Lafora Disease: Science Terms 101 for the Patient Community

Our community benefits from a number of dedicated research champions who work alongside our families to find a cure for this devastating disease. There is a lot that we can learn about Lafora Disease from our scientists. As you read their scientific publications and listen to their presentations, here are a few terms that will help you understand their research:

Glycogen: When our bodies have extra sugar (glucose), they store it in the form of glycogen, which is made up of a bunch of sugars linked together. Our bodies use sugars to make fuel for our cells (the way that gasoline or electricity fuel a car). When your body needs energy quickly, it can remove the sugar from this storage device and use it for fuel.

Protein-Coding Gene: A piece of DNA that contains instructions for synthesizing a protein. Patients with Lafora Disease have mutations in one of two genes:

1. **EPM2A**: the gene with instructions for making the protein laforin.
2. **EPM2B** (also called NHLRC1): the gene with instructions for making the protein malin.

Proteins: These are the biological machines your body makes in order to perform important functions in your cells. Here are a few important proteins in Lafora Disease Research:

Laforin: This protein interacts with glycogen. It provides a scaffold for other proteins to do their job related to creating or destroying glycogen. Laforin also pulls a small molecule called "phosphate" off of glycogen, which helps to make sure glycogen stays the right "shape" so that your body can take it apart for making fuel.

Malin: This protein tells other proteins when they need to start doing their jobs, where they need to go, and when they need to leave. It does this by attaching a small protein called "ubiquitin." For example, malin attaches ubiquitin to laforin to tell it when it needs to take a break from being a scaffold on glycogen.

Glycogen Synthase & Glycogen Branching Enzyme: Both of these proteins are responsible for linking sugars together to form glycogen

Glycogen Phosphorylase & Glycogen Debranching Enzyme: Both of these proteins are needed to remove sugars from glycogen storage.

Alpha-Glucosidase (GAA): This protein helps to break apart glycogen that cannot be degraded by Glycogen Phosphorylase or Glycogen Debranching Enzyme. This protein normally stays in the lysosome of our cells (think of the lysosome like the cell's trash can).

Knock-out Mouse Model: A mouse that has been genetically altered to remove a specific gene. In Lafora Disease, the two common Knock-Out Mouse models are Laforin (or EPM2A) Knock-out mice and Malin (or EPM2B) Knock-Out mice. Because these mice do not have that gene, they can be used to study genetic diseases and test potential therapies.

Knock-in Mouse Model: A mouse that has been genetically altered to express a specific gene mutation. These mice are not missing a gene, instead, they are expressing a mutated form of the gene. These mice can be used to study the effect of specific patient mutations and to test potential therapies.

Biomarker: A *measurable* marker of disease or infection. Clinical trials use biomarkers to measure the impact of a potential therapy on disease progression in the patient.

Antibody: A type of protein used by our immune system to identify foreign proteins in our bodies, like viruses, and mark them for destruction. In biological research, antibodies can also be used to identify a specific protein they need to study.

Enzyme: A specific type of protein. Enzymes facilitate chemical reactions in our cells that would not happen often enough or quickly enough without help from the enzyme.

Antibody-Enzyme Fusion (AEF): A type of therapy that fuses together an antibody and an enzyme. The antibody tells the enzyme where to go, and the enzyme facilitates the chemical reaction. *In Pompe Disease, patients have a mutated or missing alpha-glucosidase. The AEF for Pompe Disease contains an antibody which helps the enzyme, alpha-glucosidase, to reach the lysosome and degrade glycogen.*

Molecule: A collection of atoms held together by force in a specific shape. You can think of them like little puzzle pieces that fit into specific areas of our cells.

Small Molecule Drugs: These molecules have a specific shape that allow them to either stop a protein from working, or improve its function. *In Lafora Disease, researchers want to design small molecules to block or reduce the function of the protein Glycogen Synthase.*

Gene Therapy: is the use of genetic material (DNA or RNA) to alter the production of a specific protein in your body. It can be used to make a correct version of a missing protein, or it can be used to decrease the activity of a specific protein by reducing production of that protein. *In Lafora Disease, researchers have two strategies for designing a therapy: In one scenario, they want to reduce the production of the protein Glycogen Synthase in order to reduce the synthesis of glycogen. In the other scenario, gene therapy would be used to express a correct version of the malin protein.*

Antisense Oligonucleotide (ASO): In order to make a protein, our cells read the instructions in the DNA, and then send out a message to start synthesizing the protein. That message comes in the form of RNA. An antisense oligonucleotide is made from the same materials as RNA, allowing it to bind to the RNA and prevent it from delivering its message. As a result, that protein does not get synthesized. *In Lafora Disease, the ASO targets the RNA carrying the message for Glycogen Synthase, reducing its expression and limiting the synthesis of glycogen.*