



National Tay-Sachs & Allied Diseases Association

Substrate Reduction Therapy (SRT)

What is SRT?

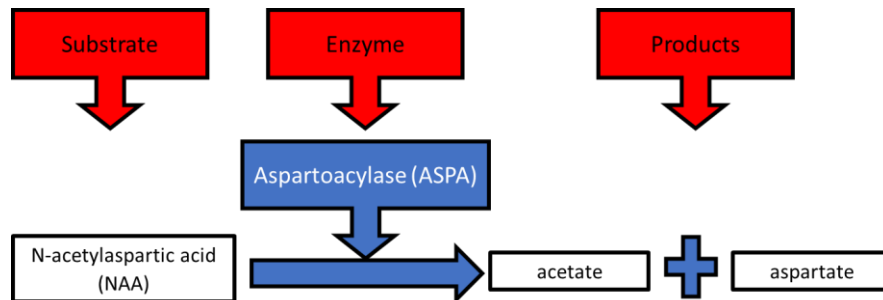
Our genes provide specific instructions to make proteins, which carry out essential functions in our bodies. An enzyme is a type of protein whose function is to break down specific substances (substrates) in our body to produce one or more products. If a gene has a harmful change (i.e., pathogenic variant), it may not provide correct instructions to produce functional enzymes. Deficiencies in certain enzymes can lead to a toxic accumulation of substances in the body. This is what happens with Tay-Sachs, Canavan, GM1 gangliosidosis, and Sandhoff diseases due to genetic changes causing reduced or absent activity in the enzymes HexA, ASPA, GLB1, and HexB, respectively.

SRT is a treatment approach that uses drugs to reduce the production of substrates that the enzymes act upon because these enzymes are not functioning properly.

How does SRT work?

There are three main components of an enzyme reaction: the substrate, enzyme, and resulting product(s) that the enzyme and the substrate produce (see figure below).

In Canavan disease, for example, the enzyme aspartoacylase (ASPA) helps to break down N-acetylaspartic acid (NAA) into two smaller products: acetate and aspartate. Reduced or absent ASPA activity leads to an increase of NAA in the brain, spinal fluid, blood, and urine (PMID: 17194761). Elevated NAA is toxic and can lead to damage to the brain and spinal cord, which result in symptoms of Canavan disease. SRT therapy for Canavan disease would aim to reduce NAA (substrate shown in figure below) since the faulty ASPA enzyme is not able to break it down into its products. SRT would be designed to target earlier steps in the metabolic pathway to inhibit production of the substrate, thus reducing its accumulation. By targeting earlier steps, SRT's goal is to reduce the accumulation of toxic substrate buildup and slow or stop progression of the disease.



How does SRT work? (GM2 Gangliosidoses example)

Clinical studies have explored SRT for GM2 gangliosidoses (Tay-Sachs and Sandhoff diseases). GM2 gangliosidoses are caused by genetic variants involved in the breakdown of GM2 gangliosides, a type of glycosphingolipid. These genetic variants lead to enzyme deficiencies in the pathway, resulting in the inability to properly break down GM2 gangliosides, which leads to their toxic accumulation and damage to the brain and spinal cord. Current SRTs work to inhibit the first step of the glycosphingolipid biosynthesis pathway. This metabolic pathway leads to the production of gangliosides, fatty substances that accumulate in individuals with GM2 disease. By targeting these earlier steps, the goal is to reduce the amount of ganglioside in the brain and spinal cord.

How are SRTs delivered?

SRT typically uses small molecule drugs that can cross the blood-brain barrier to reach target cells in the central nervous system (brain and spinal cord). This therapy is administered orally, typically through a pill or capsule, making the therapy more convenient and less invasive than alternative options.

What are the limitations of SRT?

Effectiveness: SRT has not yet been proven to significantly improve neurological symptoms of patients with GM2 gangliosidoses. There are no current clinical trials of SRT for GM1 gangliosidosis or Canavan disease.

Age: SRT may be most effective when given earlier in the disease course, as early treatment can minimize damage caused by the condition.

Side-effects: Potential side-effects of miglustat include diarrhea, stomach issues, and neuropathy (PMID: 18339196, based on Gaucher patients who took SRT).

Accessibility: Currently, there are no FDA approved SRTs for GM2 gangliosidoses, GM1 gangliosidosis, or Canavan disease. Furthermore, SRT in general remains expensive and inaccessible to many.

What is Miglustat?

Miglustat is the most common SRT drug and is clinically approved to treat patients with Gaucher disease. However, there currently no approved SRTs for Canavan disease, GM2 gangliosidosis, or GM1 gangliosidosis. Venglustat is a similar SRT drug that was studied in the GM2 gangliosidosis clinical trial that was closed in April 2024 (more information below).

Miglustat works to competitively inhibit glycosphingolipid synthase and is able to cross the blood-brain barrier. Mice models demonstrated that miglustat has the potential to reduce GM2 ganglioside accumulation in the brain. However, when used in patients with Tay-Sachs disease, miglustat did not stop neurologic dysfunction from progressing (PMID: 30524313). Patients affected with Sandhoff disease also did not see improvements or prevention of neurological impairment when taking miglustat (PMID: 35865957). While miglustat may delay neurological symptoms, clinical studies have not led to significant neurological benefits for Tay-Sachs or Sandhoff disease patients.

What SRT trials are currently available?

While there are clinical trials underway, there are no SRT clinical trials accepting new patients.

Azafaros (Closed)

Phase 2 Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Oral AZ-3102 in Patients With GM2 Gangliosidosis or Niemann-Pick Type C Disease (RAINBOW): [Clinical Trial #NCT05758922](#)

Sanofi Genzyme (Active, not recruiting) **

A Multinational, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Pharmacodynamics, Pharmacokinetics, and Safety of Venglustat in Late-onset GM2 (AMETHIST): [Clinical Trial #NCT04221451](#)

****Sanofi recently announced that this clinical trial was discontinued for the treatment of GM2 gangliosidosis because they did not see positive results on the clinical endpoints they were studying.**

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 August 2024.