



National Tay-Sachs & Allied Diseases Association

Small Molecule Therapy

Some therapeutic approaches use small molecules, which are drugs that are small enough to easily enter cells, to target specific parts of the cell and possibly modify disease processes. Below are some relevant small molecule therapies being investigated which may eventually be important for the treatment of Tay-Sachs, Sandhoff, GM1 gangliosidosis, and Canavan diseases. Please note that this is not an inclusive list and only highlights a couple of approaches that are currently being studied.

Modified amino acid (leucine) therapy

IntraBio investigated a small molecule treatment in pediatric (≥ 6 years) and adult patients with GM2 Gangliosidosis (Tay-Sachs and Sandhoff disease). This therapeutic agent is based on small modifications to the amino acid leucine, turning it into a drug called N-Acetyl-L-Leucine (NALL), which is orally administered (PMID: 34349180). Results from a recent clinical trial showed that the drug was safe, well tolerated, and demonstrated improvements to cerebellar function, fine motor skills, gait and stance, and speech (PMID: 36456200). Additional information can be found here: [Clinical Trial #NCT03759665](https://clinicaltrials.gov/ct2/show/study/NCT03759665). This drug was approved in September 2024 for the treatment of Niemann-Pick disease type C (NPC) patients. It is also known as Aqneursa (brand name), levacetylleucine (generic name) and IB1001 (previous name), see <https://www.drugs.com/history/aqneursa.html>.

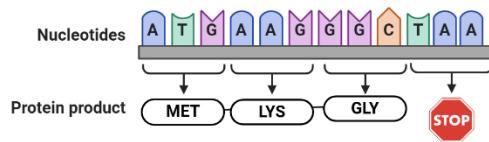
For more information about clinical trial processes, please check out the following educational resources created by the American Society of Gene and Cell Therapy (ASGCT): Clinical Trial Process: <https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process>

Premature Termination Codon (PTC) readthrough therapy

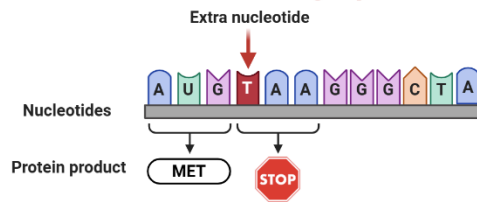
Our genes provide specific instructions to make proteins, which carry out essential functions in our bodies. Genes are made up of a series of nucleotides, the building blocks of DNA, and are represented by four 'letters' that form the DNA code. If a gene has a harmful 'spelling' change in its DNA code (i.e., pathogenic variant or mutation), it may not provide correct instructions to produce functional proteins. Sometimes, there is a 'spelling' change called a nonsense variant that causes a premature "stop" in the code. When this

happens, the DNA code cannot be read all the way through, preventing it from producing a full-length functioning protein (see figure below). Some, but not all, patients with GM2 gangliosidosis, GM1 gangliosidosis, or Canavan disease have nonsense variants in the *HEXA*, *HEXB*, *GLB1*, and *ASPA* genes, respectively, that are responsible for their disease. Premature Termination Codon (PTC) readthrough therapy is a therapy that may be applicable for patients with nonsense variants.

Normal nucleotide sequence



Nonsense variant causing a premature stop codon



Created in BioRender.com 

These agents can also be referred to as Premature Termination Codon (PTC) suppressing agents, translational readthrough-inducing drugs (TRIDs), or nonsense suppression agents, and they are typically small molecules that promote readthrough of the premature stop codon. Although this type of therapy is specific to the type of variant present, it is promising for many patients because it is estimated that about 11% of variants causing human genetic diseases are nonsense variants that introduce a premature stop codon (PMID: 37371567). PTC readthrough therapy works to read through the premature “stop” in the code, allowing full length functional protein to be produced. While there are multiple methods to induce PTC readthrough, small molecules have been the focus of many therapeutic studies (PMID: 37371567). This type of therapy has been investigated in lysosomal storage diseases, including GM1 gangliosidosis (PMIDs: 26169295; 35857082; 22056610; 36901952). A study using GM1 patient fibroblast cells showed a small increase in enzyme activity with gentamicin treatment (PMID: 26169295). Gentamicin is a type of small molecule that can induce PTC readthrough. Although the side-effects associated with long-term gentamicin treatment prevent it from being a viable therapeutic option in patients, currently more than 50 small molecule compounds can promote PTC readthrough and this may lead to better therapeutic options in the future for a subset of patients with nonsense variants (PMID: 37371567).

While most studies have focused on PTC readthrough therapy in the context of other lysosomal storage conditions, such as MPS I, the presence of nonsense variants in patients with GM2 gangliosidosis, GM1 gangliosidosis, and Canavan disease may lead to future PTC readthrough therapeutic agents being developed that may be effective for these conditions as research progresses.

Enzyme Enhancement Therapy /Pharmacological Chaperone Therapy

Enzyme enhancement therapy (EET), also known as pharmacological chaperone therapy (PCT), is another small molecule therapy. This therapy aims to rescue and improve the function of deficient enzymes in the body. For more information, NTSAD has a full document dedicated to describing EET/PCT on our website.

To access the literature reference, enter the PMID number into the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) search box or Google “PMID XXXXXXXX”, replacing the “X’s” with the appropriate number.

Data is current as of September 2024.