Applying Antisense Technology for the Treatment of Transthyretin Amyloidosis

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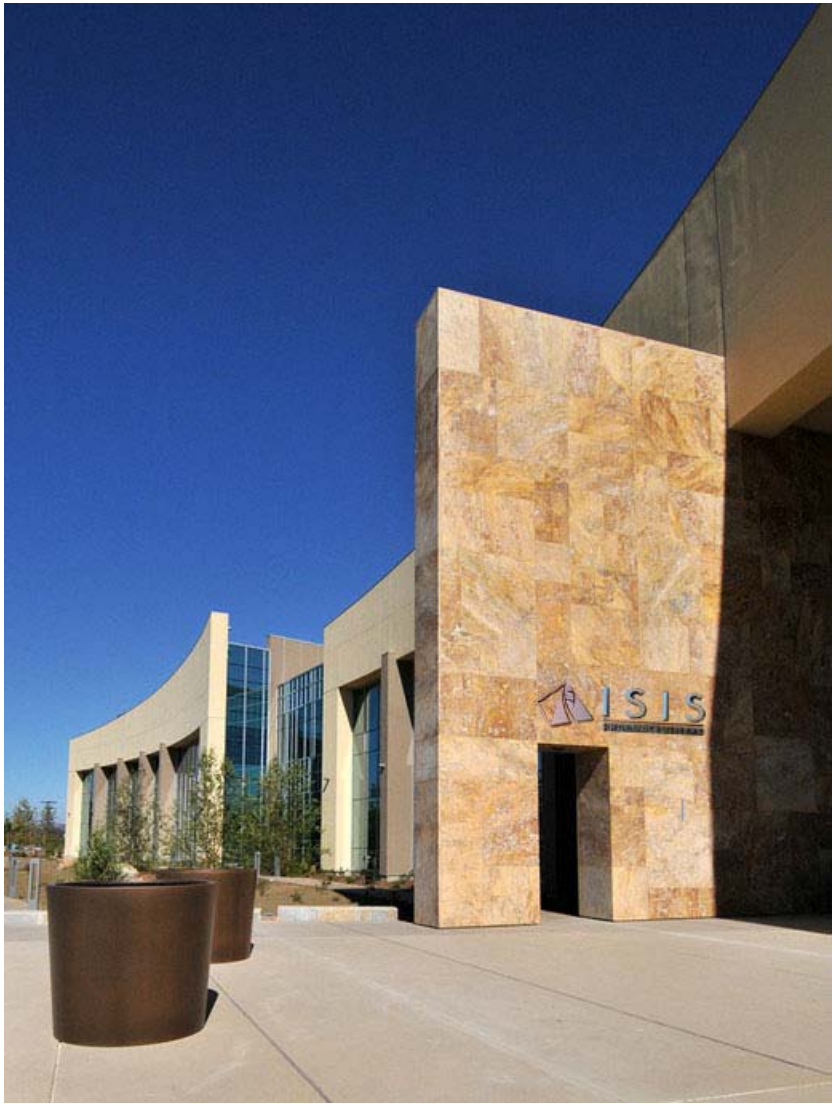
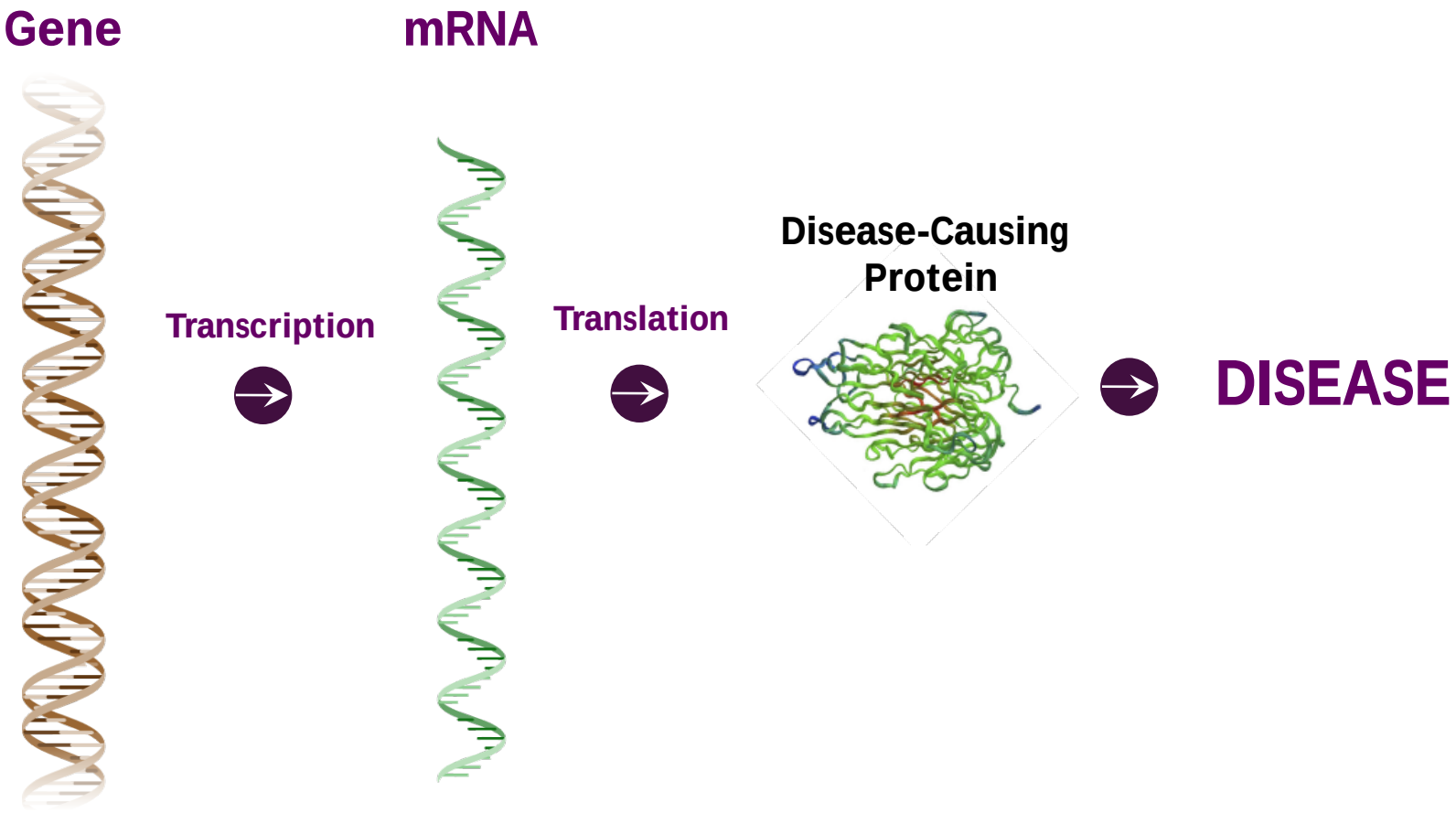
Isis Pharmaceuticals

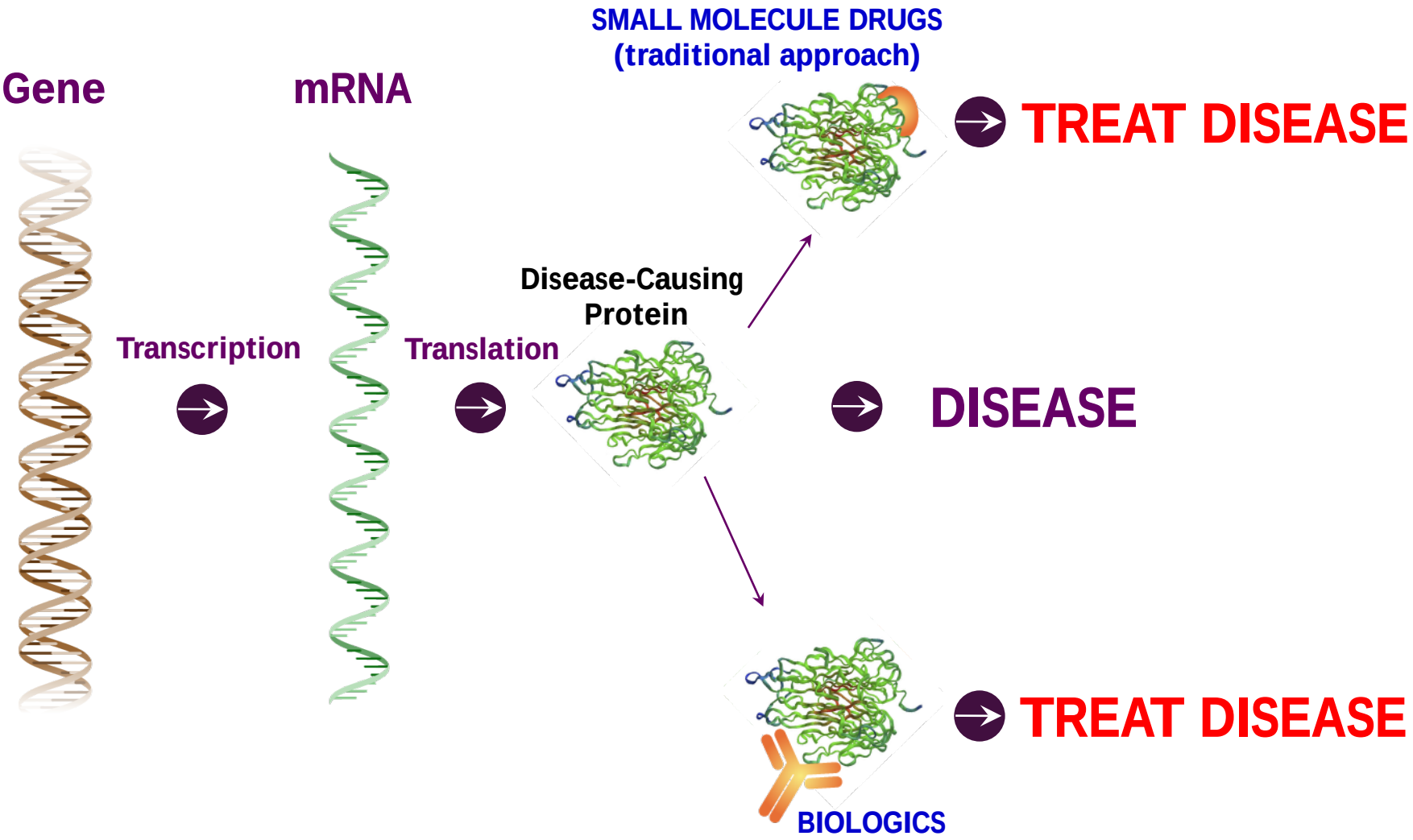


- Founded: 1989
- Location: Carlsbad, California
- Company Focus: RNA Targeted Therapeutics
  - Antisense Drugs
- ~300 employees
- Capabilities:
  - Drug discovery
  - Early development
  - Manufacturing

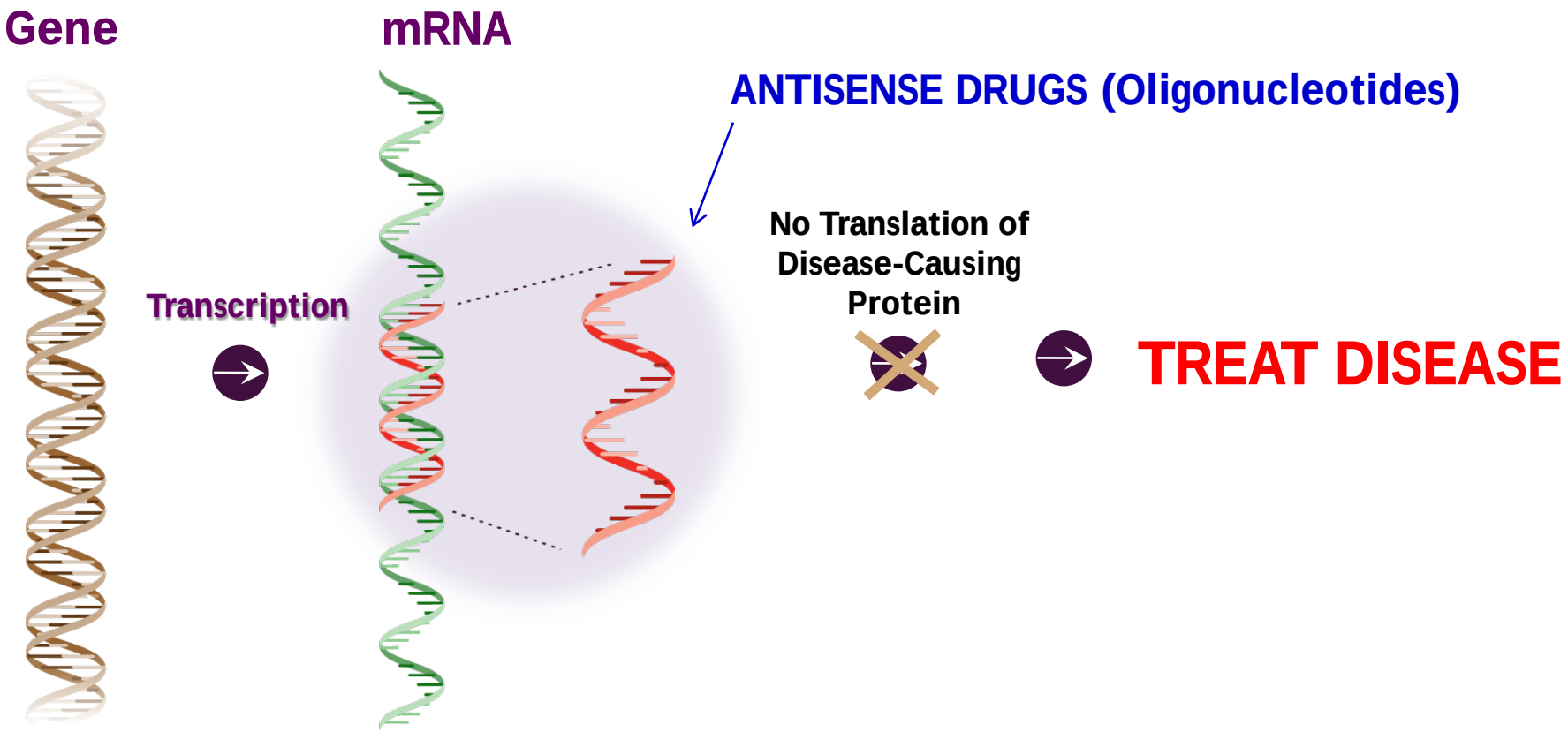
Proteins are Made from Genes via mRNA



Small Molecules & Biologics Target Proteins

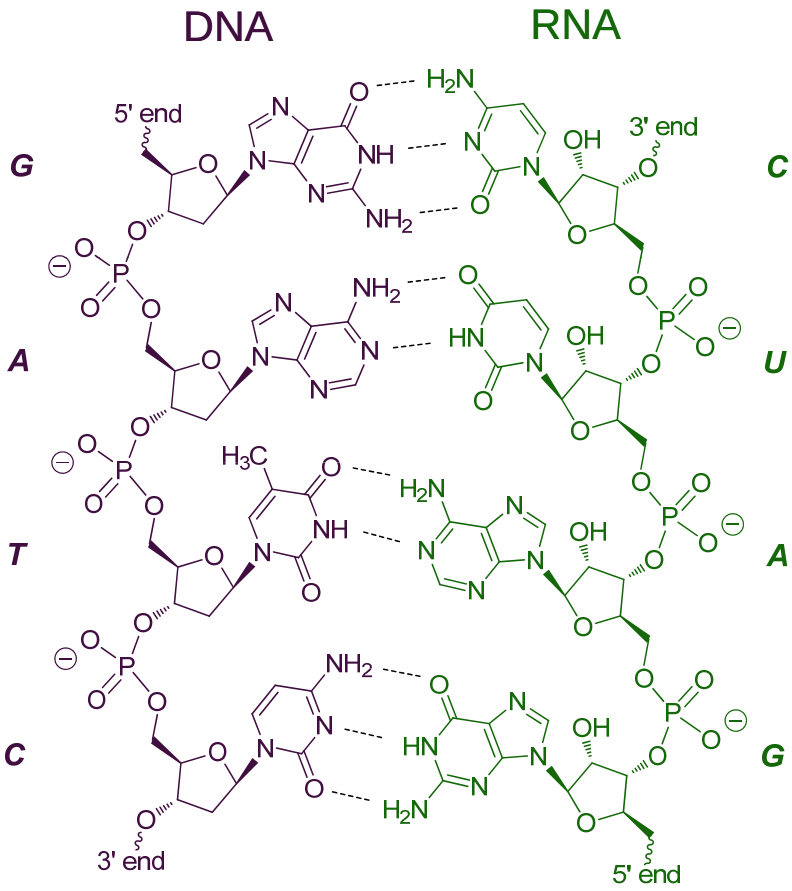


Antisense Drugs Target RNA, not Proteins

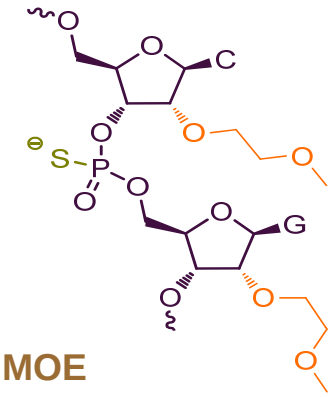


Natural Nucleic Acids Have Poor Drug-like Properties

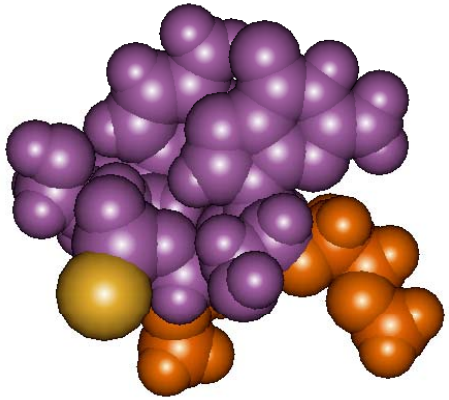
- Rapid degradation by nucleases present in plasma and tissues
- Rapid clearance by kidney
- Poor cellular uptake



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

Isis Pipeline (2011)

■ partnered

PROJECT	INDICATION	TARGET	PRECLINICAL	PHASE I	PHASE II	PHASE III	APPROVED
CARDIOVASCULAR							
Mipomersen	High Cholesterol	apoB				genzyme	
ISIS-CRP$_{Rx}$	CAD/Inflammation/Renal	CRP					
ISIS-APOCIII$_{Rx}$	High Triglycerides	apoC-III					
ISIS-FXI$_{Rx}$	Clotting Disorders	Factor XI					
BMS-PCSK9$_{Rx}$	CAD	PCSK9				Bristol-Myers Squibb	
METABOLIC							
ISIS 113715	Diabetes	PTP-1B					
ISIS-SGLT2$_{Rx}$	Diabetes	SGLT2					
ISIS-GCCR$_{Rx}$	Diabetes	GCCR					
ISIS-GCGR$_{Rx}$	Diabetes	GCGR					
ISIS-FGFR4$_{Rx}$	Obesity	FGFR4					
CANCER							
OGX-011	Cancer	clusterin				TEVA / OncoGeneX	
LY2181308	Cancer	survivin				Lilly	
ISIS-EIF4E$_{Rx}$	Cancer	eIF-4E					
OGX-427	Cancer	Hsp27				OncoGeneX	
ISIS-STAT3$_{Rx}$	Cancer	STAT3					
SEVERE & RARE NEURODEGENERATIVE							
ISIS-SOD1$_{Rx}$	ALS	SOD1					
ISIS-TTR$_{Rx}$	Severe & Rare	TTR				gsk	
ISIS-SMN$_{Rx}$	Spinal Muscular Atrophy	SMN2					
ISIS-AAT$_{Rx}$	AAT-Liver Disease	α1-Antitrypsin				gsk	
INFLAMMATION & OTHER							
Vitravene®	CMV Retinitis	CMV				NOVARTIS	
Alicaforsen	Ulcerative Colitis	ICAM-1				Atlantic	
ACHN-490	Severe Bacterial Infection	Aminoglycoside				ACHAOGEN	
ATL1102	MS	VLA-4				antisense	
EXC 001	Local Fibrosis	CTGF				EXCALIARD	
iCo-007	Ocular Disease	C-raf kinase				iCo Therapeutics Inc.	
ATL1103	Acromegaly	GHr				antisense	

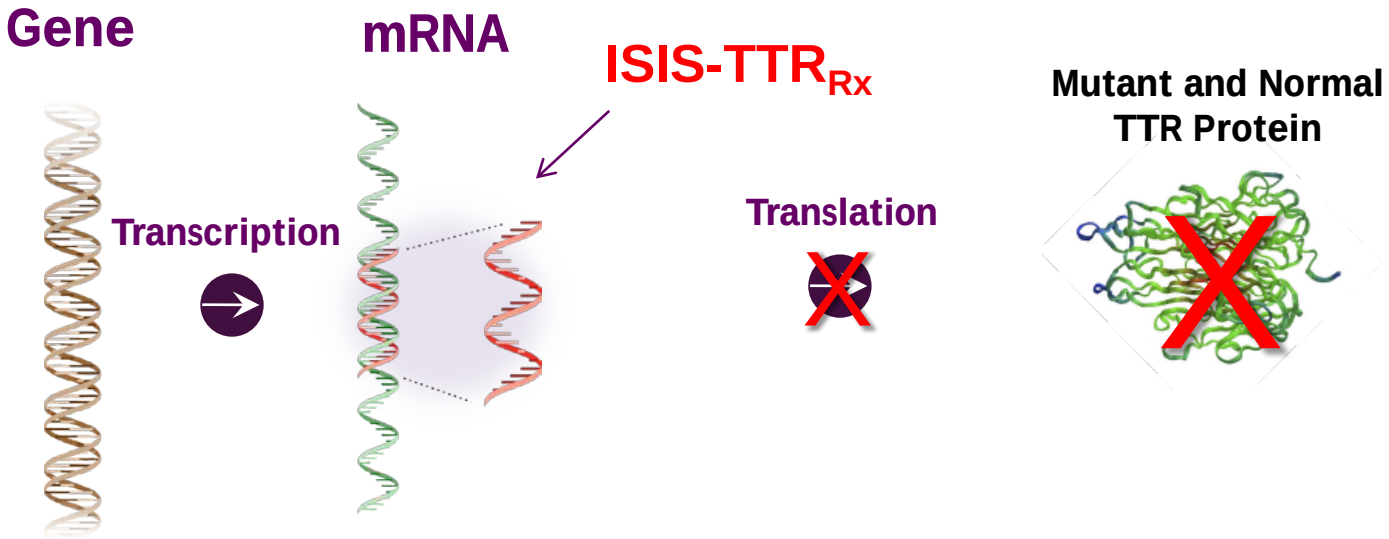
The Isis Clinical Experience

- > 5,000 patients treated, approximately 2,900 with 2nd generation (2'-*MOE*) drugs
- > 500 patients treated ≥ 12 weeks, > 280 treated ≥ 6 months, > 120 treated ≥ 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

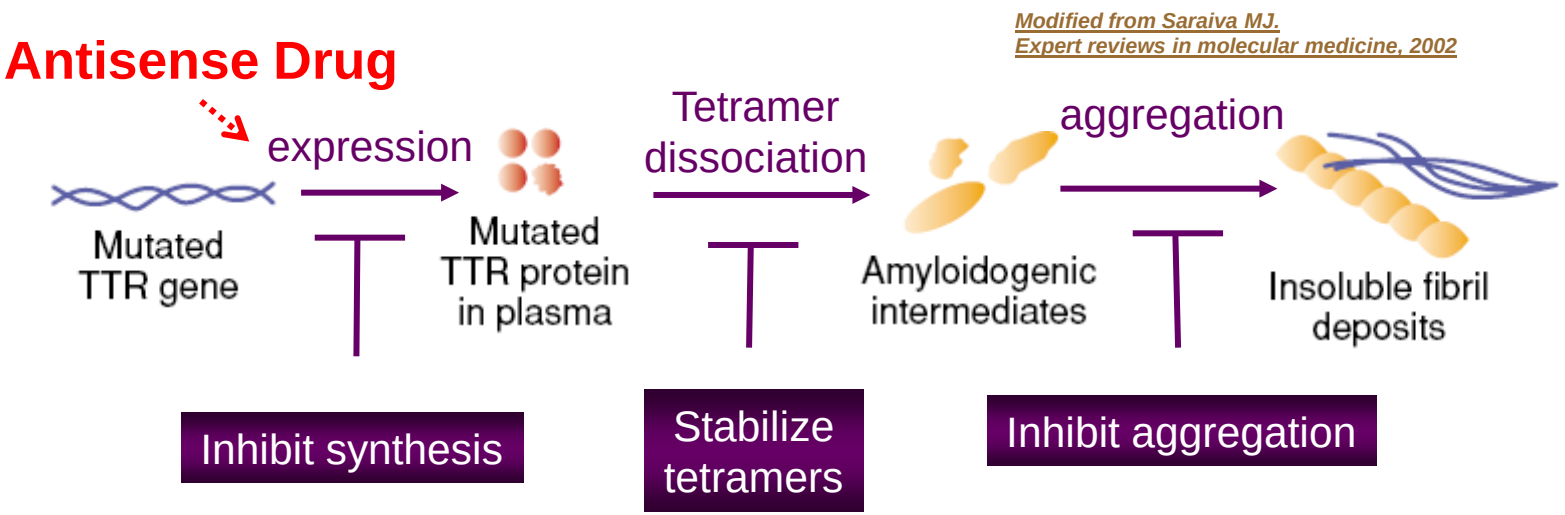
What is ISIS-TTR$_{Rx}$?

- **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**



Modified from Saraiva MJ. Expert reviews in molecular medicine, 2002

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**