RARE DISEASES, COMMON INSIGHTS

Rare-disease research—like rare diseases themselves—doesn’t occur in a biological vacuum. It’s often intertwined with investigations into fundamental cellular activities. “I think it’s now a reflex of anybody working on any rare condition to see what else might be represented by the same mechanisms but in a different part of the body, at a different time in life, or [in the context of] cancer,” says Heather Etchevers, a developmental biologist at the French National Institute of Health and Medical Research (INSERM).

For instance, her work on giant congenital melanocytic nevus (CMN)—a large, pigmented birthmark—could be helpful in understanding common cancers, such as adult-onset melanoma, as well as other developmental disorders. “There are a couple of genes (known to cause CMN) whose proteins work together to tell cells when to proliferate,” she explains. “When those mutations happen early in development and in a particular set of lineages, it turns out that it can lead to a whole bunch of different disorders, including many other kinds of skin malformations, vascular malformations, and brain malformations.” She adds that the reason those genes initially appeared on scientists’ radars was because they “came up over and over again in cancers.”

Such unexpected associations between rare and common diseases are uncovered “more often than [those outside the orphan disease community] realize,” says Ellen Sidiras, a physician and molecular geneticist at the National Institutes of Health (NIH). Her work revealed that mutations in the gene encoding glucocerebrosidase (GBA), which causes Gaucher disease, were also present in many individuals with Parkinson’s disease—a discovery that launched more than a decade of research into the link between the two conditions (Mauron, 93:737-46, 2017). For most rare disease researchers, this is one of the key arguments justifying investments in conditions that affect far fewer people than common ailments such as heart disease, lung cancer, and obesity.

There are dozens of examples of rare disease-related insights that have led to breakthroughs for more frequently occurring conditions. Perhaps the most-cited case is that of familial hypercholesterolemia, which is caused by an extremely rare mutation in the gene encoding the low-density lipoprotein (LDL) receptor that can lead to fatally high cholesterol levels. Research into this condition, conducted in the 1970s by geneticist Michael Brown and biochemist Joseph Goldstein, led to a greater understanding of LDL’s role in cholesterol synthesis (PNAS, 71:88-92, 1974). These findings helped reveal the mechanism of action of statins, the widely used cholesterol-lowering drugs that help prevent cardiovascular disease, and earned the duo the 1985 Nobel Prize in Physiology or Medicine.

“That, to me, is a perfect example of how the worst aberration of a pathway has revealed how you can intervene for milder aberrations and interfere with a population risk that’s enormous,” says William Gahl, head of the Undiagnosed Diseases Program at the NIH. Statins went on to become some of the best-selling drugs of all time, still earning billions of dollars in sales every year.

Biotechs such as Perlara, based in the Bay Area, are seeking to develop treatments for both rare and common conditions by mapping the genetic connections between them. To accomplish this goal, the company is creating genetically engineered animal models of ultra-rare monogenetic conditions with the aim of generating new treatments and identifying how the genetic mutations are associated with more prevalent maladies.

For example, insights into NGL Y1 deficiency, a rare, congenital condition Perlara researchers are investigating, may lead to better treatments for certain cancers, such as multiple myeloma (ACS Cent Sci, 3:1143-55, 2017). “Our premise is that we’re not scared of the economics of these diseases, because if you realize that these rare diseases are connected to something more common, there is not an economic problem anymore,” says Ethan Perlstein, the company’s CEO. “You just have to figure out what that connection is.”

THE LDL RECEPTOR PATHWAY IN MAMMALIAN CELLS: LDL receptors are first synthesized in the endoplasmic reticulum 1. After maturing in the Golgi apparatus, the receptors are transported in vesicles to the cell membrane 2. Once an LDL molecule has bound to the receptor 3, the complex is endocytosed into the cell 4. Then, the resulting endosome is split, and the LDL is gobbled up by a lysosome while the receptor returns back to the cell surface 5. In the lysosome, LDL is degraded into cholesterol and amino acids 6. Increased levels of cholesterol in the cell suppress the transcription of the gene encoding HMG-CoA reductase, a key enzyme required for cholesterol synthesis within the body 7, and the production of more LDL receptors.