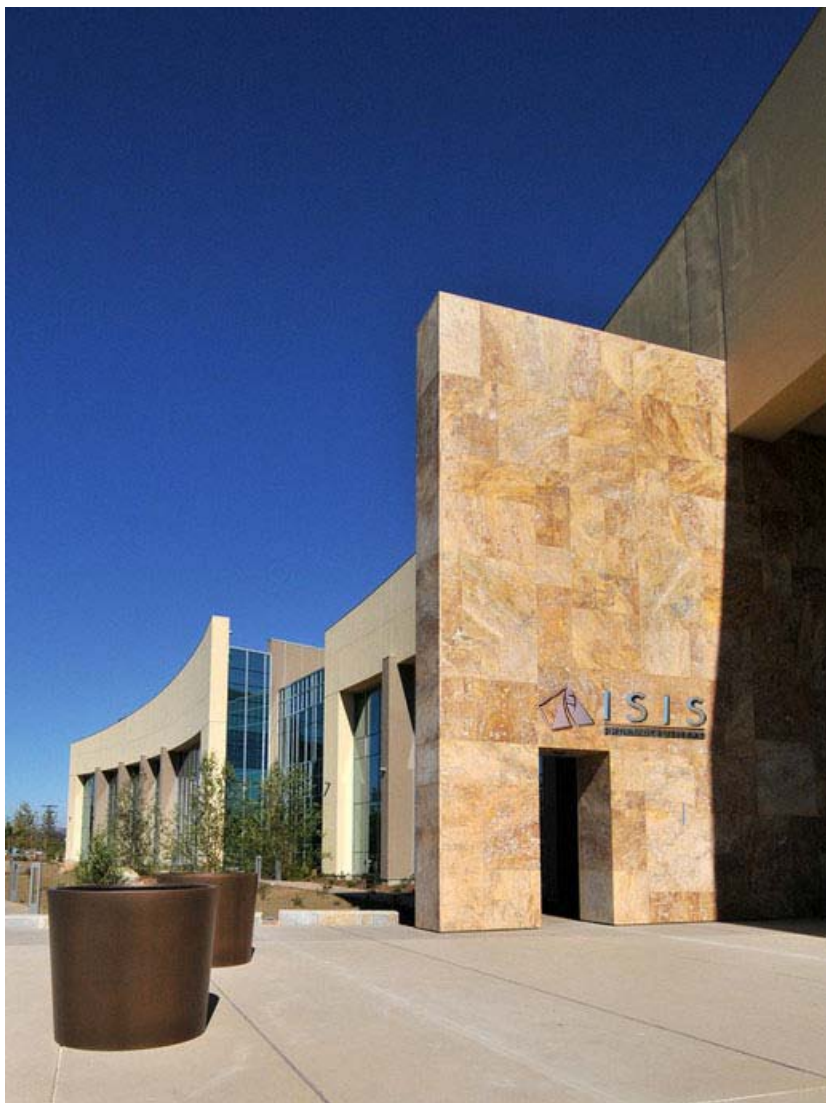


Applying Antisense Technology for the Treatment of Transthyretin Amyloidosis

Elizabeth “Lisa” Ackermann, Ph.D.
Associate Director Clinical Development

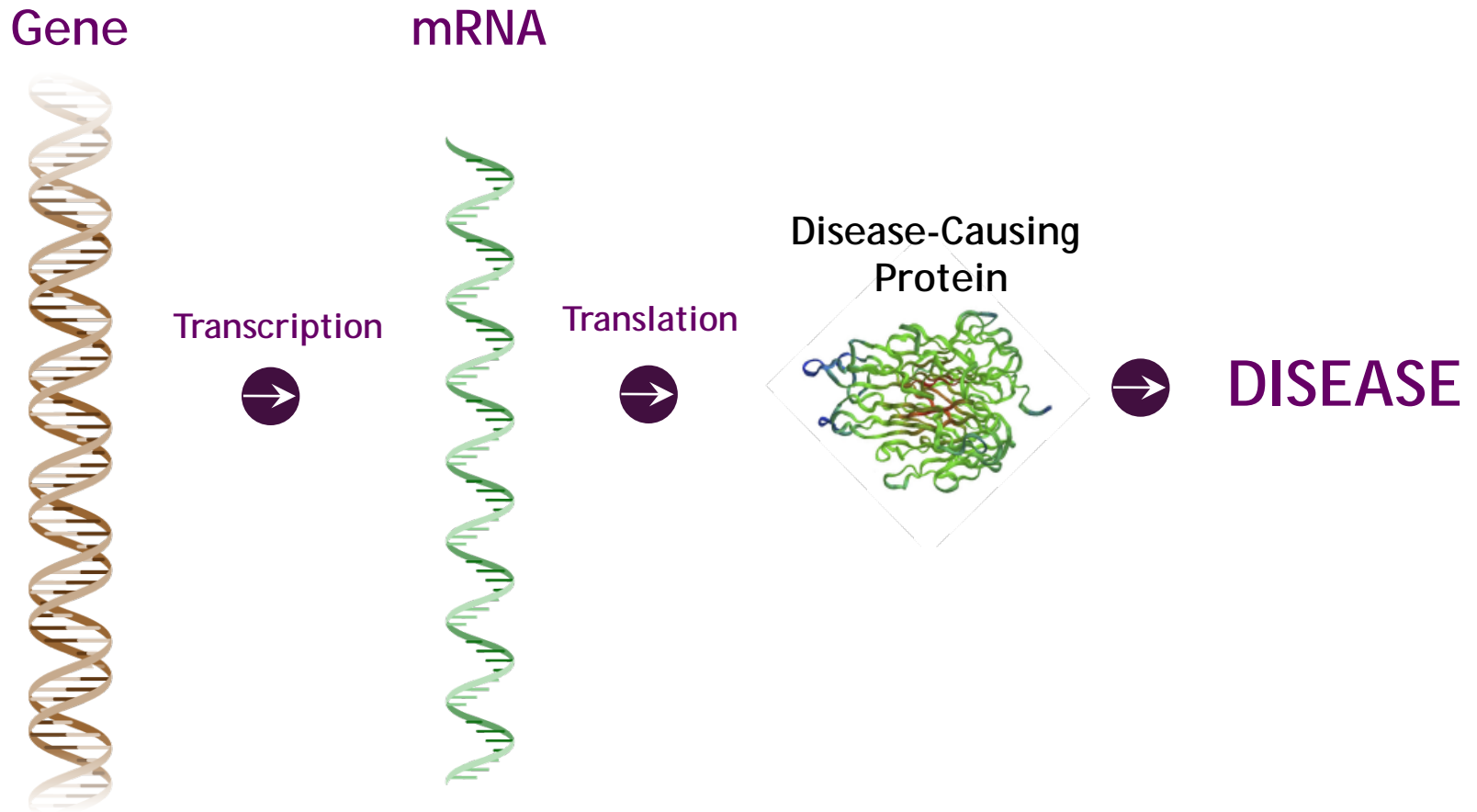
October 29, 2011

Isis Pharmaceuticals

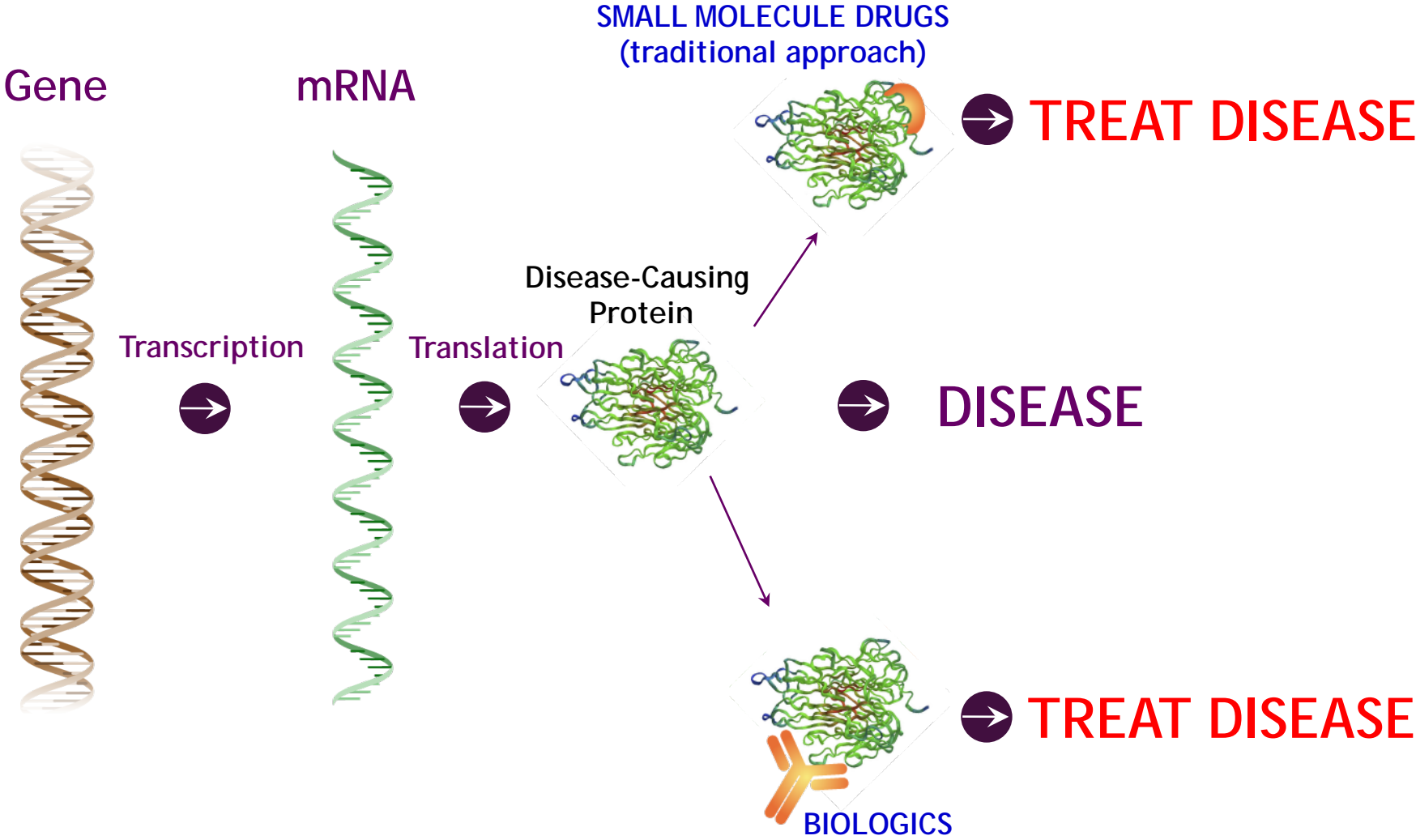


- Founded: 1989
- Location: Carlsbad, California
- Company Focus: RNA Targeted Therapeutics
 - Antisense Drugs
- ~300 employees
- Capabilities:
 - Drug discovery
 - Early development
 - Manufacturing

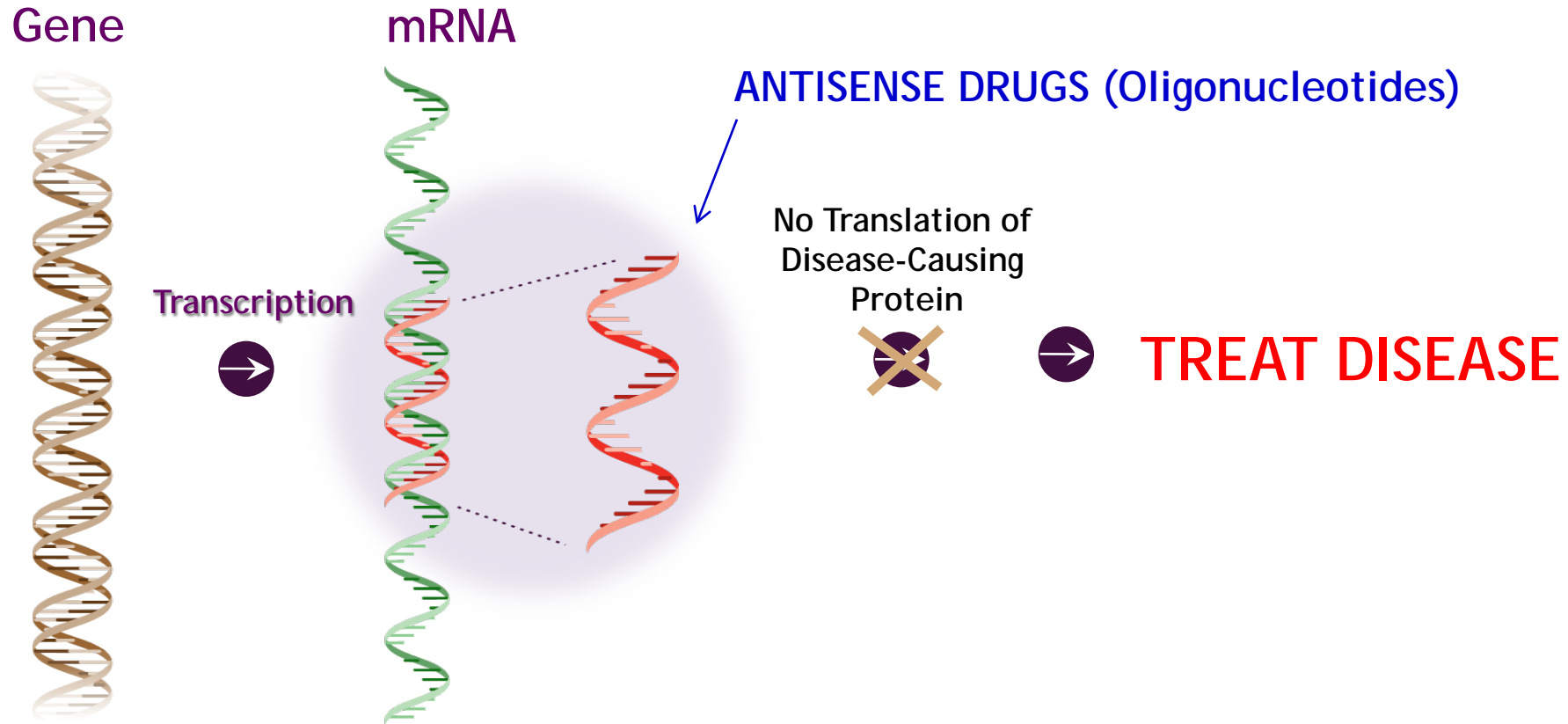
Proteins are Made from Genes via mRNA



Small Molecules & Biologics Target Proteins

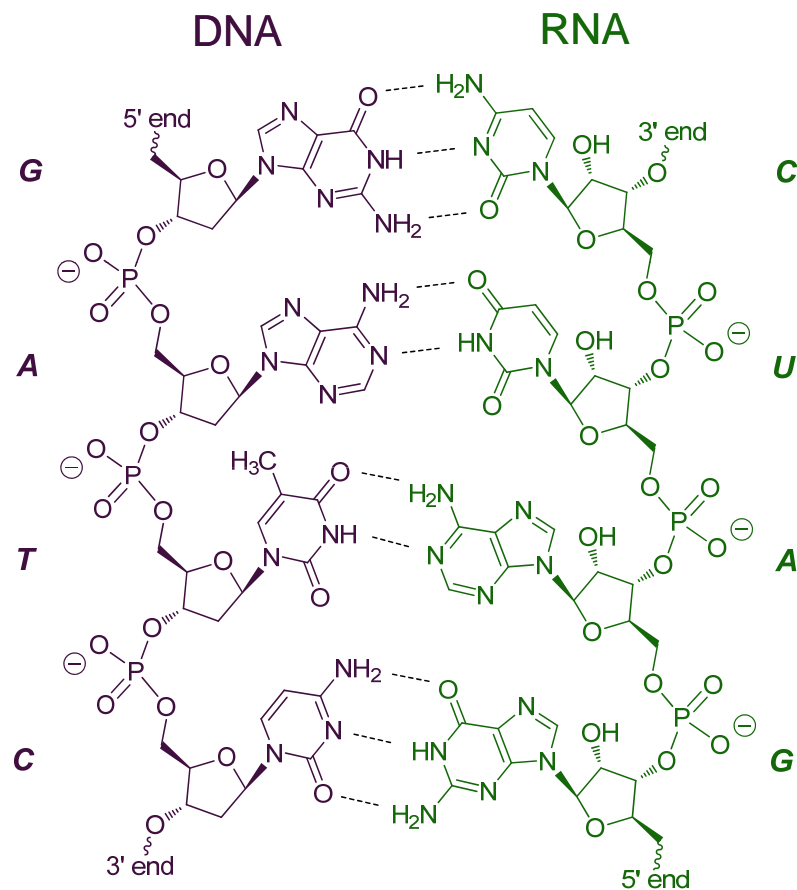


Antisense Drugs Target RNA, not Proteins

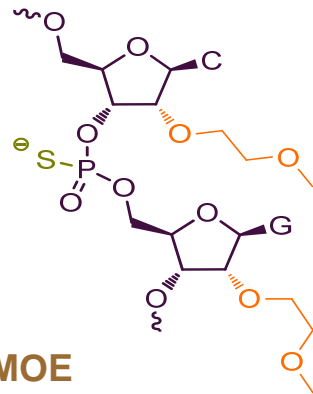


Natural Nucleic Acids Have Poor Drug-like Properties

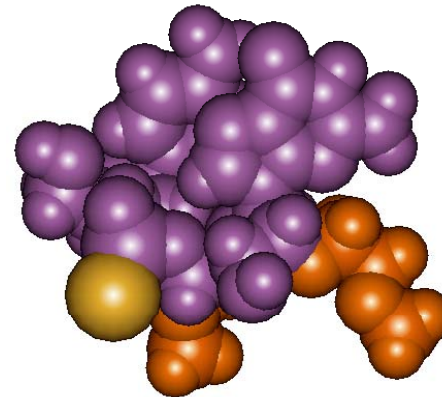
- Rapid degradation by nucleases present in plasma and tissues
- Rapid clearance by kidney
- Poor cellular uptake



2nd Generation Antisense Oligos have been Developed that have Better Drug-Like Properties



2'-Methoxyethyl, MOE



Chemistry Attributes

Increases potency

Increases stability to nucleases

Reduces toxicities observed with PS modified DNA oligos.
No new toxicities

Drug Properties

Potency ~50 to 400 mg/week

Dose Frequency Weekly to monthly

Cost of Therapy Competitive with upper end of branded small molecules

Routes of Administration Sub Q, I.V., inhalation, topical, intrathecal

The Isis Clinical Experience

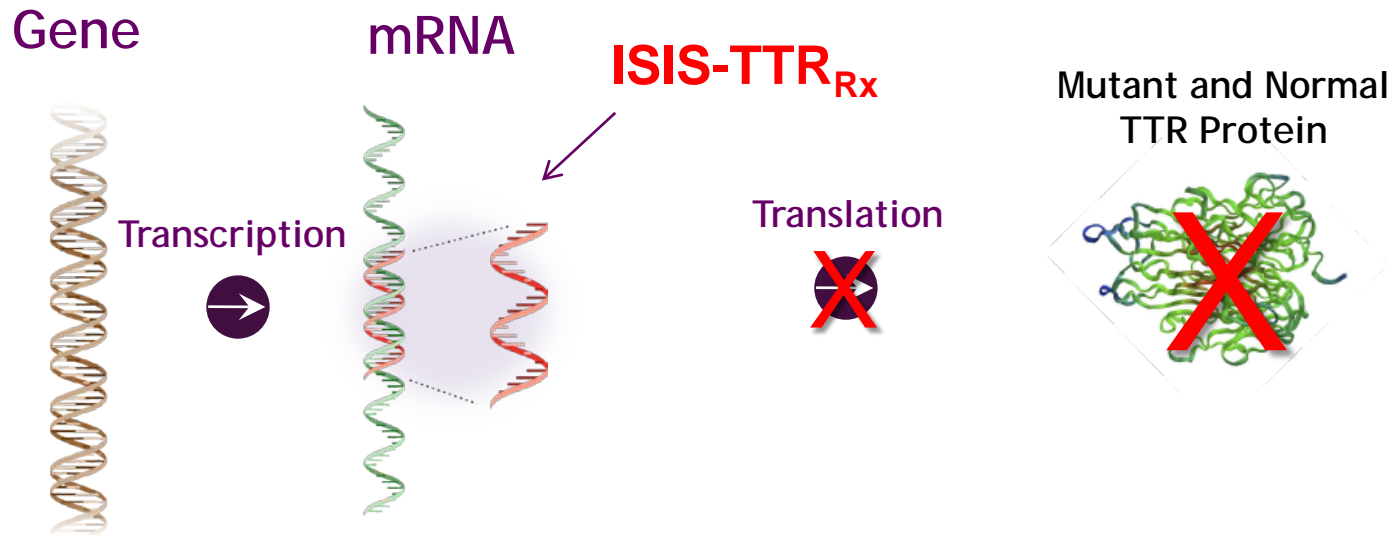
- ▲ **> 5,000 patients treated, approximately 2,900 with 2nd generation (2'-MOE) drugs**
- ▲ **> 500 patients treated \geq 12 weeks, > 280 treated \geq 6 months, > 120 treated \geq 1 year**
- ▲ **2nd generation antisense oligos have been well tolerated**
- ▲ **2nd generation antisense oligos are generally given as once weekly sc injections**
- ▲ **Liver and kidney are sensitive tissues to antisense oligo treatment**



Developing ISIS-TTR_{Rx} for Treating Transthyretin Amyloidosis

What is ISIS-TTR_{Rx}?

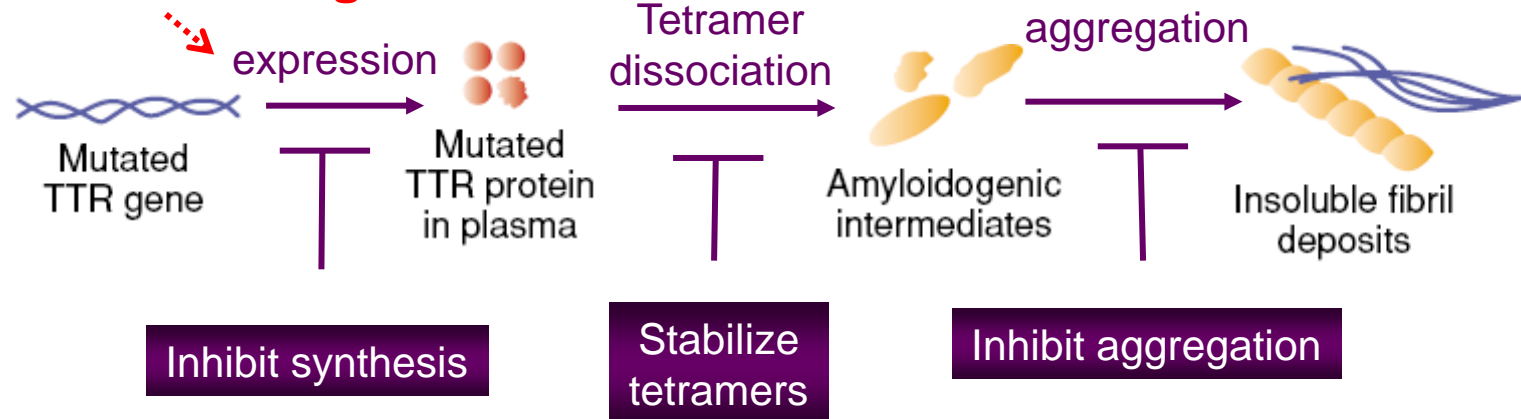
- **ISIS-TTR_{Rx} is a second generation antisense drug that destroys the TTR mRNA**
- **This prevents the production of both mutant and normal TTR protein**



Rationale for ISIS-TTR_{Rx}

- Mutant and normal TTR protein can form amyloid deposits in tissue and cause transthyretin amyloidosis
- The only currently approved therapy for transthyretin amyloidosis is liver transplant which lowers the levels of mutant TTR
- TTR is produced by the liver which is particularly sensitive tissue to the action of antisense oligos
- Thus, ISIS-TTR_{Rx} treatment strategy which lowers both mutant and wild-type TTR may be an effective approach to treating this disease

Antisense Drug



Selection Process for Identifying ISIS-TTR_{Rx}

- ▲ **First many antisense oligos are made that will bind to the TTR mRNA**
- ▲ **Oligos are then screened in tissue culture cells**
- ▲ **A subset of those oligos are tested in mouse and monkey animal models**
 - **Demonstrate lowering of TTR protein in plasma**
 - **Demonstrate lowering of TTR mRNA in liver**
 - **Study safety**
- ▲ **The best oligo is selected to test in clinical trials**

Status of ISIS-TTR_{Rx}

- ▲ Drug identified and characterized
- ▲ Efficacy in mouse and monkey models shown
- ▲ Required toxicology studies are completed
- ▲ Phase 1 clinical trial in healthy volunteers is on-going

Importance of Phase 1 Clinical Trials

- **The first study to deliver a drug to humans is very important**
- **Provides key information about:**
 - **Safety in humans (what are the side effects?)**
 - **Pharmacokinetics (what are the drug levels in the human body?)**
 - **In some cases it can also provide information that the drug is working as predicted**
- **Results from Phase 1 studies are used to design future studies of the drug**

Status of the Phase 1 Study with ISIS-TTR_{Rx} in Healthy Volunteers

- ▲ A Phase 1 study in healthy volunteers was initiated in May 2011
- ▲ Single and multiple doses of ISIS-TTR_{Rx} are being evaluated at 4 different dose levels
- ▲ The study is designed to evaluate effects of ISIS-TTR_{Rx} on:
 - safety (are there any side effects?)
 - pharmacokinetics (what are the levels of drug in the blood?)
 - pharmacodynamics (do plasma TTR levels go down?)
- ▲ To date, ISIS-TTR_{Rx} appears to be well tolerated
- ▲ Reductions in plasma TTR levels have been observed
- ▲ The study is on track to complete on schedule. All patients will have completed the treatment period by Dec 2011

Antisense Approaches Against Transthyretin

Summary

- ▲ Antisense oligonucleotides have been shown in multiple animal and human studies to reduce levels of disease-causing proteins and have been generally well tolerated
- ▲ ISIS-TTR_{Rx} is an antisense drug that targets normal and mutant TTR and effectively lowers TTR levels in animals including non-human primates
- ▲ ISIS-TTR_{Rx} is currently being tested in healthy human volunteers in a Phase 1 safety study
- ▲ Evaluation of ISIS-TTR_{Rx} in patients with familial amyloid polyneuropathy is projected to start in the second half of 2012