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ONE BREAKTHROUGH

INFORMED BY ANOTHER

FOCUS: Developing novel oral therapies for rare metabolic diseases.

Glucosylceramide-based glycosphingolipidoses, including Gaucher disease type 3, Fabry disease, Tay-Sachs, Sandhoff disease, and GM1 gangliosidosis, are rare, often fatal disorders that involve the central nervous system (CNS). The absence of therapeutics that distribute to the central nervous system has rendered these disorders unresponsive to treatment.

A small molecule that distributes into the CNS and inhibits the synthesis of glycosphingolipid, a part of the cell membrane, may be of therapeutic benefit to patients afflicted with these diseases.

Dr. Shayman developed eliglustat, the first stand-alone oral treatment for Gaucher disease type 1 now in worldwide use. However, the poor brain exposure of eliglustat renders it unsuitable for the treatment of CNS-based glycosphingolipidoses. To address this need, he and his team developed compounds with structures similar to eliglustat with the aim of finding a molecule able to cross into the brain and retain metabolic activity.

"In effect, we looked at the chemical properties of eliglustat, identified those that are unfavorable to penetrating the brain, and designed compounds around those," Dr. Shayman says. "Also, some patients cannot properly metabolize eliglustat, so it is necessary to design our new compounds around that liability as well, and find a therapy that is not subject to metabolism through this route."

The findings of Dr. Shayman's team holds promising results in mouse models of Gaucher disease type 3, and with support from the Harrington Discovery Institute they hope to progress into clinical trials toward an eventual treatment for this class of diseases.

"It reflects well on Harrington that they have flexibility to assist with programs in both early and later stages of development."

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