Overview of Zacharon's Ganglioside Inhibitor Program

Background

Zacharon's unique glycobiology expertise has enabled the development of an entirely new class of drugs selectively targeting the biosynthesis of carbohydrates. Zacharon scientists overcame historical challenges by integrating cell-based high-throughput screening technologies and highly sensitive carbohydrate structural analysis tools, thus unlocking the potential of small molecule drugs which modify carbohydrate biosynthesis.

One of Zacharon's advanced programs involves the development of a novel small molecule inhibitor of the biosynthesis of gangliosides, a family of lipid-linked carbohydrates. This first-in-class program has the potential to address substantial morbidity and mortality resulting from the Gangliosidoses, a family of lysosomal storage diseases with no existing treatment options, as well as several forms of neural crest-derived tumors.

Zacharon has partnered with the National Cancer Institute and the National Institute of Neurological Disorders and Stroke for financial support for this important program. Currently, Zacharon is completing important preclinical development activities necessary to advance this program (and other programs) through clinical trials and subsequent commercialization. The successful completion of these activities will enable the first effective therapy for the Gangliosidoses as well as a novel therapy targeting an entirely new mechanism of action for neural crest tumors.

Introduction to Gangliosides

Gangliosides are lipid-linked carbohydrates synthesized in the endoplasmic reticulum and Golgi compartments of the cell. Gangliosides are present on the cell surface and are involved in the regulation of receptor tyrosine kinases, modulation of the structure of the lipid bi-layers, and other biological roles[1-5]. Gangliosides are eventually trafficked to the cell lysosome where they are degraded and recycled by a series of lysosomal enzymes.

The Gangliosidoses: A Family of Rare Diseases

The Gangliosidoses results from genetic errors leading to a deficiency in the enzymes responsible for lysosomal degradation of gangliosides. Depending on the enzyme deficiency, this family of rare diseases includes Tay-Sachs, Sandhoff, AB variant, and GM1 gangliosidosis[6]. As illustrated in **Figure 1A**, ganglioside synthesis is normally balanced with degradation thus enabling normal lysosomal function. In patients with the Gangliosidoses (**Figure 1B**), the impaired degradation prevents normal lysosomal function resulting in the accumulation of undigested gangliosides and dramatic morbidity and mortality. The incidence of these diseases is 1 in 55,000 births.

Figure 1A. Normal Ganglioside Synthesis and Degradation

Figure 1B. Impaired Degradation in the Gangliosidoses Results in the Accumulation of Gangliosides in Lysosome

Burden of Illness of the Gangliosidoses

Patients with gangliosidosis experience a variety of neurological symptoms resulting in dramatic reductions in quality and duration of life [7]. The progressive clinical course includes gait and speech disturbances, behavioral and psychiatric symptoms, muscular weakness, severe intellectual impairment, sleep problems, and other serious neurological symptoms. In addition to the direct morbidity and mortality experienced by the patient, the slowly progressing symptoms leave the patient blind, deaf, mentally retarded, paralyzed, and non responsive to the environment, resulting in a substantial emotional and financial burden for the caregivers. Life span is significantly reduced with many patients dying in the first decade of life.

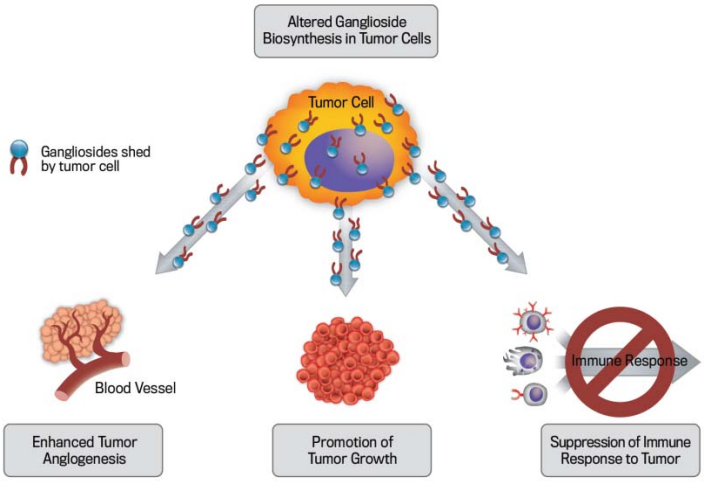
Lack of Existing Treatment Options for the Gangliodoses

For certain other LSD's, enzyme replacement therapy (ERT) based on recombinant forms of the deficient enzymes has proven effective. However, no experimental or approved therapy has demonstrated efficacy for the Gangliosidoses, and only supportive care is presently available [6]. ERT is not an attractive option as the symptoms involve the CNS and the IV-administered enzymes do not adequately cross the blood-brain barrier. Additionally, a unique ERT must be developed for each individual class of the Gangliosidoses because each has a distinct enzyme deficiency, further limiting the viability of strategies designed to correct the enzyme deficiency. Another strategy involves reducing ganglioside biosynthesis to balance the rate of synthesis with the impaired rate of ganglioside breakdown. This approach has been validated in both the Tay Sachs and Sandhoff mouse models using non-selective inhibitors of gangliosides. However, the required doses of these non-selective inhibitors are > 100 fold higher than the maximum tolerated dose in humans, and unfortunately several clinical studies have failed to demonstrate efficacy even at the maximum tolerated dose [22].

Gangliosides and Cancer

Gangliosides also play critical roles in the growth of neural crest tumors including neuroblastoma, glioma, and melanoma as illustrated in **Figure 2**.Tumor progression depends on angiogenesis requiring vascular endothelial cell migration, and proliferation, triggered by tumor-derived vascular endothelial cell growth factor (VEGF). Studies have shown that tumors actively over-express and shed gangliosides which bind to normal vascular endothelial cells and enhance their ability to respond to VEGF [8]. In addition, the shedding of gangliosides has been shown to suppress the beneficial immune response to tumor cells and trigger enhanced growth of the tumor[9-11]. Gangliosides as an anti-cancer target has been further validated through the use of the non-selective ganglioside inhibitors described above. When these inhibitors are fed to mice, the growth and spread of neural crest tumors can be inhibited [12-14]. The important role of gangliosides in various neural crest tumors has further been demonstrated genetically through the use of antisense constructs which inhibit gangliosides [15, 16]. Together, these and other data strongly suggest that ganglioside inhibitors can have therapeutic benefits in neural crest tumors, however no clinically viable ganglioside inhibitors exist.

Figure 2. Critical Roles Played by Gangliosides in the Pathogenesis of Cancer



Introduction to Zacharon's Ganglioside Inhibitor Program

Zacharon is leveraging its innovative technology platform to develop the first selective inhibitor of gangliosides, thus enabling an entirely new therapeutic strategy. For patients with the Gangliosidoses, this strategy is based on developing a small molecule inhibitor of the biosynthesis of gangliosides with excellent brain penetration to reduce the accumulation of gangliosides in the lysosome of affected patients (see **Figure 3**). Important, by targeting the gangliosides (which are common across the various classes of the Gangliosidoses) rather than correcting the enzyme deficiency (which is specific to each class), this strategy can result in one therapy treating multiple classes of the Gangliosidoses. For patients with neural crest-derived tumors, this same ganglioside inhibitor is designed to reduce the ability of tumor cells to shed gangliosides and spread through the mechanisms described in **Figure 2**.

Figure 3. Zacharon Ganglioside Inhibitor Prevents Lysosomal Accumulation in the Gangliosidoses

Small molecule inhibitor of glycan biosynthesis

Ganglioside Inhibitor Program Update

Zacharon has completed important preclinical development activities including the demonstration of proof of concept using in vitro and animal models. Additional preclinical development activities required to advance this exciting new strategy are presently being conducted to enable this novel therapy for reducing the devastating symptoms associated with the Gangliosidoses and neural crest-derived tumors.

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