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Genes, Cells and Discovery in Basic Science and Disease

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Our understanding of the basic processes of life at the cellular and molecular level has substantially changed the outlook for the treatment of the greatest diseases of mankind.

As a result of the development of tools to explore genes and chromosomes and the protein molecules they encode, therapies to treat heart disease and cancer have been designed with a level of precision that has saved countless lives. Beginning with the discovery of the structure of DNA and continuing with the elucidation of the path taken to express the genes in our genome, we are now able to modify genes that show promise of curing genetic diseases such as sickle cell anemia. These breakthroughs will surely lead to treatments for cancers and neurodegenerative diseases where heritable mutations are the source of illness.

My interest began with a toy microscope that I received as a gift which stimulated a fascination with the microbial world. That interest matured at University and in my PhD work where I learned the powerful tools of biochemistry from Arthur Kornberg, a Nobelist who discovered an enzyme that copies DNA stands. For my independent career, I took the lessons from Kornberg and from broader readings on modern approaches to the elucidation of complex cellular processes and applied them to a molecular genetic dissection of the process of protein secretion in a simple eukaryotic organism, Baker's yeast. Using simple genetics to discover essential genes required for protein secretion, my research team elucidated a pathway similar to that discovered in pancreatic tissue by the great Romanian Nobelist, George Palade.

The genes we discovered are evolutionarily conserved and employed in mammals to execute the diverse processes in secretion essential to normal physiology. This conservation allowed the biotechnology industry to harness yeast cells as a secretion platform for the production of clinically important proteins such as human recombinant insulin.

Following on the genetics, we developed biochemical approaches to identify the functions of a number of the secretion genes in yeast and their equivalents in human cells. Several of the genes encode subunits of the channel in the endoplasmic reticulum (ER) membrane responsible for the first step in the transfer of newly-synthesized secretory proteins from their site of synthesis on ribosomes in the cytoplasm across the ER membrane into the interior luminal space. Another set of the genes encode subunits of a coat protein complex that pinches transport vesicles carrying secretory cargo proteins for traffic from the ER to the Golgi apparatus. Some of these genes have been found to be the basis of human genetic diseases of protein secretion. Knowledge of these precise mechanisms contributes directly to the development of novel therapeutic interventions.