



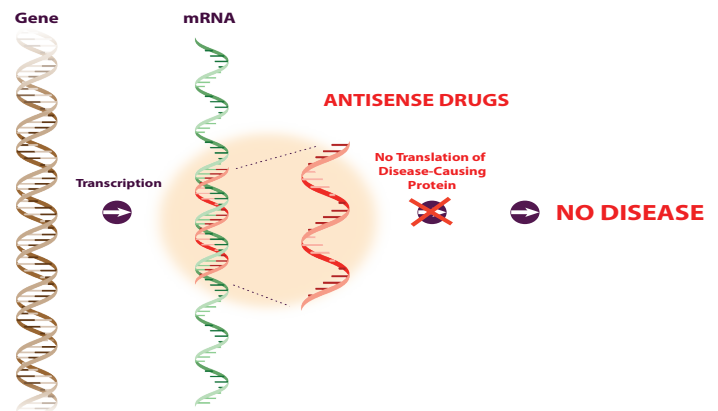
ISIS[®]
PHARMACEUTICALS

Transthyretin Amyloidosis

ISIS-TTR_{Rx}

Isis Pharmaceuticals is developing a drug to treat Transthyretin (TTR) Amyloidosis (also called Familial Amyloidosis). TTR Amyloidosis is caused when the protein TTR misfolds and builds-up in tissues. The build-up of TTR can cause nerve damage and/or heart disease. Most patients with TTR amyloidosis produce both normal and mutated forms of the TTR protein. It has been shown that both forms of TTR protein build-up in tissues as amyloid fibrils.

Isis' drug, ISIS-TTR_{Rx} is an antisense drug that works by reducing the amount of mutant and normal TTR made by your body. Treatment with ISIS-TTR_{Rx} will lower the amount of TTR protein found in the blood, and therefore should lower the amount of amyloid fibrils that buildup in tissues, thus slowing or halting disease progression. As with liver transplantation, ISIS-TTR_{Rx} decreases the amount of mutant TTR produced, however ISIS-TTR_{Rx} also lowers normal TTR, offering a unique approach to treating this disease. Because normal TTR can continue to deposit as amyloid fibers after liver transplant, this distinction may represent a therapeutic advantage.



Isis has completed a Phase 1 study evaluating the safety and activity of ISIS-TTR_{Rx} in healthy volunteers. In this study, ISIS-TTR_{Rx} produced a rapid and sustained reduction in TTR protein. Subjects treated with ISIS-TTR_{Rx} generally tolerated the drug well.

ISIS-TTR_{Rx} Phase 3 Study

Isis Pharmaceuticals is currently enrolling a Phase 3 study that is designed to evaluate the safety and activity of ISIS-TTR_{Rx} in patients with Familial Amyloid Polyneuropathy (FAP), the form of TTR amyloidosis that causes nerve damage. The purpose of this study is to determine if ISIS-TTR_{Rx} can slow or stop the nerve damage caused by TTR deposits. Patients will be randomly assigned to receive ISIS-TTR_{Rx} or placebo (there is a 2 in 3 chance of being assigned to receive ISIS-TTR_{Rx} and a 1 in 3 chance of being assigned to receive placebo). ISIS-TTR_{Rx} or placebo will be given as a subcutaneous injection once a week for 15 months (except in the first week when it will be given 3 times). A subcutaneous injection is a shot given in the fatty layer of tissue just under the skin.

To be eligible for this study, you must have the FAP form of TTR amyloidosis that is caused by a mutation in TTR, have a certain level of detectable nerve damage, and have the ability to walk unaided or with the use of no more than one cane/stick. Patients who have received a liver transplant are not eligible. You can find out more details about the study at www.clinicaltrials.gov.

For More Trial Information: www.clinicaltrials.gov Identifier: NCT01737398

Understanding Transthyretin and Its Role in Disease

TTR is a protein made mainly by the liver and secreted into the blood. Its role in the body is to assist in the transport or movement of other molecules in the blood. In the blood, TTR is found in a unit called a tetramer (four TTR proteins hooked together). Mutations in TTR can cause the tetramer to break apart, which causes the individual TTR proteins to misfold and to then clump together as amyloid deposits. These amyloid deposits are found in many tissues including the peripheral nerves, gastrointestinal tract, and heart. The amyloid deposits may cause local damage to the cells in these tissues and lead to loss of nerve function, decreased absorption of nutrients and heart disease. There are several different clinical presentations of TTR Amyloidosis depending on the primary site of amyloid deposition. These include a polyneuropathy, autonomic neuropathy and cardiomyopathy.

There are over 100 mutations in TTR that can cause TTR Amyloidosis. This disease is inherited as an autosomal dominant disease, which means that only one copy of the abnormal gene is necessary. Most patients have one copy of the normal gene and one copy of the mutated gene.

Patient Support Groups & Organizations

- Amyloidosis Foundation - www.amyloidosisresearchfoundation.org
- Amyloidosis Support Groups - www.amyloidosisupport.com
- National Organization for Rare Disorders, Inc. - www.rarediseases.org
- The Neuropathy Association - www.neuropathy.org

Antisense Therapeutics

Antisense drugs are small DNA- or RNA-like compounds that are chemically modified to engineer in good drug properties. Isis' antisense drugs have been evaluated extensively in both animals and man with more than 5,000 subjects dosed with Isis' antisense drugs. Isis has conducted approximately 80 clinical trials in more than a dozen different patient populations from cardiovascular disease to cancer. The most advanced antisense drug, mipomersen, completed a broad Phase 3 program in patients with high cholesterol and is currently being evaluated for marketing approval in the US & Europe.

About Isis

We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas in which our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets, we can build a large and diverse portfolio of drugs designed to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, ocular, severe and rare diseases, and cancer.

You can find more information on Isis and Antisense Drugs at: www.isispharm.com

Clinical Trials

Clinical trials are studies conducted using human participants designed to assess the safety and activity of new therapies in development. Clinical trials can be categorized into distinct Phases (Phase 1 – 4) depending upon the stage of clinical development of the drug. Phase 1 studies are the initial studies conducted in humans designed to primarily evaluate the safety and pharmacokinetics of the drugs in humans. Phase 2 and 3 studies are larger, longer studies in patients that continue to evaluate the safety of the drug and the activity of the drug prior to requesting regulatory agencies for marketing approval. Phase 4 studies are studies designed to provide additional information for a drug that has been approved for marketing and is already available to qualified patients.

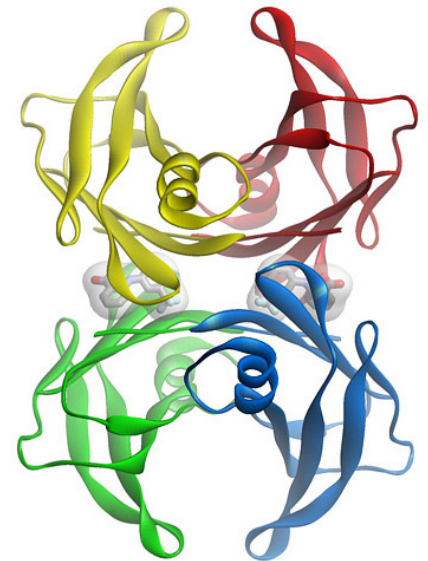


image: The Scripps Research Institute -
The Kelly Group