ASHBi SEMINAR

Cracking the Code of Rare Diseases: Understanding Mechanisms and Developing New Therapies

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Date: Tuesday, 15th October 2019
Time: 18:00-19:00
Venue: Meeting room C, 5th floor, Outpatient Treatment Ward

The advent of modern sequencing methods has greatly amplified the number of human genetics findings and continuously generates many novel genotype-phenotype correlations across the spectrum of both the frequency of the genetic variant as well as the phenotype – i.e. covering common diseases, as well as rare, and ultra-rare ones. However, even in the space of monogenic (Mendelian) disorders where the link between a genetic variant and disease is most often causal, the biological mechanisms through which the genetic variant of interest results in disease is most often not obvious. Understanding those biological and molecular mechanisms are a prerequisite to the development of therapies (particularly disease-modifying, rather than palliative therapies) for any given rare genetic disorder. Such understanding not only sets the stage for rational exploration of therapies but also provides novel insights into basic biological mechanisms and the function of genes in vivo. During my seminar I demonstrate this premise using fibrodysplasia ossificans progressiva (FOP) as a first example. I will describe how our findings on the mechanism of action of the FOP-causing variant of the receptor-encoding gene ACVR1 has provided paradigm-breaking insights on signaling via this receptor and also provided a potential part to therapy, culminating into a clinical trial in FOP with a putative disease- modifying drug. Then I will discuss some of the work that we have been pursuing at the Regeneron Genetics Center, focusing on several novel discoveries from our genotype- phenotype ascertainment in Founder Populations (i.e. genetically isolated populations), particularly the Amish. Lastly, I will describe a new method for enzyme replacement therapy to demonstrate the importance of continued technological advancement in biologic drugs. These three vignettes, although distinct in content, provide the three pillars that are required for expanding our understanding of Rare Genetic Diseases: genetic discovery (and proper diagnosis), ascertainment of the biological mechanism resulting in the disease, and technological breakthroughs in drug design in order to provide better therapeutic options.

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