# THE ASCB PRESIDENT'S COLUMN – Harvey Lodish:
# Should Cell Biologists Study Human Disease?

Why is it that so few cell biologists work directly on understanding the molecular and cellular basis of human disease? Clearly there are many cultural, historical, political, and educational aspects of this problem. But solution of these issues is not difficult and would greatly enhance our ability to understand and eventually treat a host of untreatable pathologies. Many of these diseases pose difficult research problems, but success in science is measured by one's achievement in solving difficult problems, not easy ones. Importantly, I see many opportunities for young independent investigators to advance their careers by studying complex disease-related problems.

When I was a junior faculty member in the late 1960's and 1970's, molecular and cellular biology were considered „pure" sciences; any implication that our research could be useful was discouraged by senior scientists. Neither I nor my compatriot PhDs had any serious knowledge of human physiology or pathobiology, and nowhere in our undergraduate or graduate curricula did we or our students learn anything about organ function or whole body metabolism or infectious disease. A few changes did occur in the early 1980's when it became apparent that the obscure work we were doing on gene structure and expression could actually be useful to the nascent biotechnology industry. As I have commented in a recent article[1], there still remains a cultural divide between scientists in academe and in industry, even though they have a common education and research training.

Unfortunately, there is also a huge cultural divide between basic, mechanistic, studies in cell biology and the great unmet needs of medicine in understanding and eventually treating major human diseases.

Students and faculty should realize that immense insights into basic cellular and genetic mechanisms have already come from intensive studies of some human diseases. Studies of cancer cells, to take just one example, have illuminated many aspects of cell growth control, receptor kinases, and cell cycle regulation, as well as the roles of integrins and extracellular matrix proteins in tissue organization. Future studies on major untreatable diseases also promise considerable insight into other basic mechanisms.

The current divide between basic and medical science – and the opportunities for basic cell biology – were pushed to the front of my mind as I attended small meetings on metabolic problems in human obesity and on new approaches to neurodegenerative disease.

Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease) are incurable. Not only are there no cures in the pipeline, there is a significant lack of understanding of the underlying pathology. Why, late in life, should specific classes of neurons degenerate? Are the tangles of precipitated tau protein (a microtubule binding protein) that accumulate in the brains of Alzheimer's disease patients the cause of the disease or a side-effect? Or is the cause related to the fibers of Aβ1-42, a 42 amino acid peptide cleaved from a membrane-spanning APP protein by combined action of a metallo-proteinase and an enzyme that apparently cleaves APP in the middle of the membrane? Why do tau and Aβ1-42 form aggregates? Do these kill the neuron and if so, how? Are defects in vesicle traffic up and down the axon a part of the problem?

These are some of the key questions in the field, and these are questions of basic cell biology. Yet until a few years ago, essentially no scientists trained in fundamental cell biology worked on these issues. The field was the provenance of neuropathologists and neurologists. Anatomic abnormalities seen at autopsy coupled with a few insights obtained from cloning disease genes from rare families with genetic predisposition were the main bases for speculation of the ultimate cause of the pathology.

In the past few years, exciting new work on the mechanism of protein folding into aggregates, coupled with genetic and cellular studies of mutant candidate proteins in flies, worms, and even yeasts, have yielded major advances in understanding of this and other neurodegenerative diseases. Yet fundamental questions remain and all too few young cell biologists are working in these areas or are even aware of the problems and opportunities presented by these diseases.

Consider obesity – currently a huge and growing epidemic in all Western countries and many in Asia. In several states, over a quarter of the adult population is clinically obese and a sizable percentage morbidly obese. Obesity will have a tremendous impact on public health since hugely overweight individuals have a very high likelihood of developing diabetes and cardiovascular disease and their sequelae of blindness, strokes, and limb amputations. Especially worrisome is the increase in obese, pre-diabetic teenagers who are already insulin resistant and likely will soon develop full-fledged diabetes; these people likely will require lifetime treatment and have poor prognoses.

The cell and molecular biology of obesity is only slowly being dissected. Work in this field has largely been done by scientists trained in nutrition and medical endocrinology; the few „basic" scientists in this field, many of whom have the MD or MD and PhD degrees, have made many of the key advancements.

Adipose (fat) tissue from obese individuals contains larger adipocytes than those in lean individuals, and these have huge fat droplets. The tissue is heavily infiltrated with macrophages and other stromal cells that produce inflammatory cytokines such as TNFα. These in turn affect the gene expression pattern in adipocytes, down regulating many proteins essential for insulin action. In particular, the profile of adipocyte-secreted proteins – including proteins like adiponectin that enhance fat and glucose catabolism by muscle and inflammatory cytokines like IL-6, is changed for the worse.

What is the nature of these „stromal" cells? Where do they come from and what attracts them to adipose tissue? Surprisingly the identities of these cells are not certain and they may well differ in different body fat depots. What is the extracellular matrix surrounding adipocytes and do matrix proteins, integrins, or hormone receptors play key roles in the development of „obese" fat tissue? What determines the size of a fat cell and the structure and metabolism of the lipid droplets within them? What are the signaling mechanisms used by adipose cell-produced hormones? These are basic cell biological problems and deserve the attention of ambitious young investigators who want both to solve important problems and perhaps have an impact on new types of therapy.

One problem is that our undergraduates and graduate students receive little training in human physiology and pathobiology and simply are unaware of the key unsolved problems in the study of human disease. I am sad to report that most of our MIT biology PhD students receive their degrees without knowing the functions of major body organs such as the liver or kidney. A few undergraduate lecture courses or graduate seminars focused on specific classes of diseases, taught collaboratively between basic science and medical faculty, would go a long way toward remediating these defects in our curricula. (Short focused „mini-courses" may be appropriate here.) Unfortunately, and as I emphasized in an earlier column[2], faculty at our medical schools often have no reason to teach such undergraduate or graduate courses and in some departments are actively discouraged from doing so.

The NIH and private foundations would do a service to science by organizing short courses on the pathobiology of specific human diseases – liver fibrosis, macular degeneration, diabetes or asthma – for young investigators trained in „basic" biochemistry or cell biology or molecular biology. These would allow PhDs and MDs to learn from each other. The goal would be to inform „basic" biologists of issues concerning these diseases, and new, creative, testable, and fundable ideas could emerge from such gatherings.

We often hear of the need for interdisciplinary studies between biologists and mathematicians, physicists, and engineers. I support and encourage these collaborations, but in my view there is an even greater need for collaborations between basically- trained biologists and medical specialists.

[1] Two Cultures and the Revolution in Biotechnology, The ASCB Newsletter, May 2004.
[2] Teaching is Good for Research, The ASCB Newsletter, February 2004.

*Comments are welcome and should be sent to president@ascb.org.*

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