

PHARMACOLOGICAL CHAPERONES



*A Deeper Understanding of
Pharmacological Chaperones and
Lysosomal Storage Disorders*

Pharmacological Chaperones

Lysosomal storage disorders are a group of more than 40 disorders, each involving a different lysosomal enzyme. Deficiency of a particular lysosomal enzyme often results in the build-up of that enzyme's specific substrate. Accumulation of substrate within the lysosome is thought to cause symptoms associated with lysosomal storage disorders.

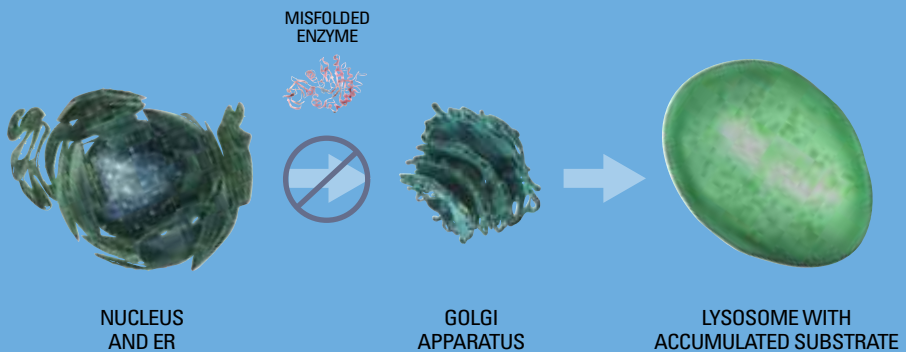
This booklet describes pharmacological chaperones, an investigational new approach to treat lysosomal storage disorders. The following pages explore how pharmacological chaperones are thought to work, provide an overview of the drug development process, and summarize the current stage of development of pharmacological chaperones for lysosomal storage disorders. A companion piece to this booklet defines what enzymes and substrates are and explains the underlying cause of lysosomal storage disorders. This booklet, entitled "What's Missing," can be found at www.amicustherapeutics.com.

lysosomal storage disorders: a deeper understanding

Lysosomal storage disorders historically have been described as disorders that are caused by “missing enzymes.” A deeper scientific understanding reveals that while some individuals who have a lysosomal storage disorder do not produce any enzyme at all, many individuals actually do make enzyme. However, genetic mutations (changes in the DNA) may cause the enzyme that they make to be misfolded.¹

Misfolded enzymes may be unstable and unable to move within the cell and perform their intended biological function.² In the case of lysosomal storage disorders, misfolded enzymes may not be sent to the lysosome, where they are needed to break down substrate. As a result, substrate may accumulate within the lysosome and cause the signs and symptoms of a lysosomal storage disorder.

Misfolded Enzymes May Lead to a Lysosomal Storage Disorder



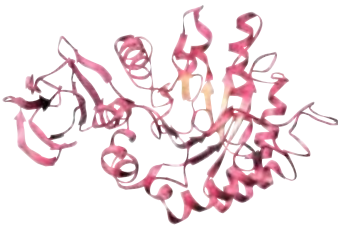
Misfolded enzymes may be stopped by the ER quality control system. Since most misfolded enzymes are never sent to the lysosome, substrate may accumulate within the lysosome, damage the cell, and cause the signs and symptoms of a lysosomal storage disorder.

the impact of protein misfolding

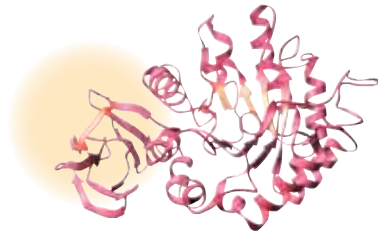
In recent years, scientists have learned more about misfolded proteins and their role in human disease. The human body is composed of tens of thousands of different proteins and each protein has a unique function. These proteins must be made correctly in order to carry out their intended function. When proteins are not

made correctly, disease may result. Research suggests that dozens of different human diseases may be caused by protein misfolding. Consequently, much research currently is being conducted to explore potential therapies for a broad range of medical conditions and diseases that are caused by protein misfolding.

STABILIZED ENZYME



MISFOLDED ENZYME



Many lysosomal storage disorders may result from protein misfolding. Enzymes are specialized types of proteins and when enzymes are misfolded, they may be unstable.

Unstable, misfolded enzymes may not be able to move within the cell to enter the lysosome, where they are needed to function. As a result, substrate may accumulate in the lysosome and cause the signs and symptoms of a lysosomal storage disorder.¹

pharmacological chaperones in development for lysosomal storage disorders

At the present time, many companies are developing therapies for disorders caused by protein misfolding. One novel approach involves using pharmacological chaperones. Pharmacological chaperones are small molecule drugs that are designed to selectively bind to a misfolded protein and thereby increase the protein's stability.³

By stabilizing a misfolded protein, pharmacological chaperones may be able to restore the intended biological function of the protein. Pharmacological chaperones currently are being developed for a number of genetic diseases including

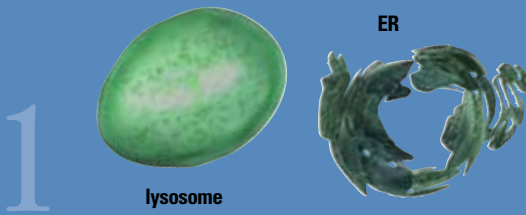
several lysosomal storage disorders and diseases of neurodegeneration.

During initial phases of drug development, pharmacological chaperones were tested in the laboratory setting. In cells and in animal models of diseases, scientists have demonstrated the ability of a chaperone to increase the level of a lysosomal enzyme and to decrease that enzyme's specific lysosomal substrate.⁴

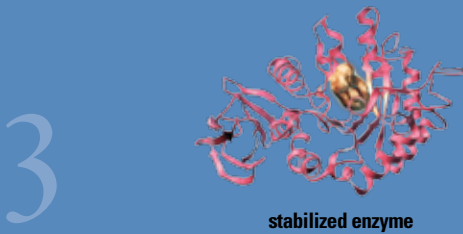
These encouraging results led to clinical trials that have tested the use of chaperones in individuals with Fabry , Gaucher and Pompe disease.

proposed mechanism of action for pharmacological chaperones in lysosomal storage disorders

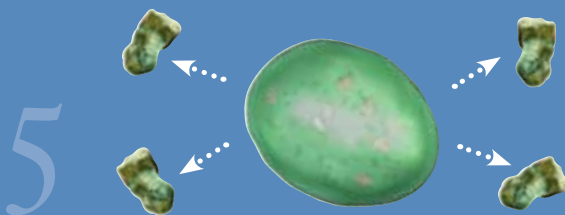
Lysosomal enzymes, which are specialized types of proteins, are made in one part of the cell and are then sent to the lysosome where they break down substrate. If an enzyme is not made correctly, it may never be sent to the lysosome. Without enzyme, substrate accumulates in the lysosomes. Pharmacological chaperones are orally administered small molecules that



Less stable, misfolded enzyme may be retained in the ER. Without enzyme, substrate accumulates in the lysosomes.



Stabilized enzyme can exit the ER and be chaperoned to the lysosomes.



The chaperone dissociates from the enzyme and the enzyme is able to break down the substrate.



are designed to bind to and stabilize misfolded enzyme. It is hypothesized that stabilized enzyme can then be trafficked to the lysosome where it can perform its intended biological function of breaking down substrate.⁵ Because each chaperone is designed to bind to only one particular lysosomal enzyme, a specific chaperone is developed for each targeted lysosomal disease.

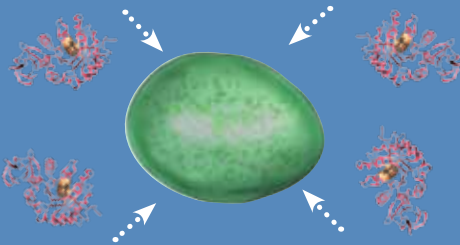
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less stable misfolded enzyme

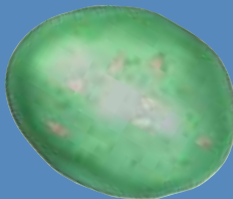
Orally administered pharmacological chaperones enter the cell and bind to less stable, misfolded enzyme in the ER.

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Stabilized enzyme enters the lysosomes.

6



In the lysosomes, enzyme remains stable and continues to breakdown substrate.

overview of the drug development process in the United States

The process of developing, testing and gaining approval for new medical therapies involves many steps. Each step has a different purpose and helps to answer different questions. The drug development process in the United

States is regulated by the Food and Drug Administration (FDA). Other countries employ a similar process for developing new medications. Although it varies, the drug development process often lasts several years or more.

Preclinical

- Basic safety
- Initial proof of concept

Clinical Phase 1

- Safety
- Healthy volunteers

Clinical Phase 2

- Safety and early efficacy
- Limited number of patients

Clinical Phase 3

- Safety and efficacy
- Larger number of patients

Post-Marketing Studies

- Additional studies conducted after approval

Preclinical Testing

In this step, scientists perform laboratory and animal experiments to collect information on safety and potential effects of a chemical compound.

Clinical Trials

Based upon a review of the preclinical science and animal testing data, approval may be granted to test an investigational product in humans. Human testing is accomplished by conducting clinical trials. In general, there are three phases of clinical trials:

- Phase 1** Phase 1 trials are conducted to evaluate the product's safety in humans and to identify potential side effects of the product.
- Phase 2** Phase 2 trials are conducted to provide additional information on safety and to determine preliminary data on potential effectiveness of the product in a small group of individuals with a specific medical condition.
- Phase 3** Phase 3 trials are designed to confirm treatment effectiveness and to monitor for potential side effects. Phase 3 trials study larger groups of individuals who have the targeted medical condition.

Approval

The results from clinical trials help the regulatory authorities to determine if the investigational product should be approved and made available for physicians to prescribe to patients. Even after a new medication is approved, additional studies, called post-marketing studies, may be performed to evaluate the effectiveness and safety of the medication during routine use.

what's next for pharmacological chaperones in lysosomal storage disorders?

Clinical trials investigating the use of pharmacological chaperones to treat lysosomal storage disorders are ongoing.

For more information about these trials, ask your health care provider.

For further details on this technology, visit:

www.amicustherapeutics.com



Resources for Fabry, Gaucher, and Pompe Disease

Fabry Support and Information Group

www.fabry.org

National Fabry Disease Foundation

www.nfdf.org

Canadian Fabry Association

www.fabrycanada.com

Society for Mucopolysaccharide Diseases (UK)

www.mpsociety.co.uk

Fabry International Network

www.fabryintnetwork.com

National Gaucher Foundation

www.gaucherdisease.org

Gauchers Association (UK)

www.gaucher.org.uk

Children's Gaucher Research Fund

www.childrengsgaucher.org

United Pompe Foundation

www.unitedpompe.com

Muscular Dystrophy Association

www.mdauusa.org

International Pompe Association

www.worldpompe.org

UK Association for Glycogen Storage Disease

www.pompe.org.uk

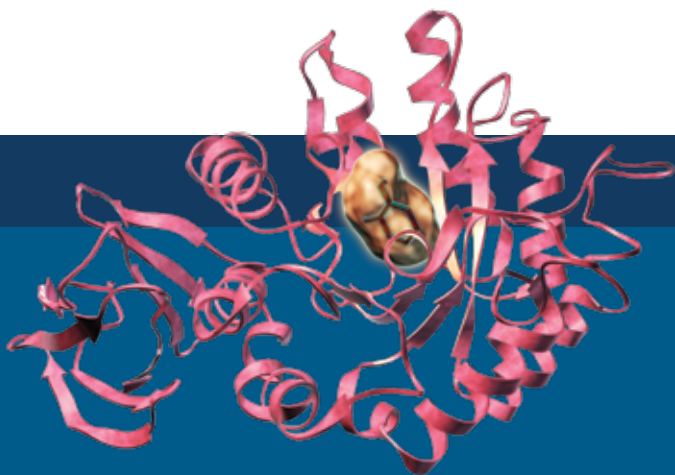
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4. Khanna, R. *et al. Mol. Genet. Met.* 93, S26 (2008).
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for more information, visit:

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