

Chaperone Therapy - an update

In the last edition of Gaucher News, Amicus Therapeutics, of New Jersey, USA reported on a potential new method to treat patients with Gaucher disease. Dr. Richie Khanna led the experimental program and provides the following update.

During the recent American College of Medical Genetics meeting held on March 21-25 in Nashville, Tennessee, Amicus Therapeutics presented data from their preclinical studies of AT2101. AT2101 is an orally administered pharmacological chaperone currently under investigation for the treatment of Gaucher disease.

Gaucher disease is a lysosomal storage disorder caused by genetic mutations that lead to a deficiency in the lysosomal enzyme acid β -glucosidase (GCase). GCase is needed in the lysosome to break down a substrate known as glucocerebroside. GCase is manufactured in a part of the cell called the endoplasmic reticulum (ER). The ER contains a quality control system that only allows stably folded GCase to exit the ER and be sent to the lysosome to break down substrate. Unstable GCase is retained in the ER, resulting in a deficiency of lysosomal GCase and progressive accumulation of substrate.

The majority of individuals with Gaucher disease make GCase enzyme. However, most Gaucher

mutations (changes in the genetic material) may result in the production of misfolded, unstable GCase which is retained in the ER and is not sent to the lysosome to break down substrate. Amicus researchers are investigating the ability of AT2101 to selectively bind to and stabilize GCase. Once stabilized the GCase meets the ER quality control requirements, can exit the ER, and is transported to the lysosome where it is needed to break down substrate.

In order to better understand the effects of AT2101, scientists performed multiple experiments in mice that make human GCase with a mutation often found in Gaucher disease. These mice develop the following findings: decreased levels of GCase in various tissues, moderately increased spleen and liver weight, and elevated blood levels of IgG and chitin III (related to the human lab marker, chitotriosidase).

Among the key findings presented by Amicus researchers during ACMG:

- Oral administration of AT2101 to the Gaucher mice

demonstrated a significant dose-dependent increase in GCase levels in the brain, lung, spleen, and skin.

- Oral administration of AT2101 significantly decreased the liver and spleen weights in the Gaucher mice and also lowered plasma IgG and (mouse) chitin III levels.
- AT2101 interacts selectively with mutant GCase enzyme; activities of other measured lysosomal enzymes were not altered by AT2101 in any tissue examined from the Gaucher mice treated with AT2101.

Additional studies are being conducted to determine the effect of AT2101 in individuals with Gaucher disease.

References:

1. Steet RA, Chung S, Wustman B, Powe A, Do H, Kornfeld SA The iminosugar isofagomine increases the activity of N370S mutant acid β -glucosidase in Gaucher fibroblasts by several mechanisms. Proc Natl Acad Sci (USA), 2006; 37: 13813-13818.
2. Lieberman, R.L, B.A. Wustman, et al. (2007) "Structure of acid beta-glucosidase with pharmacological chaperone provides insight into Gaucher disease." Nat Chem

New Guide to Gaucher Disease Published

A new resource for patients with Gaucher has been produced by Sante Communications on behalf of Actelion Pharmaceuticals to help in understanding the disease and provide practical information on how to cope with it.

The information booklet, called 'Understanding Gaucher Disease', has been produced to act as a comprehensive guide to both patients and their carers. This booklet covers a wide range of topics including genetics and the

mechanism of the disease. There is a strong focus on pain management and the booklet includes a pain diary so that chronic pain can be self-monitored. It was supported by Actelion Pharmaceuticals and has been independently reviewed by the

Gaucher Association, specialist nurses and doctors.

Guidance includes information on specialist centres, diet and exercise tips, travel advice and financial support.

Copies of the booklet have been sent to all new patients contacting the Gaucher Association. If you would like a copy please contact the Gaucher Association or your specialist centre.