GLOSSARY OF TERMS

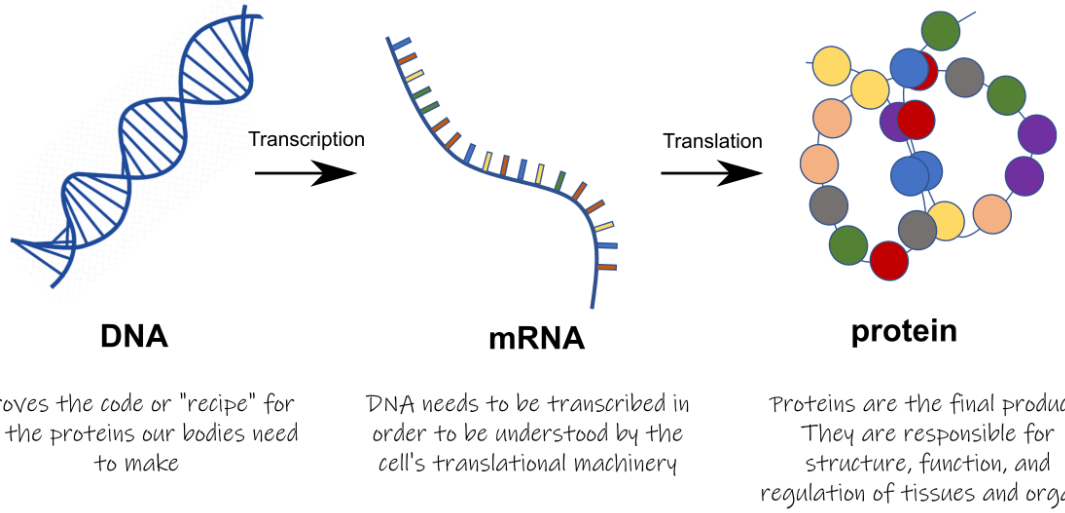
AAV or Adeno Associated Virus: AAVs are small vectors commonly used for gene therapies. They are viruses that can not replicate themselves or cause disease as the viral genes have been removed, and instead have been manipulated to deliver genes to humans.

Amino Acid: Amino acids are the building blocks of proteins; a specific order of amino acids is required to make a functional protein.

ASO (Antisense Oligonucleotide): A short synthetic RNA that uses a specific DNA sequence to locate a specific region (gene) where it can hide a mutation that is present in the gene.

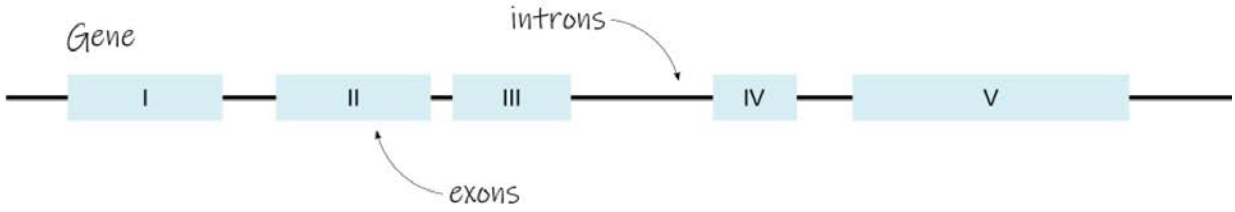
Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Central Dogma: Refers to the flow of information; generally speaking, how DNA makes RNA, and how RNA helps to make protein.



Exon: The sequence of nucleotides within a gene that are “protein encoding”. Exons are separated by introns, which are removed by splicing, so that translation can occur.

Gene Therapy: A therapeutic approach that aims to correct the gene that is dysfunctional.



There are a few different ways to do this, including “new” gene delivery by AAV, or “masking” or correcting a gene using an ASO.

Intron: The sequence of nucleotides within a gene that separates exons. It was thought that these sequences were junk, simply removed during protein synthesis. It is understood now that sequences within the introns have many functions. See the image under “exon”.

Leukodystrophy: A category of diseases and disorders that predominantly affect the white matter of the brain and spinal cord.

Leukoencephalopathy: A term to describe all diseases of the white matter.

Missense Mutation: A missense mutation (or variant) is a type of change in the DNA sequence in which the altered nucleotide changes the protein code. This change can alter the structure of a protein, which can affect function.

Mutation or Variant: A mutation, also called a gene variant, is a change to the DNA sequence. Generally, all people carry variants, the vast majority of which have no consequence, but certain variants in important areas, or areas that are highly conserved (DNA sequence is the same across many species), can have debilitating consequences.

Natural History Study: A study that follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease. A natural history study collects health information in order to understand how a medical condition or disease develops and how to treat it.

Nucleotide: Nucleotides are the basic building blocks of nucleic acids (RNA and DNA). A nucleotide consists of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base.

Organoid (or mini-brain): This is essentially a ball of cells that are allowed to differentiate as they would in a brain. It starts with pluripotent stem cells, which hold the capacity to become any cell type. The cells replicate and change into different cell types, forming an organization similar to what they would in a brain. These models are good because in a brain, cells of a different type (different types of neurons, astrocytes, etc.) interact; this model allows that interaction to happen and we can observe the effects of treatments, or disease/injury on these cell interactions.

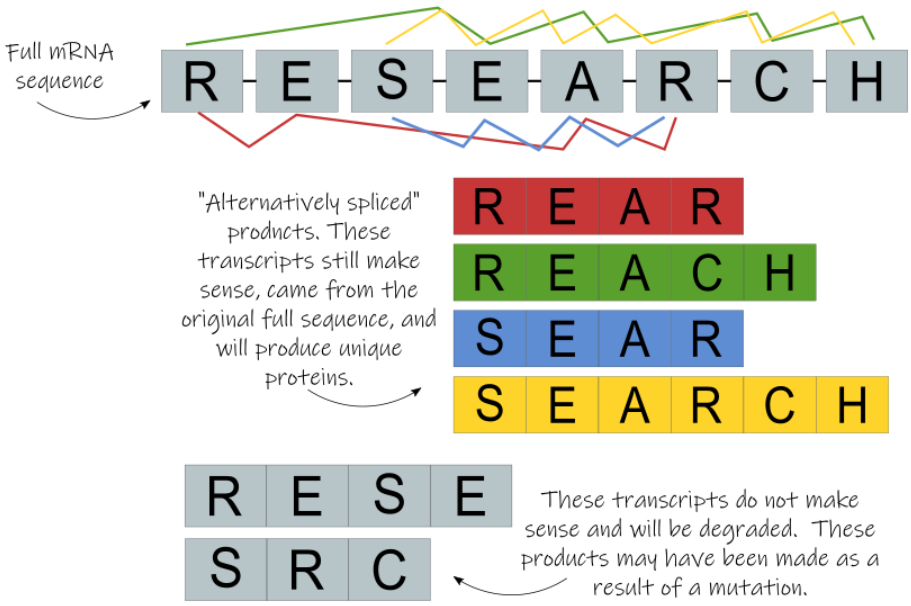
Phenotype: The set of observable characteristics or traits of an organism.

Proprioception: The body's ability to sense its position, movement, and orientation in a space.

Respiratory Chain Complex (or the Electron Transport Chain): A series of protein complexes that operate in sequence to produce energy for the cell. A very large number of these protein groups are contained per mitochondria, and cells can have hundreds to hundreds of thousands of mitochondria.

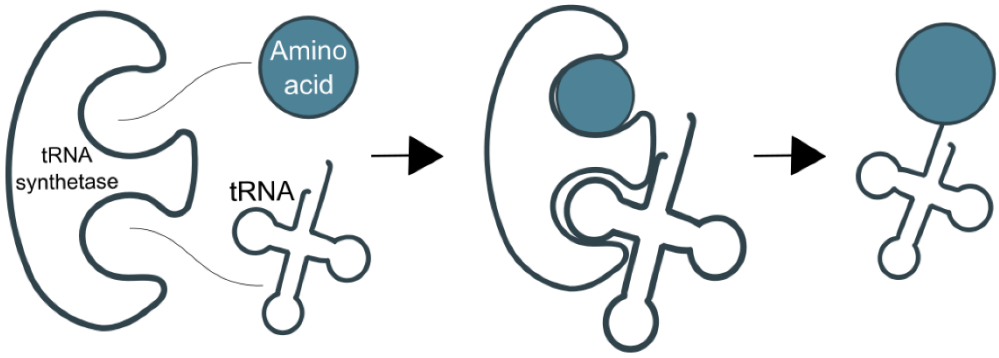
Splice Site (and splice site variant): A splice site is the area in a sequence where the splicing cuts are made to either remove introns, or link exons. In LBSL, a common variant is located in the splice site, which affects the ability of the protein to be made correctly.

Splicing: Splicing is the process in which the protein-making machinery removes unneeded nucleotides from a gene sequence (called Introns), leaving only the sequences (called Exons) that code for proteins. "Alternative splice products" means that many proteins can be made from the same gene sequence, but the exons are in a different order, producing a unique protein. In the event that a sequence is produced that doesn't make sense, the cell will degrade it (most of the time). See figure below.



tRNA: tRNAs are small molecules that match the genetic code to the appropriate amino acid. tRNAs help to build chains of amino acids that become proteins. Please refer to the figure under "tRNA Synthetase".

tRNA Synthetase: Synthetases, like DARS2, link tRNAs to the amino acid for protein translation. For Dars2, this happens in the cell's mitochondria. Other tRNA synthetases exist outside of the mitochondria, in the cell body.



tRNA synthetases catalyze the binding of amino acids to tRNAs.

White Matter: White matter refers to fatty (lipid rich) tissue, or myelin, that wraps around nerve cell axons. Information and communication between cells can be sent and received quickly when traveling via these insulated "highways".