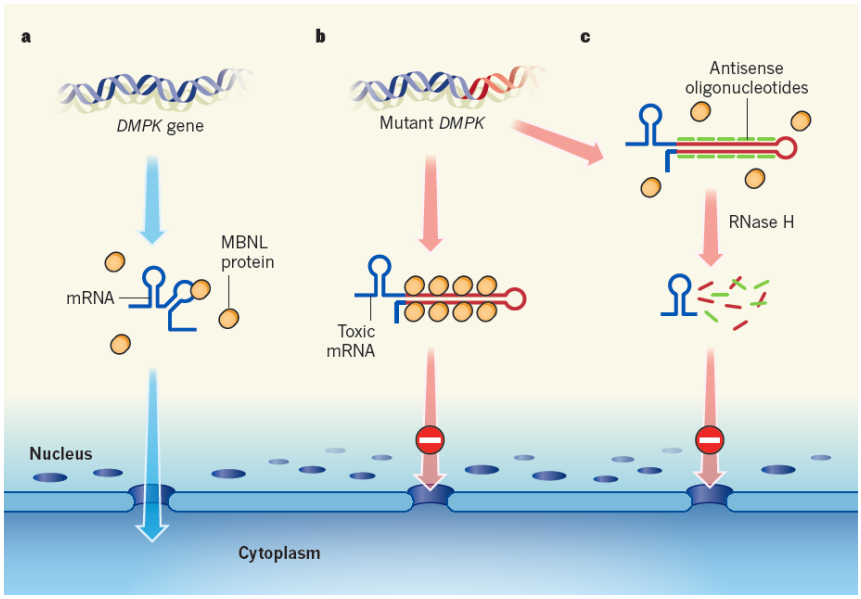
ISIS PHARMACEUTICALS

Myotonic Dystrophy Type 1 & ISIS-DMPK$_{Rx}$

Isis Pharmaceuticals is developing a drug (ISIS-DMPK$_{Rx}$) to treat Myontonic Dystrophy Type 1 (DM1, also called Steinert's Diseases). DM1 is a dominantly inherited, degenerative disorder that affects many systems in the body. DM1 is mainly characterized by progressive muscle wasting, weakness, and myotonia, but additional clinical features include early cataracts, cardiac conduction dysfunctions, hypersomnia, gastrointestinal abnormalities, insulin insensitivity, and infertility. DM1 is estimated to affect 1 in 8,000 people worldwide, or approximately 150,000 patients in the US, Europe and Japan. Currently, there are no disease-modifying therapies for patients with DM1 and treatments are intended only to manage symptoms. ISIS-DMPK$_{Rx}$ is an antisense drug being developed for the potential treatment of DM1. ISIS-DMPK$_{Rx}$ is currently being studied in a Phase 1 study in healthy volunteers to evaluate its safety.

Understanding DMPK and Its Role in DM1

DM1 is caused by an abnormal expansion of three nucleotides repeats within the DMPK gene. The severity and age of onset of DM1 correlates with the number of triplet repeats, which increases from one generation to the next. The genetic defect in the DMPK gene creates a toxic RNA rather than a disease-causing protein. The toxic RNA accumulates within the nucleus of the cell and prevents the production of proteins essential for normal cellular function. ISIS-DMPK$_{Rx}$ is designed to target the toxic RNA and reduce its accumulation thereby restoring normal cellular function. In animal studies, we showed that an antisense compound targeting the DMPK RNA entered muscle cells and significantly reduced the toxic RNA. Effective reductions of toxic RNA led to a reversal of the disease symptoms, mainly myotonia that was sustained for up to one year after treatment in a mouse model of DM1. Therefore by removing toxic RNA, ISIS-DMPK$_{Rx}$ could be an effective approach to treating patients with DM1.



Understanding ISIS-DMPK$_{Rx}$

DNA is found in the nucleus of the cell. It carries the genetic information of a cell and consists of thousands of genes. Each gene serves as a recipe on how to build a protein molecule. When proteins are needed, the corresponding genes within the nucleus are transcribed into mRNA, and this mRNA then

exits the nucleus of the cell to be translated into proteins. The long expansion of nucleotide repeats seen in DM1 prevents the DMPK mRNA to exit the nucleus. At the same time, other molecules get stuck to the expanded mRNA within the nucleus and are thus also kept within the nucleus.

ISIS-DMPK$_{Rx}$ Clinical Studies

A Phase 1 study to evaluate the safety of ISIS-DMPK$_{Rx}$ in healthy volunteers is currently being conducted outside the United States. A Phase 1/2a study to evaluate the safety and dose-range finding of ISIS-DMPK$_{Rx}$ in patients with DM1 is being planned for the end of the year 2014. Details on this study, including eligibility criteria, will be posted on www.clinicaltrials.gov as soon as they will become available, which is anticipated to be late in 2014.

Patient Support Groups & Organizations

- ·Myotonic Dystrophy Foundation - www.myotonic.org
- ·Muscular Dystrophy Association - www.mda.org/disease/myotonic-muscular-dystrophy
- ·National Organization for Rare Disorders, Inc. - www.rarediseases.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 8,000 subjects dosed with Isis' antisense drugs. Isis has conducted approximately 100 clinical trials in more than a dozen different patient populations from cardiovascular disease to cancer.

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.

More information on clinical trials can be found at: www.clinicaltrials.gov

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