Moving from Pond Scum to Human Diseases and Back

A Basic Scientist Thinks about Translational Research

Translational research is defined by the National Institutes of Health (NIH) as "the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease."[1] By this definition, most ASCB members are contributing to translational research. There is no doubt that many discoveries of cell biologists and geneticists have furthered patient care.

The Path of Progress

Over the last 15 years, the true significance of Darwin's theory of evolution has become increasingly obvious with the sequencing of over 450 genomes. It is clear that many of the key genes involved in cellular processes—from DNA replication and repair to mRNA transcription and translation to cell cycle progression and protein trafficking—are highly conserved. Many of the signaling pathways that guide development are apparent in sea slugs and insects as well as humans. The study of those signaling pathways in nonhumans informs us about their role in human development and how defects in these processes can lead to a range of problems from neural tube closure defects to cancer.

More often than not, the functions of genes responsible for human diseases were first elucidated through the study of experimentally accessible organisms. The path of progress has never been clearer: from humans to model organisms and back to humans. This kind of investigation does not just catalog genes. Rather it establishes the mechanistic understanding of their roles in cells and organisms that will advance the practice of medicine.

One Disease, Many Genes

New genomic resources and techniques are bringing within reach an understanding of the basis of common, complex human diseases such as diabetes and heart disease. "One gene, one enzyme" may still be (mostly) true, but "one gene, one disease" is patently false when it comes to the diseases that afflict the largest number of people. A multitude of genes, working together and often against each other, contribute to conditions like hypertension, cancer, diabetes, obesity, and neurodegeneration. For example, common variants of 25 genes have thus far been implicated in diabetes. Yet those 25 variants explain only part of the disease, meaning that knowing an individual's genotype at those 25 genes will not make it possible to predict prognosis with perspicacity. We need to learn more to be able to do this, which in turn calls for studies of experimentally tractable organisms. It is important to remember that the bench-to-bedside paradigm is incomplete if it doesn't go back to the bench in a repeating loop that is necessary to refine and explore the pathways and learn their clinical impact.

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Cilia and a True Believer

My research over the last 25 years has centered on understanding the role of basal bodies (also known as centrioles) as organizing centers for cytoplasmic and spindle microtubules and cilia. The significance statement of my NIH grant applications always explained how understanding these organelles would illuminate the basis of cancer. I actually believed what I wrote, but I admit to being secretly skeptical that we would really achieve that goal. But about six years ago I became a true believer in the Church of Translational Research. The work of Greg Pazour, Doug Cole, George Witman, and Joel Rosenbaum with the green alga *Chlamydomonas*, and Brad Yoder with mice,

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led to the realization that a protein called Ift88 in *Chlamydomonas* and polaris/Tg737 in mice is evolutionarily conserved; moreover, it suggested a role for cilia in polycystic kidney disease. This convinced me that studies of pond scum could lead to important insights into human disease and eventually improve patient outcomes.

Since these discoveries, cilia have been implicated in an increasing number of signaling and mechanical pathways that impact human health. This provides beautiful examples of how discoveries made at the bench can and do make important contributions at the bedside.

Once we knew that known ciliary proteins are conserved across phyla, our lab searched for additional genes encoding components of cilia. Cilia are present on almost every cell in a human but are missing in flowering plants. Thus one can look for genes that are present in humans and in algae but absent in flowering plants. Among this collection we identified the *BBS5* gene, one of several responsible for Bardet Biedl Syndrome (BBS). Children homozygous for rare mutations in this gene have kidney disease, obesity, diabetes, retinal degeneration, and loss of the ability to smell, too many fingers, and learning disabilities. Numerous labs are now learning the role of the BBS proteins in various signaling pathways that act through cilia. Cracking this story relied in large part on basic research in algae, flies, and worms.

The role of cilia in BBS is but one example of how basic research can have a major impact on the understanding of human disease. But how do we take these observations back to the bedside? Just knowing that cilia are involved in signaling that affects obesity, kidney disease, and retinal degeneration is useful, but how can model organisms help to close the loop back to patient care?

Once again, the experimental power of simple model organisms can contribute to this goal. It should be possible to identify targets for drugs for ciliary diseases through a screen for suppressors of ciliary defects in *Chlamydomonas*. It is easy to screen 10^{10} *Chlamydomonas* cells for mutations that restore motility and/or sensory function to the organism. Recessive mutations provide excellent targets for therapeutics because their loss of function in the background of the disease mutation mimics the wild-type phenotype.

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The conservation of protein sequence and function throughout the tree of life allows the elucidation of cellular processes and provides possible targets for drug development. It requires collaboration among scientists with diverse expertise and interests to move discoveries from the clinic to the lab bench and then back to the clinic. But we should not turn our backs on the serendipity of research. We must keep experimenting on things like pond scum, just because we want to know about them, always confident that our efforts will inform, maybe even improve, the human condition. ■

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Reference

[1]http://grants.nih.gov/grants/guide/pa-files/PAR-05-158.html (accessed May 20, 2008).

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