Principal Investigator: Professor Frances M. Platt
Grant Title: Role of glycosphingolipids in severe human neurological diseases

(a) Abstract:

In 2003, our collaborator, Prof. Andrew Crosby (St George's Medical School, London) mapped the gene responsible for a severe epilepsy syndrome. The gene encoded GM3 synthase (GM3S), a sialyltransferase that catalyses the initial step in the biosynthesis of a- and b- series complex gangliosides that are particularly prevalent in the brain. We confirmed that the patients lacked GM3 ganglioside and its derivatives in plasma samples [1]. This was the first proven disease that results from a biosynthetic defect in the glycosphingolipid (GSL) pathway. The original plan was to characterize further, the $GM3S^{-/-}$ mouse and why it is asymptomatic and doesn't have severe epilepsy. We also wished to evaluate GM3 replacement therapy using cultured skin fibroblasts from patients. Before the Mizutani grant was awarded, Prof. Crosby contacted us because he had identified a second, putative, GSL biosynthetic disorder which causes a complex form of hereditary spastic paraplegia. As a result of this important finding, it was agreed with the Mizutani Foundation that we could use the grant awarded to study GSL expression in cultured skin fibroblasts and blood samples from these patients. We were able to show that this disease is indeed the second proven example of a disorder of GSL biosynthesis. It is caused by a frameshift insertion in the last exon of the beta-1,4-N-acetyl-galactosaminyl transferase 1 (B4GALNT1) gene which encodes GM2 synthase (GM2S) [2]. With the description of two neurological human diseases involving defects in two sequentially acting enzymes in ganglioside biosynthesis, there is the real possibility that a previously unidentified family of ganglioside deficiency diseases exist. The study of patients and animal models of these disorders will pave the way for a greater understanding of the role gangliosides play in neuronal structure and function and provide insights into the development of effective treatment therapies.