Experiments of Nature

This column was written by Vann Bennett at the invitation of Brigid Hogan.

Brigid Hogan enticed me to write this column with the promise that it would provide an opportunity to "ride my hobby horse." Who could refuse such an offer? I would like to take this opportunity to celebrate naturally occurring cellular adaptations and the pioneers who have opened these areas to cell biologists. I also would like to comment on opportunities for future pioneers in the genomic era.

Brigid Hogan

Revolutionary Scientists, Far-reaching Impact

A classic example of an experiment of nature with fundamental impact on cell biology is the extrachromosomal genes of *Tetrahymena* exploited by Joe Gall, Elizabeth Blackburn, Carol Greider, and their colleagues in the discovery of telomerase. Elizabeth Blackburn and Carol Greider shared the 2009 Nobel Prize in Physiology or Medicine with Jack Szostak for this work.

Another amazing adaptation is sarcomeres in striated muscle, with their nearly crystalline organization of actin and myosin. Sarcomeres were initially studied by Albert Szent-Gyorgyi and Hugh Huxley and their colleagues, providing the basis for the cytoskeleton revolution in cell biology.

My personal favorite is the erythrocyte plasma membrane, which is the sole membrane of the simplest cell in our body. It was used in the 1920s by Gorter and Grendel to generate the concept that biological membranes are formed from phospholipid bilayers. Vincent Marchesi, Dan Branton, and Ted Steck brought the erythrocyte membrane into the modern era. This simple system has provided a paradigm for membrane-cytoskeletal interactions and led to discovery of spectrins, ankyrins, aquaporins, and the Rh family of ammonium transporters. That is to name just a few ubiquitously expressed proteins first described in red blood cells. Together, telomerase and constituents of sarcomeres and erythrocyte membranes have provided the basis for over 100,000 papers in the biomedical literature.

It is humbling to consider the boldness of early investigators in these model systems. Albert Szent-Gyorgyi, in isolation from a broad scientific community during World War II, was able to demonstrate the first cell-free movement with ATP-dependent contraction of an actomyosin extract from skeletal muscle. Hugh Huxley had the audacity for his Ph.D. thesis to place skeletal muscle in an X-ray beam and obtained diffraction patterns revealing evidence of an amazing level of organization of sarcomeric actin and myosin. Imagine how a modern study section would react to a proposal for such an experiment!

Tetrahymena, skeletal muscle, and erythrocyte membranes share several features that may be instructive. These models cannot be reproduced in tissue culture, and necessitated some serious effort to isolate and characterize novel proteins. Moreover, critical breakthroughs required considerable ingenuity and were not simply extensions of existing algorithms. Given the spectacular success of these systems, and the greatly improved technology, it seems likely that biochemistry and curiosity-driven research still have much to offer cell biology.

Future Opportunities, General Suggestions

Looking ahead, it is interesting to ask what would excite a young Albert Szent-Gyorgyi? First a disclaimer: If I knew of a sure thing, I would work on this myself instead of writing this article. However, I would like to make a few general suggestions. One is to purchase a good histology text. My favorite is by Bloom and Fawcett. (Don Fawcett was the first president of the ASCB and was a gifted electron microscopist with great insight into the beautiful organization of cells and tissues.)

Another suggestion is to use the ongoing revolution in determining the genetic basis for human disease for gene discovery. A perusal of

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Vann Bennett

Online Medelian Inheritance in Man (OMIM) (initiated by Victor McKusick, a major figure in human genetics) reveals an increasing number of disease-causing genes of unknown function. Once you select a gene, then bring to bear the powerful tools of biochemistry, molecular biology, and cell biology to isolate the protein, determine its neighbors, and elucidate its function in cells and at an organismal level.

A compelling example of how successful this approach can be is provided by the dystrophin story. Dystrophin is encoded by the gene mutated in Duchenne muscular dystrophy and was identified by Louis Kunkel and his colleagues. Kevin Campbell (at that point skilled in isolation of muscle proteins from his training with David MacClennan), together with James Ervasti and other colleagues, isolated dystrophin along with dystroglycan and other components of a dystrophin glycoprotein complex. Their work represents a major discovery, both in basic science and for understanding of the pathophysiology of muscular dystrophy. Louis Kunkel and Kevin Campbell were awarded the 2009 March of Dimes Prize in developmental biology for this collaboration between innovative genetics and biochemistry.

A New Era?

Has the heroic era of biology passed? I doubt it and believe that we are still in a major discovery phase. It is, perhaps, comparable to the situation in Europe in 1491, before exploration of the New World and Australia. However, our funding system does produce considerable inertia and risk avoidance. I hope that we and our students can internalize some of the chutzpa of early cell biologists and venture outside the security of our National Institutes of Health study sections. I also hope that we who evaluate grants can be supportive of these innovative efforts. ■

—Vann Bennett
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