientists should stop satisfying their curiosity with government funds and focus on translational biomedical research instead. This type of pressure may explain why the funds for needed fundamental research have been continually decreasing at the US National Institutes of Health (NIH),[5] leading to a sense among young scientists that those who want to pursue fundamental research have little chance of obtaining grant support. Thus, I have been distressed to receive emails from postdoctoral researchers who thank me for emphasizing the continued importance of fundamental research in a talk that I just gave at their university, while reporting that they have been told repeatedly that the only academic careers feasible today are those pursuing translational research in human or mouse systems. Would they be foolish to explore instead the types of exciting, central biological mysteries that I have recommended for young scientists?

The de-emphasis on fundamental research by the NIH is made worse by 2 other factors. One is the tiny proportion of NIH resources being awarded to young independent investigators: today nearly 99% of all funds are being awarded to principal investigators older than 35 years. How innovative would Silicon Valley be if its resources were similarly distributed? The second factor is the conservative nature of most grant review processes. As emphasized in the 2005 National Academies report, *Bridges to Independence*:

American science would benefit from a system that encourages new investigators to try out new ideas and approaches as they begin their independent research careers. The present system of research support does just the opposite. New investigators are ranked relative to previously funded investigators by study sections, even though new investigators lack the "preliminary results" that study sections rank highly. New investigators thus tend to continue their postdoctoral projects because proposing something different with greatly increased risk places even more obstacles to obtaining funding.[6]

I view the current situation as a disaster, urgently requiring strong national leadership to reverse. With my colleagues Shirley Tilghman, Marc Kirschner, and Harold Varmus, a new organization has been founded—Rescuing Biomedical Research (RBR)—with the aim of ameliorating several counterproductive aspects of the current US biomedical research enterprise.[7] If RBR is to be successful, it must work to provide the next generation of scientists with a much larger voice in policy making.

One example epitomizes the efforts of RBR. Led by Tony Hyman, the director of the Max Planck Institute of Molecular Cell Biology and Genetics, a task force of the 16-member RBR Steering Committee has been examining whether a program for funding young scientists modeled after that of the European Research Council (ERC) could be implemented in the United States. The ERC, founded in 2007, carries out 3 completely separate competitions: one for scientists who are just starting a laboratory, another for a scientist's second grant, and the third for everyone else. The criteria for funding are designed to encourage novelty, interdisciplinarity, and high-risk, high-gain research. Each review group is composed of outstanding scientists with a wide range of expertise, avoiding the silo-like focus of many NIH study sections. A successful starting applicant is funded for 5 years for as much as €2 million total, and the median age of successful applicants is 35 years. A just-completed retrospective evaluation of completed grants finds a remarkably positive outcome, with almost three-fourths of the grants judged to have produced either a scientific breakthrough or some major advance.[8]

Based on the ERC example, RBR has been developing a proposal for the United States. Its aim is to at least regain the 2000 NIH principal investigators younger than 36 years who have been lost since the mid-1980s, while incentivizing innovative, fundamental research from many of the nation's most outstanding young scientists. A recent brief iBiology talk, entitled Encouraging Innovation,[9] provides a status report for this initiative.

ARTICLE INFORMATION

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REFERENCES

1. Alberts B. The cell as a collection of protein machines. *Cell*. 1998;92(3):291-294.

2. Hutchison CA III, Chuang RY, Noskov VN, et al. Design and synthesis of a minimal bacterial genome. *Science*. 2016;351(6280):aad6253.

3. National Academy of Sciences. Beyond discovery. http://www.nasonline.org/publications/beyond-discovery. Accessed August 29, 2016.

4. Alberts B, Johnson A, Lewis J, et al. *The Molecular Biology of the Cell*. 6th ed. New York, NY: Garland Publishing; 2015.

5. National Institute of Neurological Disorders and Stroke. Back to basics: a call for fundamental neuroscience research. https://blog.ninds.nih.gov/2014/03/27/back-to-basics/#more-170. Accessed September 1, 2016.

6. National Research Council. Bridges to independence. http://www.nap.edu/catalog/11249/bridges-to-independence-fostering-the-independence-of-new-investigators-in. Accessed August 29, 2016.

7. Rescuing Biomedical Research website. http://rescuingbiomedicalresearch.org. Accessed August 29, 2016.

8. Abbott A. Europe's premier funding agency measures its impact. *Nature*. 2016;535(7613):477-478.

9. Hyman A. Encouraging Innovation. http://www.ibiology.org/ibiomagazine/encouraging-innovation.html. Accessed August 29, 2016.