Globoid Cell Leukodystrophy (Krabbe’s Disease) is a lysosomal storage disease characterized by a lack of galactocerebrosidase with the subsequent accumulation of intermediate ganglioside metabolites, such as psychosine and galactosylceramide. Affected people and animals invariably die at a young age with numerous large, globoid, PAS positive cells infiltrating the neuropil of the brain and spinal cord.

Much of the previous work is focused on psychosine and its affect on the molecular mechanisms and machinery of the cell, but has ignored how or why the globoid cells accumulate to such large numbers in the brain and spinal cord. With this in mind, our hypothesis is that the components of the innate immune system are involved in amplifying the inflammatory process in the brain, leading to the final histologic appearance in terminally affected people and animals.

We will investigate this hypothesis through two established innate immune pathways. The first involves pattern recognition receptors known as Toll-like receptors (TLRs). TLRs are a heterogenous group of receptors expressed by most nucleated cells that recognize molecules either not present in most mammalian cells or present in immune privileged sites. Among these molecular patterns are lipopolysaccharide (LPS), lipoarabinomannan, and peptidoglycan; however, the literature also reports that certain TLRs can detect gangliosides. Because galactosylceramide and psychosine can build up to toxic levels in Krabbe’s disease, the role of TLRs in the progression of Krabbe’s disease warrants exploration.

The second innate immune pathway we will explore is the stimulation of invariant natural killer T (NKT) cells. These specialized T-cells have the ability to recognize lipids presented to them on MHC-like molecules known as CD1d tetramers. It is well-known in the literature that α-galactosylceramide is able to upregulate invariant NKT cells through interactions with CD1d. In Krabbe’s disease, β-galactosylceramide accumulates in the cells but the affect of this lipid on NKT cells has never been investigated in the context of Krabbe’s disease.

If the initiating events in globoid cell leukodystrophy can be elucidated, then treatments aimed at blocking these pathways may help prolong the life of a person affected by this disease.