

Building Momentum in Human Genetic Diseases™

In the human body, proteins are involved in almost every aspect of cellular function. Proteins are linear strings of amino acids that fold and twist into specific three-dimensional shapes in order to function properly. Certain human diseases result from mutations in specific genes that lead to the production of misfolded proteins. The majority of genetic mutations that cause misfolded proteins are called missense mutations. These mutations result in the substitution of a single amino acid for another in the protein. Because of this error, missense mutations often result in proteins that have a reduced level of biological activity. In addition to missense mutations, there are also other types of genetic mutations that can result in proteins with reduced biological activity.

Proteins generally fold in a specific region of the cell known as the endoplasmic reticulum, or ER. The cell has quality control mechanisms that ensure that proteins are folded into their correct three-dimensional shape before they can move from the ER to the appropriate destination in the cell, a process generally referred to as protein trafficking. Misfolded proteins are often eliminated by the quality control mechanisms after initially being retained in the ER. In certain instances, misfolded proteins can accumulate in the ER instead of being eliminated.

The retention of misfolded proteins in the ER interrupts their proper trafficking, and the resulting reduced biological activity can lead to impaired cellular function and ultimately to disease. In addition, the accumulation of misfolded proteins in the ER may lead to various types of stress on cells, which may also contribute to cellular dysfunction and disease.

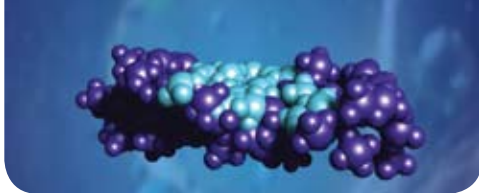
Our Technology

At Amicus, we have developed a novel approach to address human genetic diseases resulting from misfolded proteins. We use small molecule drugs, which are called pharmacological chaperones, to selectively bind to a target protein and increase its stability. The binding of the chaperone molecule helps the protein fold into its correct three-dimensional shape. This allows the protein to be trafficked from the ER to the appropriate location in the cell, thereby increasing protein activity and cellular function and reducing stress on cells.

We believe that our pharmacological chaperone technology may be applicable to many types of diseases that involve misfolded proteins. In particular, pharmacological chaperone therapies could, in our view, provide a benefit in areas such as neurological disease, metabolic disease, cardiovascular disease and cancer, the causes of which have been linked to various misfolded proteins. We are also exploring other applications in which the ability of pharmacological chaperones to increase the activity of normal proteins may provide a therapeutic benefit.

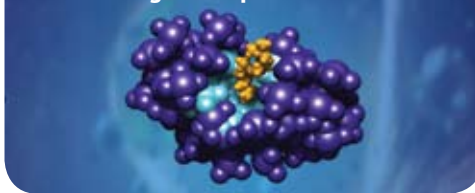
Mechanism of Action

Misfolded Protein Inside the Endoplasmic Reticulum



Proteins, including enzymes, are formed in the cell's endoplasmic reticulum (ER), where they fold into a specific, three-dimensional shape required for the protein to work properly. Genetic mutations can prevent proteins from folding properly, causing the ER's quality control system to "flag" these misfolded proteins and send them to be degraded.

Properly Folded Protein Bound to a Pharmacological Chaperone



A pharmacological chaperone selectively binds to and stabilizes a mutant protein in the ER and helps it fold properly, thereby allowing it to successfully pass through the ER's quality control system.

Properly Folded Protein Performing Its Normal Biological Function



After leaving the ER, the protein-chaperone complex can be trafficked to its final destination in the cell, where the chaperone is displaced and the protein is now free to perform its normal biological function to reduce accumulated substrate.