# Overview of Zacharon's Mucopolysaccharidoses I, II, and III Program

## Disease Background

Mucopolysaccharidoses (MPS) I, II, and III are a family of rare lysosomal storage diseases resulting from recessive errors present in the DNA of otherwise normal individuals[1]. When two individuals with the same recessive error have children, the children can inherit the same error from both parents and thus be affected by the resulting genetic disease. In MPS, the genetic error leads to a deficiency in enzymes responsible for the degradation of glycosaminoglycans (GAGs), a group of related carbohydrates. As illustrated in **Figure 1A**, GAG synthesis is normally balanced with degradation thus enabling normal lysosomal function. In patients with MPS (**Figure 1B**), the impaired degradation prevents normal lysosomal function resulting in the accumulation of undigested GAGs. This chronic accumulation leads to dramatic morbidity and mortality.

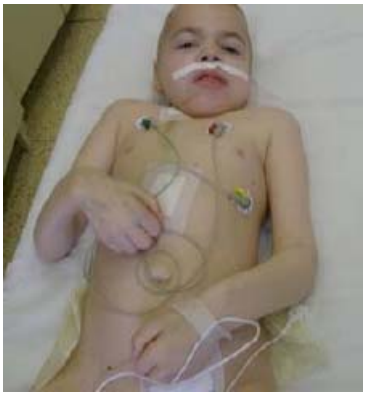
**Figure 1A.** Normal GAG Synthesis and Degradation


**Figure 1B.** Impaired Degradation of GAGs Results in the Accumulation of GAGs in the Lysosome


## Burden of Illness of MPS I, II, and III

With the exception of those mildly affected, patients with MPS I, II, and III experience neurodegeneration which becomes apparent in early childhood, and children may exhibit behavioral abnormalities, sleep disturbances, and speech delay. Mental retardation becomes obvious over time, and severe and progressive neurologic degeneration occurs. Severe behavior problems are common including hearing and vision loss, uncontrollable hyperactivity, temper tantrums, destructive behavior, vacuous chewing, and physical aggression. Patients with MPS III have few, if any, symptoms other than those affecting the central nervous system (CNS). However, patients with MPS I and II also experience respiratory complications, cardiac disease, loss of mobility, hearing and vision loss, spinal cord compression, and other serious symptoms. Life span is significantly affected and most patients do not survive beyond twenty years of age. **Figure 2** illustrates MPS II. The combined incidence of MPS I, II, and III is approximately 1 in 35,000 births.

**Figure 2.** MPS



## Existing Treatment Options

Current therapies for MPS and other lysosomal storage diseases are aimed at restoring the activity of the specific defective enzyme. The most successful approach is enzyme replacement therapy (ERT) where recombinant enzyme is infused into the bloodstream. ERTs are currently approved for treating certain non-CNS symptoms of MPS I and II [2, 3]. There is no therapy for any of the types of MPS III. While ERT is a substantial advance, significant morbidity and mortality remains due to several key limitations. ERT does not address neurological symptoms because it does not cross the blood brain barrier (BBB). Direct CNS delivery of ERT is being explored (by direct infusion or BBB penetrating agents). However, delivering a protein therapeutic to the

brain and penetration of other critical tissues remains a significant technical and clinical challenge. Additionally, ERT must be uniquely developed for each sub-class of MPS (as each has a unique enzyme deficiency). In addition to neurological degeneration, other major symptoms such as cardiac disease and respiratory dysfunction may remain largely unaddressed by ERT. As a result, the primary causes of morbidity and mortality in MPS may remain largely unaddressed by ERT[2, 4, 5].

## Introduction to Zacharon's MPS I, II, and III Program

Zacharon's unique glycobiology expertise has enabled the development of an entirely new class of drugs targeting the biosynthesis of GAGs and other 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.

Zacharon is leveraging this technology platform to enable an entirely new treatment strategy for patients with MPS and other related diseases. Rather than attempting to correct the enzyme deficiency (historical approach), Zacharon is developing small molecule drugs which selectively modify the structure of the GAG so that the deficient enzyme is not required for degradation. This strategy, termed "substrate optimization therapy", represents the first small molecule approach to treating MPS and other lysosomal storage diseases. This difference of using a small molecule creates the potential to penetrate the CNS and other critical tissues largely unaddressed by existing therapies. Furthermore, by targeting the GAGs (which are common across MPS I, II, and III) rather than correcting the enzyme deficiency (which is specific to each MPS class), this strategy can result in one therapy treating multiple classes of MPS. **Figure 3** illustrates the concept of Zacharon's approach to treating MPS I, II, and III in which the balance between GAG synthesis and degradation is restored.

**Figure 3**. Zacharon GAG Inhibitor Prevents Lysosomal Accumulation in MPS I, II, and III


## MPS I, II, and III Program Update

Zacharon has completed important preclinical development activities including the demonstration of proof of concept using MPS animal models including reduction in GAG accumulation in the brain. (Please visit the News and Publications section of Zacharon's web site at http://www.zacharon.com/pages/news/index.html to download the most recent scientific poster presentation for this program.) Additional preclinical development activities are currently be conducted with the goal of advancing this program through clinical trials and subsequent commercialization. The successful completion of these activities is designed to enable the first small molecule therapy capable of addressing neurological decline and other needs of patients with MPS I, II, and III. Zacharon has also partnered with the National MPS Society, Team Sanfilippo, and the National Institute of Neurological Disorders and Stroke for financial support for this important program. For more information, please visit www.zacharon.com or contact info@zacharon.com.

## References

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