

Lay Language Summary

Lysosomal diseases are genetic disorders caused by the inability to breakdown large molecules in the lysosomes, which are the recycling units in the cells. Metachromatic leukodystrophy (MLD) is one of these diseases and is caused by the deficiency of a specific enzyme in the lysosomes called arylsulfatase A. In MLD, the accumulation of undegraded material (sulfatides) results in dysfunction of the lysosomes, compromising the entire cells and ultimately multiple organs/systems. The mechanisms how the storage of sulfatides can severely affect brain causing severe mental disabilities have not been fully elucidated.

Over two thirds of the lysosomal diseases are associated with severe and progressive neurological problems such as seizures, coordination and cognitive problems, muscle weakness and atrophy. Unfortunately, the few therapies available today for patients suffering of these diseases poorly focus on treating the brain disease. In terms of the enzyme replacement therapy, the infused enzyme, being a large molecule, is unable to cross a very selective and tight barrier that surrounds the brain vessels, which is called blood-brain barrier. For this reason, the enzyme replacement therapy is unable to treat neurological problems commonly seen in patients with lysosomal diseases.

Sometimes, the defected enzyme in MLD carries a small ability to breakdown the sulfatides. What was discover by others and us is that some lysosomal enzymes are deficient because they have a weak, known as unstable, structure, that makes them to “misfold”. As, in this misfolded form the enzymes may become toxic, cells have a system to early destroy them, resulting in reduction of their levels in the lysosomes.

Based on previous studies, we identified chemical compounds, also called small molecules, that are capable of binding to the defected enzymes, make them more stable and prevent their early degradation. Given our expertise, and the availability of MLD patient cells, we developed a method to screen collections of chemical compounds in order to identify those that are able to rescue the lysosomal enzyme deficient in MLD. This method was published in a peer-review journal (Geng *et al* 2011).

In this project funded by NTSAD, we develop expertise to convert skin cells into brain cells, called “induced-neuronal cells”. We converted skin cells from GM2 gangliosidosis patients (both Tay-Sachs and Sandhoff variants) into the induced-neuronal cells. These cells can be used to elucidate how the disease affects the brain disease in this devastating disease. We are now able to use these converted brain cells without the need to perform brain or nerve biopsies, which is, brings a high risk for the patients.

We will be utilizing these skin-derived brain cells to further study the chemical compounds that are able to rescue the enzyme deficiency in MLD. These novel technologies, both the screening using patient cells and conversion of skin cells into neuronal cells can be applied to any lysosomal disease, especially those that are associated with neurological problems. These will be powerful tools to use in the discovery of new treatments for several lysosomal and neurological diseases.