Severe & Rare/Neurodegenerative Franchise: Discovering New Options for Underserved Patients

RARE, ORPHAN DISEASES, THE OPPORTUNITY

Rare, Orphan Diseases, The Opportunity

- Rare diseases are defined as any disease that affects less than 200,000 persons (~1:1,500 incidence for US; ~1:2,000 for EU)
- In the US the orphan drug act provides financial incentives for research & production of therapies for the treatment of rare diseases & provides for more access to regulatory agencies
- Many rare diseases are severe & life threatening
- Most rare diseases do not have any approved therapies
- Rare disease market is a major growth sector for the pharmaceutical industry
  - 2011 sales estimated to be ~$80 billion
- Many rare diseases have a genetic basis which can be uniquely targeted with Antisense Technology

Administration of Antisense Drugs to Treat Severe & Rare

- Local & direct administration of antisense drugs for severe & rare
  - SC dosing for drugs to be administered systemically
  - Cerebral spinal fluid administration through the intrathecal space for drugs targeted to neurodegenerative diseases

Severe Rare Diseases/Neurodegenerative Franchise Pipeline

SYSTEMICALLY ADMINISTERED DRUGS FOR THE TREATMENT OF RARE DISEASE

Transthyretin Amyloidosis *A Fatal Genetic Disease*

- Fatal severe & rare genetic disease characterized by the slow degeneration of peripheral nerve &/or heart tissues
- Patients with TTR amyloidosis inherit a mutant gene that produces a misfolded form of protein, TTR
- Mutations in TTR destabilize its native structure, leading to dissociation of tetramers, which can self-assemble into amyloid fibrils
- Manifestations: familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy (FAC), nephropathy, enteropathy & vitreous opacities

Transthyretin Amyloidosis Clinical Syndromes

Two common types of transthyretin amyloidosis:

- Familial Amyloid Polyneuropathy (FAP)
  - Progressive neurodegeneration
    - TTR build up in peripheral nerve tissue leading to the loss of nerve function & wasting
    - Patients typically die from wasting due to the accumulation of TTR in the intestinal tract, which prevents the proper absorption of nutrients
- Familial Amyloid Cardiomyopathy (FAC)
  - TTR build up in the heart muscle
  - Patients succumb to heart failure five to six years after symptom onset

Currently no approved drugs – only available option is a liver transplant

- Limited option due to low availability of donors
- Expensive & invasive procedure

Hereditary ATTR Clinical Presentation & Epidemiology

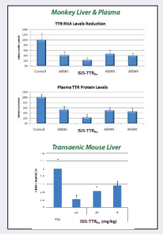
	Familial Amyloid Polyneuropathy (FAP)	Familial Amyloid Cardiomyopathy (FAC)
TTR Deposits	Peripheral nerves	Heart
Clinical Phenotype	Progressive peripheral sensory, motor, autonomic neuropathy & wasting	Myocardial amyloidosis, diastolic dysfunction, progressive heart failure
Population Size	Worldwide ~ 10,000	Worldwide ~40,000
Age of Onset	30-50 years	60-70 years
Life Expectancy After Diagnosis	9-11 years	5-6 years

Coelho et. al., Prog. Opt. Acad., Dec 8 06 (2010)

ISIS-TTR$_{Rx}$ *Key Attributes & Target Rationale*

- Reduces both normal & mutant TTR
  - Potentially more effective than liver transplant; because TTR protein continues to build up after transplantation
- Targets all known mutations
- Robust activity in mouse & monkey models

Potent Reductions in TTR mRNA Levels Following Treatment with ISIS-TTR$_{Rx}$ in hTTR Transgenic Mice & Monkeys



ISIS-TTR$_{Rx}$ *Advancing in Development*

- ISIS-TTR$_{Rx}$ is being developed initially for patients with FAP
  - Goal to inhibit production of TTR in these patients to halt progression of disease
- ISIS-TTR$_{Rx}$ in Phase 1 study in normal volunteers
- Phase 2 to begin next year in patients with FAP
- ISIS-TTR$_{Rx}$ is the first drug to enter development from Isis' strategic alliance with GSK
  - $10 million in milestones associated with ISIS-TTR$_{Rx}$ earned to date
  - Potential to earn additional development milestones prior to licensing
  - Isis controls early drug development to facilitate rapid advancement to Phase 2 Proof-of-Concept, at which time GSK can license the drug

MORE RARE DISEASES

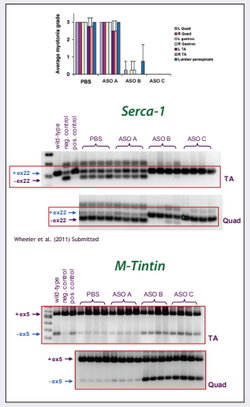
Tri-nucleotide Repeat Expansion Diseases (Triplet Repeat Diseases)

- Several mammalian genes have trinucleotide repeats as a normal part of their genetic code
  - i.e. …CAACAGCAGCAGCAGCAG…
- These triplet repeats are genetically unstable & can become mutated to greatly increase the number of repeats
  - normal = 15 to 20 repeats; mutant = 100 to 2,000 repeats
- Expanded triplet repeats can result in a toxic RNA species or toxic protein species
- Antisense drugs can uniquely target transcripts with abnormal triplet repeats
- Examples of known triplet disease
  - Myotonic Dystrophy
  - Huntington's Disease
  - Spinocerebellar Ataxias
  - Friedreich's Ataxia
  - Fragile X Syndrome

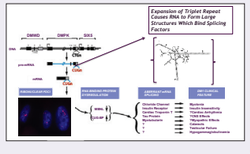
Late-stage Research – Isis' DM1 Program *Myotonic Dystrophy A Severe & Rare Genetic Disease*

- Autosomal dominant genetic disease
  - Multi-systemic disease affecting skeletal muscle, CNS, endocrine, GI, ocular & cardiac tissues
  - Characterized by muscle hyperexcitability (myotonia)
  - Death generally due to respiratory failure, sudden cardiac arrest or complications from GI symptoms
- Two forms of the disease
  - DM1 - triplet expansion in 3'-UTR of DMPK (Dystrophia Myotonica-Protein Kinase)
  - DM2 – 4 nucleotide repeat in ZNF9 (milder form of disease)
- "Anticipation"- each generation gets more severe form of disease due to expansion of repeat
  - Child born with congenital form of disease → mother diagnosed shortly after birth of child (30s) → grandparent diagnosed with mild form of disease (60 or 70s)
  - Patients broadly classified as neonatal, juvenile or adult onset
- Overall prevalence of 1:7,000 to 1:8,000 worldwide (DM1 & DM2)
  - 1 in 7,400 in US (40K total) for DM1 only
  - 1 in 500 in Province of Quebec for DM1 only
- No treatment has been shown to stop or slow the progression of DM1
  - Current treatments are focused on preventing cardiac events & managing symptoms
- Isis plans to identify a development candidate soon to move into its pipeline
- Program will complement other programs Isis is pursuing in its severe & rare disease efforts

Systemic Delivery of Antisense Drugs Completely Reverses Myotonia & Splicing Defects in HSA-LR Mouse



DM1 Molecular Pathology *Disease is Due to a Mutation That Causes an RNA to Become Toxic*



NEURODEGENERATIVE DISEASES

Neurodegenerative Diseases

- Neurodegenerative diseases are a collection of chronic, often fatal, diseases that result from selective loss of neurons
- Majority of neurodegenerative diseases are considered severe & rare diseases
- Current therapies primarily treat symptoms of the disease & do little to prevent the loss of neurons
- Large unmet medical need
  - Potential to significantly impact patients' lives
  - Severe life-threatening diseases
  - Most diseases do not have any approved therapies
  - Most therapies treat symptoms rather than the underlying cause of the disease
- Local & direct administration of antisense drugs
  - Cerebral spinal fluid administration through the intrathecal space

Why Antisense Drugs For Neurodegenerative Diseases?

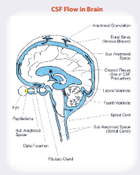
- The genetic bases for several neurodegenerative diseases have been identified as mutations in a single gene
  - Huntington's Disease → mutation in huntingtin gene
  - Spinal muscular atrophy → Loss of survival motor neuron gene
  - Spinocerebellar ataxias → SCA genes
- There are inherited forms of other neurodegenerative diseases that are also due to a mutation in a single gene
  - ALS (Lou Gehrig's disease) → superoxide dismutase gene
  - Parkinson's disease → α-synuclein & Lrrk-2 genes
  - Alzheimer's disease → amyloid precursor protein & presenilin genes
- Antisense technology can directly target the genes that cause neurodegeneration, blocking the progression of the disease
- The attributes of second-generation antisense drugs provide an opportunity for developing therapies for neurodegenerative diseases
  - Increased potency
  - Longer duration of action, less frequent administration
  - Better tolerability

Neurodegenerative Disease Strategy

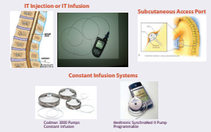
- Demonstrate applicability of antisense technology for the treatment of neurodegenerative diseases
- Focus on targets uniquely approachable by antisense technology
- Initial focus
  - Orphan diseases
  - Diseases with an identified genetic cause
  - The genetic defect results in production of a toxic molecule
  - High unmet medical need
  - Diseases severe enough to support direct CNS administration
  - Diseases with clear clinical endpoints such as motor function
  - CNS malignancies
- Broaden program to include
  - More common forms of neurodegenerative diseases that do not have an identified genetic cause
  - Other applications (i.e. spinal cord injury)

Antisense Delivery To CNS Tissues

- Antisense drugs do not cross an intact blood-brain barrier
- Delivery technologies are available which deliver drugs directly into the cerebral spinal fluid (CSF)
- CSF surrounds the brain & spinal cord tissue, providing broad access to different regions of the brain & spinal cord

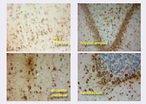


Intrathecal Delivery Solutions Are Available Today



Antisense Drugs Broadly Distribute to Multiple Cell Types in the Brain Following Intrathecal Infusion

(Antisense Drug = Brown)



Summary

- Antisense drugs do not cross an intact blood-brain barrier
- However, antisense drugs can be delivered directly into the CNS using commercially available devices
- Administration of antisense drugs into the cerebral spinal fluid (CSF) results in broad distribution of the drug in various brain regions & the spinal cord
- Antisense drugs distribute out of the CSF to neurons & other cell types in the brain & spinal cord
- We can easily monitor drug concentration in the CSF & brain by measuring drug in plasma

TARGET: SPINAL MUSCULAR ATROPHY (SMA)

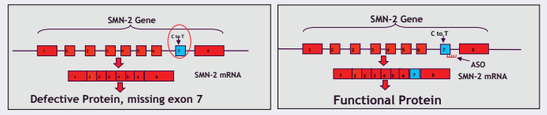
Spinal Muscular Atrophy (SMA) *RNA Splicing Based Therapy*

- Leading genetic cause of infant mortality
- Severe genetic neuromuscular disease
- Caused by mutation in the survival motor neuron (SMN) gene
- Incidence of 1 in 6,000-10,000 births
- Well-defined patient population: 50,000+ in US/EU/Japan
- Affects all racial & ethnic groups
- Common rare disease comparable to: Cystic Fibrosis, Duchenne Muscular Dystrophy, Sickle Cell Anemia & ALS
- No treatment is available

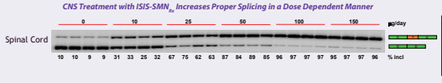
Spinal Muscular Atrophy: An Example of a Severe Disease Treatable with a Splicing Modulatory Antisense Drug

- Spinal Muscular Atrophy (SMA) is caused by loss of a gene called SMN-1
- Humans have a second copy of the gene that produces a defective protein due to an RNA splicing defect

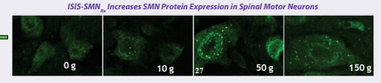
Our antisense drug corrects the splicing disorder resulting in the production of a fully functional protein



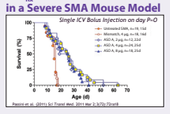
CNS Treatment with ISIS-SMN$_{Rx}$ Increases Proper Splicing in a Dose Dependent Manner



ISIS-SMN$_{Rx}$ Increases SMN Protein Expression in Spinal Motor Neurons



ISIS-SMN$_{Rx}$ Increases Survival & Behavior in a Severe SMA Mouse Model



Distribution of ISIS-SMN$_{Rx}$ Following Intrathecal Bolus Injection in Non-Human Primates

ISIS-SMN$_{Rx}$ – Advancing in Development

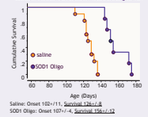
- Granted orphan drug status
- Will be administered as an intrathecal injection
- Plan to start clinical trials in late 2011/early 2012

TARGET: SOD1

What is SOD1 Familial ALS?

- Approximately 10% of patients with ALS have a family history of the disease
- Familial ALS is caused by a change in a gene (DNA)
- SOD1 (superoxide dismutase) is a gene that can cause ALS when its genetic code is changed
- This genetic change causes the protein produced to become toxic to neurons
- ALS animal models show that decreasing mutant SOD1 is beneficial

ISIS-SOD1$_{Rx}$ *Treatment of Familial Amyotrophic Lateral Sclerosis (fALS)*



Saline: Onset 102+/11, Survival 126+/-8
SOD1 Oligo: Onset 107+/-4, Survival 156+/-12

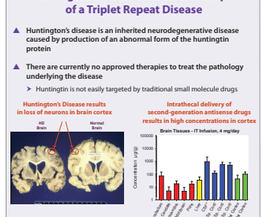
ISIS-SOD1$_{Rx}$ Advancing in Development

- ISIS-SOD1$_{Rx}$ selected as first-in-man antisense drug
  - Genetic basis of disease well characterize
  - No effective therapies
- ISIS-SOD1$_{Rx}$ status
  - Directly targets the known cause of this form of ALS
  - Granted orphan drug status
  - Successfully completed IND-enabling toxicology studies
  - Phase 1 clinical study ongoing in patients with familial ALS who have mutations in SOD1 gene

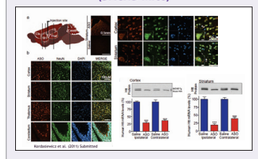
TARGET: HUNTINGTON'S DISEASE

Huntington's Disease: Another Example of a Triplet Repeat Disease

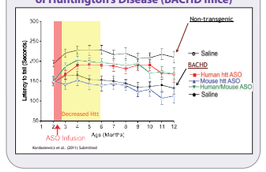
- Huntington's disease is an inherited neurodegenerative disease caused by production of an abnormal form of the huntingtin protein
- There are currently no approved therapies to treat the pathology underlying the disease
  - Huntingtin is not easily targeted by traditional small molecule drugs



Antisense Drug Selectively Reduces Human Htt Expression When Infused into CSF in a Mouse Model of Huntington's Disease (BACHD Mice)



Infusion of Huntingtin ASOs Improves Motor Coordination in Mouse Model of Huntington's Disease (BACHD mice)



FRANCHISE

Isis' Severe & Rare Disease Franchise

- Antisense drugs are showing promise for the treatment of a wide range of rare diseases including neurodegenerative diseases
- The most advanced project, ISIS-SOD1$_{Rx}$, for the treatment of familial forms of ALS (Lou Gehrig's disease), has started clinical trials
- ISIS-TTR$_{Rx}$ is the first drug for our GSK alliance that has started clinical trials
- ISIS-SMN$_{Rx}$ for the treatment of Spinal Muscular Atrophy has entered development
- We have demonstrated feasibility of treating Huntington's disease & myotonic dystrophy in mouse models
  - Optimization of the human clinical candidates are in progress for both programs
- We are investigating antisense technology in other rare diseases