RNA: The Quiet Revolution

Jeffrey S. Deitch, PhD
Drexel University College of Medicine
ALS Hope Foundation
Philadelphia, PA
Therapeutic Revolutions

Gene Therapy
Therapeutic Revolutions

Gene Therapy

Stem Cells
Therapeutic Revolutions

Gene Therapy

Stem Cells

RNA Interference
Therapeutic Revolutions

Gene Therapy

Stem Cells

RNA Interference – What?
Transcription of DNA to RNA
Translation of RNA to Protein
Here's our strand of DNA

CGGCTGCTGCTTCCCTACCAACTACACACTGGCAGCTGCAAGCTGAGTTACGGGATGGGACTAGGGATGGGCACCCTGCCG-
GCCGACGACGAAGGGATGGGTGTGTGACACCCTCGAGCAGTCAATCCCTACCCGTCGACATCCCTACCGTGAGCCGCG-
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GCCGACGACGAAGGGATGGGTGTGTGACACCCTCGAGCAGTCAATCCCTACCCGTCGACATCCCTACCGTGAGCCGCG-
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TTGTAGAGAATATCGACCGGCCGACGACGAAGGGATGGTTGATGTGTGACCGTCGACGTTCGACGTCAATCCCTACCGTGAG-
Transcription Regulation

*E. coli* lac transcription-control genes

(a) lac repressor
- lactose
+ glucose (low cAMP)

(b) + lactose
+ glucose (low cAMP)

(c) + lactose
- glucose (high cAMP)

High transcription

Low transcription

No mRNA transcription
Transcription – A Closer Look

1. Transcription, 5’ capping
2. Cleavage at Poly(A) site
3. Polyadenylation
4. RNA splicing
The calcitonin gene generates primary mRNA transcript that is spliced to produce two different forms of mature mRNA—that coding for calcitonin, which is produced primarily in the thyroid gland, and that coding for calcitonin-gene-related product (CGRP), which is produced mainly in the hypothalamus.
Alternative Splicing in Disease

A. SMN1 and SMN2

- SMN1 (Gene / pre-mRNA): 6-7-8
- SMN2 (Gene / pre-mRNA): 6-7-8
- mRNA / Protein (SMN Normal): 6-7-8
- mRNA / Protein (SMNΔ7): 6-8
- SMNΔ7: Spinal muscular atrophy (SMA)

B. Dystrophin

- Dystrophin (Gene / pre-mRNA): 30-31-32
- mRNA / Protein (Normal): 30-31-32
- mRNA / Protein (Duchenne muscular dystrophy (DMD)): 30-32

C. MAPT

- MAPT (Gene / pre-mRNA): 9-10-11
- mRNA / Protein (Normal): 9-10-11
- mRNA / Protein (4R tau = 3R tau): 9-11
- mRNA / Protein (4R tau > 3R tau): 9-10-11
- 4R tau > 3R tau: Frontotemporal dementia (FTDP-17)

D. CFTR

- CFTR (Gene / pre-mRNA): (UG)9-11(U)5-7-9
- mRNA / Protein (Cystic fibrosis (mild)): 8-9-10
- mRNA / Protein (Cystic fibrosis (severe)): 8-10
- (UG)12-13(U)3-5
- mRNA / Protein (Cystic fibrosis (severe)): 8-10
The Spliceosome
mRNA is translated into protein in the ribosome via t-RNA - Briefly
TDP-43 and FUS are RNA-binding proteins involved in ALS

T. Arai et al. / Biochemical and Biophysical Research Communications 351 (2006) 602–611

Kwiatkowski, Jr., et al. (2009) Science 323, 1205
Proposed physiological roles of TDP-43 and FUS/TLS.


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### Diseases Associated with Mutations in RNA Processing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Mutation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prader Willi syndrome</td>
<td>SNORD116</td>
<td>ribosome biogenesis</td>
</tr>
<tr>
<td>Spinal muscular atrophy (SMA)</td>
<td>SMN2</td>
<td>splicing</td>
</tr>
<tr>
<td>Dyskeratosis congenita (X-linked)</td>
<td>DKC1</td>
<td>telomerase/translation</td>
</tr>
<tr>
<td>Dyskeratosis congenita (autosomal dominant)</td>
<td>TERC</td>
<td>telomerase</td>
</tr>
<tr>
<td>Dyskeratosis congenita (autosomal dominant)</td>
<td>TERT</td>
<td>telomerase</td>
</tr>
<tr>
<td>Diamond-Blackfan anemia</td>
<td>RPS19, RPS24</td>
<td>ribosome biogenesis</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>SBDS</td>
<td>ribosome biogenesis</td>
</tr>
<tr>
<td>Treacher-Collins syndrome</td>
<td>TCOF1</td>
<td>ribosome biogenesis</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>SNHG5</td>
<td>ribosome biogenesis</td>
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<tr>
<td>Myotonic dystrophy, type 1 (DM1)</td>
<td>DMPK (RNA gain of function)</td>
<td>protein kinase</td>
</tr>
<tr>
<td>Myotonic dystrophy, type 2 (DM2)</td>
<td>ZNF9 (RNA gain of function)</td>
<td>RNA binding</td>
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<tr>
<td>Spinocerebellar ataxia 8 (SCA8)</td>
<td>ATXN8/ATXN8OS (RNA gain of function)</td>
<td>unknown/noncoding RNA</td>
</tr>
<tr>
<td>Huntington's disease-like 2 (HDL2)</td>
<td>JPH3 (RNA gain of function)</td>
<td>ion channel function</td>
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<tr>
<td>Fragile X-associated tremor ataxia syndrome (FXTAS)</td>
<td>FMR1 (RNA gain of function)</td>
<td>translation/mRNA localization</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>translation/mRNA localization</td>
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<tr>
<td>X-linked mental retardation</td>
<td>UPF3B</td>
<td>translation/nonsense-mediated decay</td>
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<td>Oculopharyngeal muscular dystrophy (OPMD)</td>
<td>PABPN1</td>
<td>3' end formation</td>
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<td>Human pigmentary genodermatosis</td>
<td>DSRAD</td>
<td>editing</td>
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<td>Retinitis pigmentosa</td>
<td>PRPF31</td>
<td>splicing</td>
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<tr>
<td>Retinitis pigmentosa</td>
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<tr>
<td>Retinitis pigmentosa</td>
<td>HPRP3</td>
<td>splicing</td>
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</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Mutation</th>
<th>Function</th>
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<tbody>
<tr>
<td>Retinitis pigmentosa</td>
<td>PAP1</td>
<td>splicing</td>
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<tr>
<td>Cartilage-hair hypoplasia (recessive)</td>
<td>RMRP</td>
<td>splicing</td>
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<tr>
<td>Autism</td>
<td>7q22-q33 locus breakpoint</td>
<td>noncoding RNA</td>
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<tr>
<td>Beckwith-Wiedemann syndrome (BWS)</td>
<td>H19</td>
<td>noncoding RNA</td>
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<tr>
<td>Charcot-Marie-Tooth (CMT) Disease</td>
<td>GRS</td>
<td>translation</td>
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<tr>
<td>Charcot-Marie-Tooth (CMT) Disease</td>
<td>YRS</td>
<td>translation</td>
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<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>TARDBP</td>
<td>splicing, transcription</td>
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<tr>
<td>Leukoencephalopathy with vanishing white matter</td>
<td>EIF2BP1</td>
<td>translation</td>
</tr>
<tr>
<td>Wolcott-Rallison syndrome</td>
<td>EIF2AK3</td>
<td>translation (protease)</td>
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<tr>
<td>Mitochondrial myopathy and sideroblastic anemia (MLASA)</td>
<td>PUS1</td>
<td>translation</td>
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<tr>
<td>Encephalomyopathy and hypertrophic cardiomyopathy</td>
<td>TSFM</td>
<td>translation (mitochondrial)</td>
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<tr>
<td>Hereditary spastic paraplegia</td>
<td>SPG7</td>
<td>ribosome biogenesis</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>DARS2</td>
<td>translation (mitochondrial)</td>
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<tr>
<td>Susceptibility to diabetes mellitus</td>
<td>LARS2</td>
<td>translation (mitochondrial)</td>
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<tr>
<td>Deafness</td>
<td>MTRNR1</td>
<td>ribosome biogenesis (mitochondrial)</td>
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<tr>
<td>MELAS syndrome, deafness</td>
<td>MTRNR2</td>
<td>ribosome biogenesis (mitochondrial)</td>
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<tr>
<td>Cancer</td>
<td>SFRS1</td>
<td>splicing, translation, export</td>
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<tr>
<td>Cancer</td>
<td>RBM5</td>
<td>splicing</td>
</tr>
<tr>
<td>Cancer</td>
<td>miR-17-92 cluster</td>
<td>RNA interference</td>
</tr>
<tr>
<td>Cancer</td>
<td>miR-372, miR-373</td>
<td>RNA interference</td>
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</table>
Coming up at the Symposium

**JOINT OPENING SESSION**

**C1 NEW PERSPECTIVE ON AMYOTROPHIC LATERAL SCLEROSIS AS TDP-43 PROTEINOPATHIES**

LEE V M-Y

Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, United States

**SESSION 4A**

**C24 TDP-43 MUTANT TRANSGENIC MICE DEVELOP BIOCHEMICAL AND PATHOLOGICAL FEATURES OF AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL LOBAR DEMENTIA**

SWARUP V, PHANEUF D, BAREIL C, JULIEN J-P

Centre de Recherche du CHUQ, Department of Neuroscience and Psychiatry, University Laval, Quebec, QC, Canada

**SESSION 11A**

**C82 NOVEL RNA BINDING PROTEINS IN ALS**

GITLER AD

Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, PA, United States

**Saturday 11 December 2010**

**SESSION 2A**

**RNA Biology in ALS**

10.30 – 11.00 Using embryonic stem cells to study motor neuron/glia interactions in ALS – T Maniatis (USA)

11.00 – 11.15 Role of RNA processing in the pathogenesis of ALS – C Lagier-Tourenne (USA)

11.15 – 11.30 Genetic and biochemical analysis of TDP-43 proteinopathy – R Tibbetts (USA)

11.30 – 11.45 Characterizing the role of TDP-43 in ALS – B Freibaum (USA)

11.45 – 12.00 RNA targets of TDP-43 identified using UV-CLIP are deregulated in ALS – J Robertson (Canada)

12.00 – 12.15 Increasing autophagy rescues neurodegeneration in flies lacking Adar RNA editing – S Paro (UK)

12.15 – 12.30 miRNA dysregulation in human sporadic ALS – T Möller (USA)
RNA in ALS: Antisense mutant SOD1

snRNAs, shRNAs, miRNAs involved in mRNA processing
small interfering RNA (siRNA)

The RNAi Natural Process

A. Small interfering RNA (siRNA), a 21-25 base pair RNA strand, is targeted to a specific gene.

B. Within cells, siRNA unwinds and is incorporated into RISC, a stable protein-RNA complex.

C. siRNA is directed to a targeted messenger RNA (mRNA) that is known to be involved in a disease pathway.

D. The mRNA undergoes degradation, thereby interrupting the protein synthesis of the targeted gene.
miRNA biogenesis and action

Cooper et al 09 Cell 136:777-793
The structure of human pri-miRNAs

Du T, Zamore P D Development 2005;132:4645-4652
Inhibition of miRNA function by a microRNA antagonist
Therapeutics that alter RNA processing

A. Antisense oligonucleotides (AOs)
- SR protein
- ESE
- (SR)n-peptide
- AO

B. snRNAs as vehicles for antisense RNA
- snRNP
- Sm core
- antisense

C. RNA interference (RNAi)
- Ataxin-1
- polyQ
- siRNA

Dystrophin
- Deletion in gene
- generates frameshift
- STOP

Partially functional dystrophin

SMN2

SMNΔ7

SMN

Degraded ataxin-1 mRNA
## Pipeline

Click on bar or (i) in the in pipeline for more information.

- **Our Proprietary Programs**
- **Co-Developed Programs**
- **Partnered Programs**
- **Joint Ventures**
- **Geographically Partnered Programs**

### Development Pipeline

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<th>Programs</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>RSV Infection</td>
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<tr>
<td>Liver Cancers</td>
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<td>TTR Amyloidosis</td>
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<td>Huntington’s Disease</td>
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<td>PCSK9/Hypercholesterolemia</td>
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### Partnered Programs

+ Collaborations

[i] ABOUT OUR PARTNERS
ALN-HTT: Huntington’s Disease

ALN-HTT, an RNAi therapeutic for the treatment of Huntington’s disease, is designed to silence the huntingtin gene, which is the cause of Huntington’s when expressed as a toxic mutated protein.

In pre-clinical studies, ALN-HTT was well tolerated following administration to the brain and was shown to silence the huntingtin gene. Silencing the huntingtin gene also translated into a therapeutic effect in animal models, including improvement in motor behavior, which is a hallmark of this debilitating and fatal disease. The RNAi therapeutic reduced expression of mutant huntingtin in the brain and sustained a benefit in motor behavior for at least one week. In preliminary studies, the RNAi therapeutic was found to be well tolerated in the brain after direct CNS administration.

ALN-HTT is being developed in collaboration with Medtronic and CHDI Foundation. ALN-HTT is being developed for delivery to the central nervous system (CNS) using an implantable infusion system developed by Medtronic. CHDI is a not-for-profit virtual biotech company that is exclusively dedicated to rapidly discovering and developing therapies that slow the progression of Huntington’s disease.
Pipeline

α-Synuclein Suppression by Targeted Small Interfering RNA in the Primate Substantia Nigra

Alison L. McCormack¹,², Sally K. Mak³, Jaimie M. Henderson⁴, David Bumcrot⁵, Matthew J. Farrer⁶, Donato A. Di Monte¹,²*


A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus

John DeVincenzo*¹, Robert Lambkin-Williams⁵, Tom Wilkinson⁶, Jeffrey Cehelsky⁷, Sara Nochur⁷, Edward Walsh⁸, Rachel Meyers⁷, Jared Gollob⁷, and Akshay Vaishnaw⁷

www.pnas.org/cgi/doi/10.1073/pnas.0912186107
<table>
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<td><strong>Cardiovascular</strong></td>
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<tr>
<td>Drug</td>
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<tr>
<td>mipomersen</td>
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<tr>
<td>ISIS-CRP</td>
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<tr>
<td>ISIS-PCSK</td>
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<tr>
<td>ISIS-FXIIIa</td>
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<td>ISIS-APOCIII</td>
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<td><strong>Metabolic</strong></td>
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<tr>
<td>Drug</td>
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<tr>
<td>ISIS-110210</td>
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<tr>
<td>ISIS-554</td>
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<td>ISIS-GCIR</td>
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<td>ISIS-GCIR</td>
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<td><strong>Cancer</strong></td>
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<td>LYS481308</td>
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<td>ISIS-EIF-4Ea</td>
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<td>OGX-427</td>
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<td>Drug</td>
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<td>ISIS-GSK108</td>
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<td><strong>Inflammation and Other</strong></td>
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<td>Vitravene</td>
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<td>Aflclazon</td>
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<td>ATL-1102</td>
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<td>EXC-001</td>
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<td>Ico-007</td>
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# Current R&D Portfolio

**Multiple Emerging Clinical Candidates**

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<tr>
<th>RX CATEGORY</th>
<th>LEAD TARGETS</th>
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<tbody>
<tr>
<td><strong>HCV</strong></td>
<td>Developing HCV therapies. Seminal paper published demonstrating ability to block specific microRNAs.</td>
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<tr>
<td><strong>FIBROSIS</strong></td>
<td>Multiple collaboration targets with demonstrated therapeutic activity</td>
</tr>
<tr>
<td><strong>ONCOLOGY</strong></td>
<td>Novel therapeutic approach to target tumors</td>
</tr>
<tr>
<td><strong>IMMUNO-INFLAMMATORY</strong></td>
<td>Multiple targets for immune-related diseases</td>
</tr>
<tr>
<td><strong>METABOLIC DISEASE</strong></td>
<td>Glucose lowering and improving insulin resistance for diabetes</td>
</tr>
</tbody>
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For wet age-related macular degeneration (AMD)

2'-F-pyrimidine RNA oligonucleotide ligands (aptamers) to human VEGF165

GACGAUGCGGUAGGAAGAAUUUGGAAGCGC(U-2’OH); t22.29-OMe4,

Eyetech, Inc.
How to Deliver RNA molecules to the Nervous System?
siRNA or miRNA in ALS Studies

SESSION 3A

C16 RNA PROBLEMS AND SOLUTIONS: LESSONS FROM MYOTONIC DYSTROPHY
THORNTON C
University of Rochester, Rochester, NY, United States
E-mail address for correspondence: Charles_Thornton@urmc.rochester.edu
No abstract available.

C17 THE ROLE OF RNA SPlicing IN SPINAL MUSCULAR ATROPHy
PELLIZZONI L
Department of Pathology and Cell Biology, Columbia University, New York, NY, United States, Center for Motor Neuron Biology and Disease, Columbia University, New York, NY, United States

P29 DIFFERENTIAL EXPRESSION AND ALTERNATIVE SPlicing OF GENES IN THE LUMBAR SPINAL CORD OF SOD1-G93A TRANSGENIC MICE
GUO Y, CHEN H, HU M, ZHANG K, WANG Q, LI Z, LI C

P76 THE BH3-ONLY PROTEIN BIM: POSSIBLE LINK BETWEEN ER STRESS AND APOPTOSIS IN CELLULAR MODEL OF ALS
SOO KY1,2, FARG M1, WALKER A1,3, HORNE M3,4, NAGLEY P2, ATKIN J1,3

P81 NFL MICRORNA EXPRESSION PROFILE IN SPORADIC ALS
STRONG M1,2, HE Z1, CAMPOUS D1

P92 CLOSE ASSOCIATION OF TDP-43 PATHOLOGY WITH LOSS OF RNA EDITING ENZYME ADAR2 IN MOTOR NEURONS IN SPORADIC ALS
AIzAWA H2, SAwADA J2, HIDEYAMA T1, YAMASHITA T1, KWAK S1
RNA: The Quiet Revolution

Jeffrey S. Deitch, PhD
Drexel University College of Medicine
ALS Hope Foundation
Philadelphia, PA
END
The antisense mechanism that has been the main focus of our research is RNase H. This cellular enzyme is activated when antisense drugs bind to their target RNA and form a duplex. Upon activation, RNase H seeks out and destroys the target mRNA, inhibiting a cell's production of a specific protein. We have cloned and characterized human RNase H and have effectively used that information to optimize the design of many of our antisense drugs. We will continue to advance our understanding of antisense mechanisms, including RNase H, in order to improve the pharmaceutical properties of our drugs. In addition to our RNase H expertise, we are the leaders in understanding and exploiting all antisense mechanisms, including the RNAi mechanism.

RNAi
RNAi is an antisense mechanism that involves using small interfering RNA, or siRNA, to target an mRNA sequence. We design antisense drugs to control splicing to make one protein versus another. In December 2009, we advanced the first antisense drug, ISIS-SMNRx, to enter our development pipeline that modulates splicing. ISIS-SMNRx is designed to treat the splicing disease, SMA, which is a neuromuscular disorder and the leading genetic cause of infant mortality. The discovery of ISIS-SMNRx resulted from a joint research collaboration between scientists at Isis and Cold Spring Harbor. In earlier published research, we and our collaborators at Cold Spring Harbor demonstrated the feasibility of using our antisense technology to control splicing for the treatment of SMA.

MicroRNA
MicroRNAs are small naturally occurring RNA molecules that are created inside cells. There are many different types of RNA that exist within the body, including mRNA. MicroRNAs are important because they appear to have critical functions in controlling processes or pathways of gene expression. There are nearly 700 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of approximately one-third of all human genes. Targeting microRNA to inhibit disease-causing pathways is an exciting development in RNA-based therapeutics. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam jointly established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics.
Vitravene®

Vitravene, approved by the FDA in 1998, is an antisense drug that we discovered and developed, to treat cytomegalovirus, or CMV retinitis in AIDS patients. Novartis Ophthalmics AG, our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis no longer markets Vitravene. Vitravene demonstrates our ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs.
ISIS

**ISIS-SOD1**

**ISIS-SOD1** is an antisense drug that targets superoxide dismutase, or SOD1, a molecule associated with an inherited, aggressive form of ALS. The FDA granted **ISIS-SOD1** Orphan Drug designation for the treatment of ALS. Because antisense drugs do not cross the blood-brain barrier, a small pump administers the drug directly into the CNS infusing the drug into the cerebral spinal fluid. Clinicians call this type of administration intrathecal infusion. Researchers reported in the Journal of Clinical Investigation that treatment with **ISIS-SOD1** prolonged life in rats that showed many symptoms of ALS. By delivering our drug directly to the fluid that circulates within the CNS, we and our collaborators lowered production of the mutant protein in neurons and surrounding cells.

The ALS Association and the Muscular Dystrophy Association are providing funding for **ISIS-SOD1**. Additionally, as part of our alliance with Genzyme, Genzyme has a right of first negotiation to license **ISIS-SOD1** from us. We are evaluating **ISIS-SOD1** in a Phase 1 study in patients with the familial form of ALS.

**ISIS-SMN**

**ISIS-SMN** is an antisense drug designed to treat SMA, a neuromuscular disorder and the leading genetic cause of infant mortality. The incidence of SMA is 1 in 6,000 to 10,000 births, and most infants born with the most severe form of SMA, Type 1, die within two years according to the National Institutes of Health’s National Institute of Neurological Disorders and Stroke. A genetic deletion of the survival motor neuron 1, or SMN1, gene is responsible for SMA. **ISIS-SMN** increases the production of the protein SMN by modulating the splicing of a closely related pre-mRNA, SMN2. Normal motor function is associated with normal levels of SMN. By altering splicing to produce SMN, **ISIS-SMN** may compensate for the underlying genetic defect.

In 2008, we and researchers from Cold Spring Harbor published data that demonstrated the feasibility of using our antisense technology to control splicing. Our collaborative work with Cold Spring Harbor led to the discovery of **ISIS-SMN**. Our SMA program is part of our collaboration in neurodegenerative disease with Genzyme, pursuant to which Genzyme has a right of first negotiation to license **ISIS-SMN** from us.

**ISIS-GSK1**

**ISIS-GSK1** is an antisense drug designed to treat an undisclosed serious and rare disease. **ISIS-GSK1** is the first drug to enter development under the recently announced partnership with GSK. We receive milestone payments from GSK as **ISIS-GSK1** advances in development, and we are responsible for development of the drug up to Phase 2 proof-of-concept, at which time GSK has the option to license **ISIS-GSK1** from us.
Genetic Code
Fig. 3. Localization of translationally repressed mRNA and miRNAs to discrete foci adjacent to or overlapping with PBs.
siRNAs have a defined structure
The miRNA biogenesis pathway.

Du T, Zamore P D Development 2005;132:4645-4652
The RNAi Therapeutic Mechanism

A. Short interfering RNA (siRNA) designed to correspond to gene target

B. siRNA synthesized with drug-like properties: stability and conjugation for delivery

C. Modified siRNAs penetrate the cell membrane and harness the RNAi mechanism for gene silencing

D. Gene silencing achieves a therapeutic effect
DNA (DeoxyRiboNucleic Acid) and RNA (RiboNucleic Acid) are composed of the following:

- Adenine (A)
- Guanine (G)
- Cytosine (C)
- Thymine (T)
- Uracil (U)
Transcription – A Closer Look
In DNA, the As, Gs, Cs & Ts form two intertwined and bound long strands (Double Helix)

G ↔ C
A ↔ T (DNA)
A ↔ U (RNA)
TDP-43 and FUS/TLS mutations in ALS and FTLD patients.


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