Disclosures:

Ionis Pharmaceuticals provided the antisense oligos used in these studies and provides research support for my lab.

Regulus Therapeutic has provided the antisense oligos used in the miRNA studies.

Biogen Idec provides research support for clinical studies.

Washington University, Ionis Pharmaceuticals, Regulus Therapeutics have filed patents regarding the use of antisense oligonucleotides in neurodegenerative disease.
Research Focus

Goal: Understand the pathophysiology of and develop novel therapeutic strategies for neurological diseases.

- **SOD1 Familial ALS**
  - To be described
- **miRNAs**
  - Understanding miRNA changes in disease
  - Developing novel tools to understand cell type specific miRNAs
- **C9ORF72**
  - Using neurons directly converted from fibroblasts to understand disease
  - Understanding clinical phenotype and biomarkers
- **Tau**
  - Understanding role of tau isoforms
  - Understanding how decreasing tau affects seizures (hyperexcitability)
  - Developing antisense oligo methods of reducing total tau mRNA or changing tau splicing patterns

Targets

- **Huntingtin** – Huntington’s Disease
- **Tau** – Alzheimers Disease, FTD, PSP, CBD
- **Prion protein** – prion disease (Creutzfeld-Jacob)
- **SMN** – spinal muscular atrophy
- **Dystrophin** – muscular dystrophy (DMD)
- **TDP-43** - FTD, ALS
- **C9ORF72** – FTD, ALS
- **Myostatin** – muscle diseases
- **TREM2** – AD, Parkinsons, FTD, ALS
- **Many other pathways**
Targeted Therapeutic Approaches

- Consider rationale for the therapeutic
  - Link to human disease?
  - Likely safe?
- Develop a method to engage that target
- Develop a method to measure the target in living humans
- Applies more broadly?
- Understand patient population
- Focused clinical trial

Methods to Increase/Replace Proteins

- Small molecules
- Viral delivery
- Change splicing (Small molecules/Antisense oligonucleotides)
Methods to Clear/Improve Toxic Proteins

- Small molecules
- Use the immune system (vaccination or passive immunization)
- RNA interference
- Antisense oligonucleotides

Antisense Oligonucleotides

Current chemistries
- 10 fold increase in potency
- 10 fold increase in duration of action
- Marked decrease in toxicities
- Increase in therapeutic index
- Clinical experience 1000+ patients outside of CNS
Amyotrophic Lateral Sclerosis

- Progressive degenerative disease
  - resulting in stiffness, weakness, and death in 2-5 years from respiratory failure
- No adequate current therapies
- Loss of neurons in the brain and spinal cord in the motor pathways
- 10% ALS familial / 90% Sporadic
- 15-20% of familial ALS caused by superoxide dismutase 1 (SOD1) mutations

Properties of SOD1

- Soluble homodimers (153aa)
- Very stably folded protein
- Binds one Cu and one Zn; active site is Cu
- Abundant (~1% of brain protein)
- Ubiquitous, Cytosolic
Rationale for Decreasing SOD1 as a Therapy for SOD1-Mediated ALS

• Mutant Superoxide Dismutase 1 (SOD1) causes disease by acquisition of a toxic property that is independent of dismutase activity
• Decreasing SOD1 likely to ameliorate disease
• Likely safe to decrease SOD1

SOD1 in Sporadic ALS

Oxidized/misfolded superoxide dismutase-1: the cause of all amyotrophic lateral sclerosis?
Kabashi E, Valdmanis PN, Dion P, Rouleau GA.
Gene Targeted Therapy for ALS

- Preclinical SOD1 Antisense oligo data
  - decrease SOD1 in vivo
  - distribute widely
  - neuroprotective
- Phase I Clinical Trial
- Other SOD1 studies to enable Phase II

Inhibition of SOD1 mRNA after antisense oligo treatment in vitro

- Effective oligos that suppress SOD1 mRNA levels
- Untreated Control
- Oligo:
  - r/hSOD\textsuperscript{146144}
  - r/hSOD\textsuperscript{146145}
  - rSOD\textsuperscript{146192}
- Intron Targeting ASOs
Intraperitoneal Administration of Antisense Oligo

Delivery of Oligos into CNS

Continuous infusion into right lateral ventricle

Cervical

Thoracic

Lumbar

Sacral

Continuous infusion into Spinal Cord
Delivery of Oligos to Rats/Mice

Anti-sense Oligonucleotides (ASOs)

Delivery by intraventricular administration to Rhesus monkey spinal cord

Anti Oligo Anti-GFAP

Oligo Treated

Saline Treated

Lumbar Ventral Horn
Intraventricular infusion delivers oligos widely

Rhesus monkey brain

Anti oligo antibody: monoclonal antibody that specifically recognizes modified oligos
100 micrograms infused per day intraventricularly for 14 days

CSF infusion delivers SOD1 Antisense oligos widely

Kordasiewicz et al. Neuron 2012
Mutant SOD1 Causes ALS-like phenotype in Rodents

- Mice, rats develop weakness and atrophy
- SOD1\textsuperscript{G93A} Rat

Richard Smith, Don Cleveland

Antisense SOD1 oligos decrease SOD1 protein in SOD1\textsuperscript{G93A} rat

Cervical Spinal Cord

N=6, +/- SD
Treatment with SOD1 Oligo Extends Survival in SOD1\textsuperscript{G93A} Rat

<table>
<thead>
<tr>
<th></th>
<th>Saline: 102+/11</th>
<th>SOD1 Oligo: 107+/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Disease</td>
<td>122+/11</td>
<td>139+/5</td>
</tr>
<tr>
<td>Survival</td>
<td>126+/8</td>
<td>156+/12</td>
</tr>
</tbody>
</table>

Doubling of survival \textit{after} onset

An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study

Timothy M Miller, Alan Pearton, William David, Jeffrey Rothstein, Erika Simpson, Stanley H Appel, Patricia L Andres, Katy Mahoney, Peggy Allred, Katie Alexander, Lyle W Ostrow, David Schoenfeld, Eric A Macklin, Daniel A Norris, Georgios Manousakis, Matthew Crisp, Richard Smith, C Frank Bennett, Katie M Bishop, Mark E Cudkowicz

www.thelancet.com/neurology  Published online March 29, 2013
Antisense Oligonucleotide in CNS in Humans

- 32 subjects, 21 individuals
Antisense Oligonucleotide in CNS in Humans

- 32 subjects, 21 individuals
- Received single, dose of Antisense oligonucleotide designed to lower SOD1 levels
- Intrathecal infusion for 12 hours
- Randomized, double-blind, placebo
- Doses (0.15 mg, 0.50 mg, 1.50 mg, 3.00 mg)
## Intrathecal Infusion

![Image of spinal cord with catheter]

## Treatment-emergent Adverse Events

Adverse events listed are those that occurred with a frequency >5% (i.e. occurring in >1 ISIS-SOD1Rx patient) or were CTCAE grade 3 or greater in severity.

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>ISIS-SOD1Rx % (# events)</th>
<th>Placebo % (# events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-LP Syndrome</td>
<td>33% (8)</td>
<td>38% (5)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>17% (4)</td>
<td>50% (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>8% (2)</td>
<td>13% (1)</td>
</tr>
<tr>
<td>Fall</td>
<td>8% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Cerebral Infarct</td>
<td>0% (0)</td>
<td>13% (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0% (0)</td>
<td>13% (1)</td>
</tr>
<tr>
<td>Cough</td>
<td>0% (0)</td>
<td>13% (1)</td>
</tr>
</tbody>
</table>

Post-LP syndrome, back pain, and nausea/vomiting incidences are not unexpected given the 17G Tuohy needle used for the infusion.
Pharmacokinetics

Plasma Concentrations Peak at End of 12-hr Infusion

ISIS 333611 Plasma Concentrations from Patients in Cohorts 3 and 4, (1.5 and 3.0 mg/12 hrs) (333611-CS1)

Cohort 1,2 were <LLOD
Pharmacokinetics - CSF

Conclusions

• SOD1 ASO was very well tolerated at doses up to 3 mg;
  – No safety or tolerability concerns related to ASO were identified

• Dose dependent CSF and plasma concentrations were observed;
  – Observed drug concentrations were reasonably consistent with expected values (generally within 2-fold)

• Results from this study suggest that antisense oligonucleotide delivery to the CNS may be a viable therapeutic strategy for neurological disorders
Antisense Oligos: C9ORF72

Targeting RNA Foci in iPSC-Derived Motor Neurons from ALS Patients with a C9ORF72 Repeat Expansion

Dhruv Sareen,\textsuperscript{1,2} Jacqueline G. O’Rourke,\textsuperscript{3} Pratap Meera,\textsuperscript{3} A. K. M. G. Muhammad,\textsuperscript{3} Shaday Grant,\textsuperscript{1} Megan Simpsonson,\textsuperscript{1} Shaughn Bell,\textsuperscript{1} Sharon Carmona,\textsuperscript{1} Loren Ornelas,\textsuperscript{1} Anais Sahabian,\textsuperscript{1} Tania Grendon,\textsuperscript{6} Leonard Petrucci,\textsuperscript{8} Michael Baughn,\textsuperscript{1} John Ravits,\textsuperscript{9} Matthew B. Harms,\textsuperscript{9} Frank Rigo,\textsuperscript{7} C. Frank Bennett,\textsuperscript{7} Thomas S. Orti,\textsuperscript{7} Clive N. Svendsen,\textsuperscript{10} Robert H. Baloh,\textsuperscript{10,11}

Targeted degradation of sense and antisense C9orf72 RNA foci as therapy for amyotrophic lateral sclerosis and frontotemporal dementia

Chih-Wen Lu,\textsuperscript{12} Michael Baughn,\textsuperscript{2} Frank Rigo,\textsuperscript{7} Shayan Seif,\textsuperscript{2} Patrick Li,\textsuperscript{12} Hai-Rui Li,\textsuperscript{2} Jie Wang,\textsuperscript{2} Andy Watt,\textsuperscript{13} Song Chen,\textsuperscript{2} Micheline Katz,\textsuperscript{13} Jiaxiang Gu,\textsuperscript{13} Peng Sun,\textsuperscript{13} Shao-Chien Lin,\textsuperscript{13} Qiang Zhu,\textsuperscript{13} Yap Yee Lim,\textsuperscript{13} Rogelio F. Hell,\textsuperscript{13} Stephen L. Oronde,\textsuperscript{13} Oliver K. Hardy,\textsuperscript{13} Edward J. Shaw,\textsuperscript{13} Zhihua Wang,\textsuperscript{13} John J. Yen,\textsuperscript{13} Peter R. C. Pringle,\textsuperscript{13} Robert H. Baloh,\textsuperscript{13} Scott R. Van Deusen,\textsuperscript{13} Gene W. Yoo,\textsuperscript{13} Xiang Dong,\textsuperscript{13} Fei,\textsuperscript{2} C. Frank Bennett,\textsuperscript{2} and John Ravits,\textsuperscript{2}

RNA Toxicity from the ALS/FTD C9orf72 Expansion Is Mitigated by Antisense Intervention

Christopher J. Donnelly,\textsuperscript{14} Ying-Wu Zhang,\textsuperscript{14} Jacqueline T. Pham,\textsuperscript{14} Aaron R. Headley,\textsuperscript{14} Noon A. Mohy,\textsuperscript{14} Svetlana Bolotina,\textsuperscript{15} Elizabeth L. Dang,\textsuperscript{15} Erin M. Politi,\textsuperscript{15} Benjamin Horner,\textsuperscript{16} Daniel M. Fine,\textsuperscript{12} Nicholas Maragakis,\textsuperscript{17} Pietro Z. Yang,\textsuperscript{15} Leonard Petrucci,\textsuperscript{16} Bryan J. Tooyoko,\textsuperscript{16} Joseph D. Wang,\textsuperscript{16} Frank Rigo,\textsuperscript{7} C. Frank Bennett,\textsuperscript{7} Sam Blackshaw,\textsuperscript{18} Maria Saffe,\textsuperscript{19} and Jeffrey S. Rothstein\textsuperscript{18}

Planning for SOD1 Phase II

• Natural history of SOD1

• SOD1 as a pharmacodynamics marker?
SOD1 as a Biomarker in CSF

• Does SOD1 in CSF reflect brain SOD1?

• Is SOD1 stable over time?

Antisense Oligo Decreases SOD1 in CSF

Winer et al., JAMA Neurology 2013
Antisense Oligo Decreases SOD1 in CSF

SOD1 in CSF Varies Little Over Time
CSF SOD1 as a Pharmacodynamic Marker

- SOD1 Knockdown in brain leads to knockdown in CSF
- SOD1 CSF varies little with repeat measurements

SOD1 half life?

Measuring SOD1 Protein Half-Life in People

[Image of a diagram showing the process of measuring SOD1 protein half-life in people, with a participant receiving a 6-C13 Lecine injection and showing CSF and blood samples at different time points.]

David Holtzman, Randy Bateman
**SOD1 Levels by Mass Spec**

- Immunoprecipitate SOD1
- Identify reliable proteolytic fragment (peptide) containing Leucine
- Measure $^{13}$C-Leucine SOD1 compared to $^{12}$C-Leucine SOD1 (mass spec shift of 6)

Collaboration with Randy Bateman, Kwasi Mawuenyega, Bruce Patterson, Kevin Yarasheski

---

**SOD1 is not adequately labeled in 6 hours**

![Graph showing % C-13 in SOD1 vs. Hour of CSF Sampling](image)

Lucy Liu
SOD1 Synthesis Rate in Brain in Rats

SOD1<sup>WT</sup> Rats labeled with <sup>13</sup>C Leucine for 3 days or 7 days (N=4)

Does the half-life matter?

Simulated Effect of SOD1 Protein Half-life on Protein Levels

- Synthesis rate = 1.71% per day
- t<sub>1/2</sub> = 29.3 days

- 143 days - 90 day t<sub>1/2</sub>
- 129 days - 60 day t<sub>1/2</sub>
- 111 days - 30 day t<sub>1/2</sub>
Stable Isotope Labeling Kinetics (SILK)

SILK Study Design

Leucine-free diet acclimation (1-2 weeks)  |  Pulse (7 days)  |  Chase
**SILK Study Design**

- **Leucine-free diet acclimation** (1-2 weeks)
- **Pulse** (7 days)
- **Chase**

<table>
<thead>
<tr>
<th>Time (t)</th>
<th>3d</th>
<th>7d</th>
<th>14d</th>
<th>21d</th>
<th>28d</th>
<th>35d</th>
<th>63d</th>
</tr>
</thead>
</table>

**Rats**
- SOD1$^{WT}$
- SOD1$^{G93A}$

**Tissues**
- Spinal Cord, Cortex, Liver, Kidney, Plasma

**SOD1 animals received sufficient label**

Bob Chott, PhD (Yarasheski Lab)
SOD1 turnover is relatively rapid in unaffected tissues

SOD1<sub>WT</sub>  SOD1<sub>G93A</sub>

![Graph showing turnover rates in different tissues](image)

SOD1 turnover is relatively rapid in unaffected tissues

SOD1<sub>WT</sub>  SOD1<sub>G93A</sub>

![Graph showing turnover rates in different tissues](image)
SOD1 turnover is slowest in affected tissues

**SOD1\textsuperscript{WT}**
- Plasma Leucine
- Liver
- Kidney
- Cortex

**SOD1\textsuperscript{G93A}**
- Plasma Leucine
- Liver
- Kidney
- Cortex

SOD1 turnover is slowest in affected tissues

**SOD1\textsuperscript{WT}**
- Plasma Leucine
- Liver
- Kidney
- Cortex
- Cervical SC
- Lumbar SC

**SOD1\textsuperscript{G93A}**
- Plasma Leucine
- Liver
- Kidney
- Cortex
- Cervical SC
- Lumbar SC
Turnover of misfolded SOD1 G93A is accelerated in the spinal cord

Misfolded SOD1 pools are turned over faster in non-affected tissues

B8H10, mouse monoclonal, MM-0070 MédiMabs
Modeling SOD1 kinetics

<table>
<thead>
<tr>
<th></th>
<th>SOD1 WT</th>
<th>SOD1 G93A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTR (pool/day)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Liver total protein</td>
<td>1.265</td>
<td>1.121 – 1.409</td>
</tr>
<tr>
<td>Cortex total protein</td>
<td>0.177</td>
<td>0.167 – 0.186</td>
</tr>
<tr>
<td>Spinal cord total protein</td>
<td>0.087</td>
<td>0.081 – 0.094</td>
</tr>
<tr>
<td></td>
<td>SOD1 WT</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>FTR (pools/d)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Liver SOD1</td>
<td>0.397</td>
<td>0.379 - 0.415</td>
</tr>
<tr>
<td>Kidney SOD1</td>
<td>0.205</td>
<td>0.197 - 0.213</td>
</tr>
<tr>
<td>Cortex SOD1</td>
<td>0.074</td>
<td>0.071 - 0.078</td>
</tr>
<tr>
<td>CSF SOD1</td>
<td>0.047</td>
<td>0.044 - 0.050</td>
</tr>
<tr>
<td>Spinal cord SOD1</td>
<td>0.044</td>
<td>0.041 - 0.046</td>
</tr>
</tbody>
</table>

|                  | SOD1 WT       |             | SOD1 G93A    |             |
|                  | FTR (pools/d) | 95% CI      | Half-life (d) | FTR (pools/d) | 95% CI      | Half-life (d) |
| Liver misfolded SOD1 | 0.868         | 0.795 - 0.941 | 0.80         |             |             |             |
| Spinal cord misfolded SOD1 | 0.325         | 0.309 - 0.342 | 2.13         |             |             |             |
**SOD1 G93A turnover is slowest in affected tissues**

- **Cortex**: 7 days
- **Spinal Cord**: 9 days
- **Liver**: 1.4 days
- **Kidney**: 3.7 days

**Measuring SOD1 turnover in human CSF**

Animal data indicated a long half-life

<table>
<thead>
<tr>
<th></th>
<th>SOD1 WT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTR (pools/d)</td>
</tr>
<tr>
<td>CSF SOD1</td>
<td>0.047</td>
</tr>
<tr>
<td>Spinal cord SOD1</td>
<td>0.044</td>
</tr>
</tbody>
</table>

**Human labeling adapted from animal study**

- **10 days** – low leucine diet (2000 mg) with $^{13}$C$_6$-leucine administered 3X daily (1000 mg total)

- Plasma and CSF collected at end of labeling and up to 84 days later
CSF SOD1 Half-life in Humans

Oral $^{13}$C$_6$-leucine Labeling

Predicted $^{13}$C$_6$-leucine labeled SOD1(2%)

Day 0 10 14 28 42 84

CSF Samples X X X X X

Plasma Samples X X X X X

Measuring SOD1 turnover in human CSF
SOD1 Labeling in Humans

Human Subject Labeling

C-13 Label (%)

End of Pulse

Time (days)

NC02 Plasma Leucine
NC02 CSF Total Protein
NC02 Plasma Total Protein

SOD1 Labeling in Humans

Human Subject Labeling

C-13 Label (%)

End of Pulse

Time (days)

SOD1 NC02
NC02 Plasma Leucine
NC02 CSF Total Protein
NC02 Plasma Total Protein
SOD1 Labeling in Humans

Conclusions/Next steps

• SOD1 CSF levels Stable

• Development of SILK paradigm in animals and human

• SOD1 turnover is slowest in affected tissues

• SOD1 turnover in CSF from human subjects is 4 fold slower than CSF total protein

• Half-life of SOD1 in humans:
  - In SOD1 ALS underway

SOD1 CSF Half life
23+/−8 days
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ALS Association
Muscular Dystrophy Association
Packard Center for ALS
Target ALS
Weston Foundation
Tau Consortium
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NIH/NIA

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Kathleen Schoch
Wade Self
Carey Shaner
Tao Shen
Amy Wegener
Former Miller Lab
Peggy Allred, Dushyanth Srinivasan
Leah Winer, C. Keboeaux

millert@neuro.wustl.edu
microRNAs

• Discovered in 1993
  - 2nd discovered in 2000

• Translational repressors; 18-22nt long

• Partial complementarity
  - Seed region
  - Typically 200-300 mRNAs

miRNA Antisense Oligonucleotide Safety:

• Phase 2a by Santaris Pharma, 36 patients with chronic HCV genotype 1 infection.
miRNAs as Targets for ALS Therapeutics

• Identify dysregulated microRNAs in ALS
  - In rodent model and in patients

• Develop method for inhibiting these miRNAs throughout CNS

• Determine if these miRNAs negatively or positively influence disease progression

Human Tissues Identifies 6 Best Targets

Koval et al. Hum Mol Genet 2013
MiR-155 is increased in human ALS

DeVos and Miller, 2013
anti-miR-155 is functional throughout CNS

Anti-miR-155 is present in all cell types
Anti-Mir-155 Does not Change Onset

**Weight Peak**

- Cumulative onset
  - Age (d)
  - n.s.

**Neuroscore 1**

- Cumulative onset
  - Age (d)
  - n.s.

SOD1<sup>G93A</sup> mice, treated at 60 days of age both intraventricularly and intraperitoneally

Anti-miR-155 Extends Disease Duration

**Percent survival**

- Age at death (d)
  - **
  - ***

**Disease duration (d)**

- 10 day extension
  - p=0.007

- 38% increase
  - p<0.001
Conclusions

• miRNAs are dysregulated in ALS in both the rodent model and in patients

• miRNAs can be inhibited broadly in the CNS with antisense oligonucleotides

• miR-155 remains an exciting therapeutic target
  - miR-155 negatively contributes to disease
  - Implications for both sALS and fALS
  - Significant increase in survival
  - Can read miR-155 in peripheral blood cells

Remaining questions

• Mechanism of how miR-155 influences disease
• Which CNS cells express miR-155?
• Other miRNAs?
• miR-155 clinical trial?
Acknowledgements

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Hope Center
Project5 for ALS
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Muscular Dystrophy Association
Packard Center for ALS
Target ALS
Weston Foundation
Tau Consortium
NIH/NINDS
NIH/NIA

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