

A case for more curiosity-driven basic research

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ABSTRACT Having been selected to be among the exquisitely talented scientists who won the Sandra K. Masur Senior Leadership Award is a tremendous honor. I would like to take this opportunity to make the case for a conviction of mine that I think many will consider outdated. I am convinced that we need more curiosity-driven basic research aimed at understanding the principles governing life. The reasons are simple: 1) we need to learn more about the world around us; and 2) a robust and diverse basic research enterprise will bring ideas and approaches essential for developing new medicines and improving the lives of humankind.

When I was a graduate student, curiosity-driven basic research ruled. Studying mating-type switching in budding yeast, for example, was exciting because it was an interesting problem: How can you make two different cells from a single cell in the absence of any external cues? We did not have to justify why it is important to study what many would now consider a baroque question. Scientists and funding agencies alike agreed that this was an exciting biological problem that needed to be solved. I am certain that all scientists of my generation can come up with similar examples.

Since the time I was a graduate student, the field of biological research has experienced a revolution. We can now determine the genetic makeup of every species in a week or so and have an unprecedented ability to manipulate any genome. This revolution has led to a sense that we understand the principles governing life and that it is now time to apply this knowledge to cure diseases and make the world a better place. While applying knowledge to improve lives and treat diseases is certainly a worthwhile endeavor, it is important to realize that we are far from having a mechanistic understanding of even the basic principles of biology. What the genomic revolution brought us



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are lists, some better than others. We now know how many coding genes define a given species and how many protein kinases, GTPases, and so forth there are in the various genomes we sequenced. This knowledge, however, does not even scratch the surface of understanding their function. When I browse the *Saccharomyces cerevisiae* genome database (my second-favorite website), I am still amazed how many genes there are that have not even been given a name.

To me the most important achievement the new genome-sequencing and genome-editing technologies brought us is that nearly every organism can be a model organism now. We can study and manipulate the processes that most fascinate us in the organisms in which they occur,

with the exception, of course, of humans. Thus, I believe that the golden era of basic biological research is not behind us but in front of us, and we need more people who will take advantage of the tools that have been developed in the past three decades. I am therefore hoping that many young people will choose a career in basic research and find an exciting question to study. The more of us there are, the more knowledge we will acquire, and the higher the likelihood we will discover something amazing and important. There is so much interesting biology out there that we should strive to understand. Some of my favorite unanswered questions are: What are the biological principles underlying symbiosis and how did it evolve? Why is sleep essential? Why do plants, despite an enormous regenerative potential, never die of cancer? Why do brown bears, despite inactivity, obesity, and high levels of cholesterol, exhibit no signs of atherosclerosis? How do sharks continuously produce teeth?

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One could, of course, argue that the knowledge we have accumulated over the past 50 years provides a reasonable framework, and it is now time to leave basic science and model organisms behind and focus on what matters—curing diseases, developing methods to produce energy, cleaning up the oceans, preventing global warming, building biological computers, designing organisms, or engineering whatever the current buzz is about. Like David Botstein, who eloquently discussed the importance of basic research in these pages in 2012 (Botstein, 2012), I believe that the notion that we already know enough is wrong and the current application-centric view of biology is misguided. Experience has taught us over and over that we cannot predict where the next important breakthrough will emerge. Many of the discoveries that we consider groundbreaking and that have brought us new medicines or improved our lives in other ways are the result of curiosity-driven basic research. My favorite example is the discovery of penicillin. Alexander Fleming, through the careful study of his (contaminated) bacterial plates, enabled humankind to escape natural selection. More recent success stories such as new cures for hepatitis C, the human papillomavirus vaccine, the HIV-containment regimens, or treatments for BCR-ABL induced chronic myelogenous leukemia have also only been possible because of decades of basic research in model organisms that taught us the principles of life and enabled us to acquire the methodologies critical to develop these treatments. Although work from my own lab on the causes and consequences of chromosome mis-segregation in budding yeast has not led to the development of new treatments, it has taught us a lot about how an imbalanced karyotype, a hallmark of cancer, affects the physiology of cancer cells and creates vulnerabilities in cancer cells that could represent new therapeutic targets.

These are but a few examples for why it is important that we scientists must dedicate ourselves to the pursuit of basic knowledge and why we as a society must make funding basic research a priority. Achieving the latter requires that we scientists tell the public about the importance of what we are doing and explain the potential implications of basic research for human health. At the same time, it

will be important to manage expectations. We must explain that not every research project will lead to the development of new medicines and that we cannot predict where the next big breakthroughs will materialize. We must further make it clear that this means we have to fund a broad range of basic research at a healthy level. Perhaps a website that collects examples of how basic research has led to breakthroughs in medicine could serve as a showcase for such success stories, bringing the importance of what we do to the public.

While conducting research to improve the lives of others is certainly a worthy motivation, it is not the main reason why I get up very early every morning to go to the lab. To me, gaining an understanding of a basic principle in the purest Faustian terms is what I find most rewarding and exciting. Designing and conducting experiments, pondering the results, and developing hypotheses as to how something may work is most exciting, the idea that I, or nowadays the people in my lab, may be (hopefully) the first to discover a new aspect of biology is the best feeling. It is these rare eureka moments, when you first realize how a process works or when you discover something that opens up a new research direction, that make up for all the woes and frustrations that come with being an experimental scientist in an expensive discipline.

For me, having a career in curiosity-driven basic research has been immensely rewarding. It is my hope that basic research remains one of the pillars of the American scientific enterprise, attracting the brightest young minds for generations to come. We as a community can help to make this a reality by telling people what we do and highlighting the importance of our work to their lives.

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REFERENCE

Botstein D (2012). Why we need more basic biology research, not less. *Mol Biol Cell* 23, 4160–4161.