Therapeutic Developments for ALS: Antisense, Gene Therapy and Stem Cells
Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
September 27-30, 2015

We are grateful to the generous support from The Greater New York Chapter of The ALS Association

Organizers: Lucie Bruijn, The ALS Association, Washington, DC
Tim Miller, Washington University, St. Louis, MO
Clive Svendsen, Cedars-Sinai, Los Angeles, CA
Dinah Sah, Voyager Therapeutics, Cambridge, MA

PROGRAM

Sunday, September 27
Afternoon    Arrival at Robertson House

6:00 pm    Registration and Reception at Robertson House

7:30 pm    Dinner at Robertson House

Monday, September 28
7:30-8:30 am    Breakfast at Robertson House

9:00-9:05 am    Jan Witkowski, Executive Director, Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York
Welcoming remarks

9:05-9:30 am    Lucie Bruijn, ALS Association, Washington, DC
Overview and Workshop Goals

9:30-12:00 pm    Session1: Antisense Oligonucleotide Therapy
9:30-9:40 am    Chair: Timothy Miller, Washington University, St. Louis, Missouri

9:40-10:05 am    Timothy Miller, Washington University, St. Louis, Missouri
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10:05-10:30 am    Don Cleveland, University of California, San Diego, California
C9orf72

10:30-11:00 am    Coffee Break

11:00-11:20 am    David Rodman, miRagen Therapeutics, Boulder, Colorado
microRNA targeting to the CNS

11:20-12:00 pm    General discussion, highlighting key points
12:15 pm    Luncheon at Robertson House
2:00-5:00 pm  **Session 2: Gene Therapy**
2:00-2:10 pm  Chair: Ray Bartus, RTBioconsultants, Inc. San Diego, California
2:10-2:30 pm  Krystof Bankiewicz, University of California, San Francisco, California
2:30-2:50 pm  Brian Kaspar, Ohio State University, Columbus, Ohio
2:50-3:10 pm  Dinah Sah, Voyager Therapeutics, Cambridge, Massachusetts
3:10-3:40 pm  Coffee Break
3:40-5:00 pm  General discussion highlighting key points

6:00 pm  Reception at Robertson House
7:00 pm  Dinner at Robertson House

**Tuesday, September 29**
7:30-8:30 am  Breakfast at Robertson House
9:00-11:45 am  **Session 3: Stem Cells**
9:00-9:10 am  Chair: David Rowitch, University of California, San Francisco, California
9:10-9:30 am  Jonathan Glass, Emory University School of Medicine, Atlanta, Georgia
  Neuralstem
9:30-9:50 am  Clive Svendsen, Cedars Sinai Medical Center, Los Angeles, California
  CIRM/Cedars-Sinai combined stem and gene therapy trial
9:50-10:20 am  Nicholas Maragakis, Johns Hopkins University School of Medicine, Baltimore, Maryland
  James Campanelli, Q Therapeutics, Inc., Salt Lake City, Utah
  Q therapeutics trial
10:20-10:50 am  Coffee Break
10:50-11:45 am  General discussion highlighting key points
12:00 pm  Luncheon at Robertson House
2:00-4:10 pm  **Session 4: Delivery and Biomarker Development**
2:00-2:10 pm  Chair: Jeff Bulte, Johns Hopkins University School of Medicine, Baltimore, Maryland
2:10-2:30 pm  Gregory Stewart, Voyager Therapeutics, Cambridge, Massachusetts
  Lost in (Therapy) Translation: It won't work, if it doesn't get there
2:30-2:50 pm  Nicholas Boulis, Emory University, Atlanta, Georgia
  Clive Svendsen, Cedars Sinai Medical Center, Los Angeles California
  Stem cell tracking techniques and delivery
2:50-3:10 pm  Eric Ahrens, University of California, San Diego, La Jolla, California
Emerging MRI methods to assess cell engraftment and host response

3:10-3:40 pm  General discussion highlighting key points

3:40-4:10 pm  Coffee Break

4:10-5:40 pm  **Session 5: Regulatory and Clinical Trial Design Panel Discussion**
Chair: Bernard Ravina, Voyager Therapeutics, Cambridge, Massachusetts

**Panelists:**  Jane Lebkowski, Asterias Biotherapeutics, Portola Valley, California
James Berry, Massachusetts General Hospital, Boston, Massachusetts
Toby Ferguson, Biogen, Cambridge, Massachusetts

5:20-5:40 pm  General discussion highlighting key points

6:00 pm  Reception at Robertson House

7:00 pm  Dinner at Robertson House

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**Wednesday, September 30**

7:30-8:30 am  Breakfast at Robertson House

9:00-12:00 pm  **Session 6: Animal Models**
9:00-9:10 am  Chair: Jeffrey Rothstein, Johns Hopkins University School of Medicine, Baltimore, Maryland

9:10-9:30 am  Robert Baloh, Cedars-Sinai Medical Center, Los Angeles, California
Overview of mouse models

9:30-9:50 am  Joan Coates, University of Missouri, Columbia, Missouri
Canine Degenerative Myelopathy: A Potential Disease Model of ALS

9:50-10:20 am  Coffee Break

10:20-10:40 am  Arthur Burghes, Ohio State University, Columbus, Ohio
SMA pig model

10:40-11:00 am  Zuoshang Xu, University of Massachusetts Medical School of Medicine, Worcester, Massachusetts
Modeling and treatment of sporadic ALS

11:00-11:45 am  General discussion highlighting key points

11:45-12:00 pm  Closing Remarks

12:15 pm  Luncheon at Robertson House
Afternoon departure
DISCUSSION POINTS FOR ALL SESSIONS

Session 1: Discussion points for Antisense Oligonucleotide Therapy
1. Selection of Target RNA
2. Identification of best ASO
3. Optimal method of delivery
4. Regions and cell types affected by ASO
5. Biomarkers

Session 2: Discussion Points for Gene Therapy
What are the key anatomical targets for an effective gene therapy product for ALS?

1. How important is targeting the upper motor neurons versus lower (spinal cord) motor neurons versus other parts of the brain (e.g., hippocampus, neocortex)?
2. Might targeting the motor neuron systems but not non-motor systems supporting cognition likely be effective? What about the opposite (i.e., target hippocampus and neocortex, only)?
3. Do both upper and lower motor neurons likely need to be targeted to reduce motor impairments, and if so, how?
4. How important is it to target the motor neuron terminals innervating the neuromuscular junction? How might this be done?
   · How important might it be to target astrocytes and other glial cells to achieve meaningful clinical benefit? Might targeting them be necessary? Sufficient?
   · How can we ensure effective targeted-cell transduction, given between-species differences in tropism/transduction that have been seen?
   · How can we control level of transgene expression; do we feel regulatable vectors may yet be valuable in the future?
   · What are the best means for selecting clinical doses? How might biomarkers for target engagement help?
   · What concerns exist for off-target side effects or other complications (e.g., inflammatory reactions, immune responses, liver effects); what might be some likely solutions?

Session 3: Discussion Points for Stem Cells
1. What cell type(s) are the focus of your stem cell approach?; what cell autonomous process and/or signaling pathway is the target(s)?
2. How might transplanted cells be modified adversely by the host environment (non-cell autonomous pathogenic features)?
3. What is your delivery method for spinal cord?
4. What conditioning and/or immune regulatory steps are needed to enhance clinical engraftment or survival?
5. How many patients do you think you will have to transplant to see any clinical effect?

Session 4: Discussion Points for Delivery and Biomarker Development
Pros and cons of potential injection routes for cell delivery applicable to ALS (IV, IA, IP)
1. How are cells currently detected in patients following administration?
2. Pros and cons of available non-invasive imaging techniques
3. Are there other (non-invasive) biomarkers that are/can be used outside imaging?

Session 5: Regulatory and Clinical Trial Design Panel Discussion
1. Target populations – genetic vs phenotypic, heterogeneity vs homogeneity, implications for study conduct
2. Manufacturing – unique issues, consistency batch to batch, quality
3. Delivery - routes, frequency, risks, sustainability
4. Dose finding – understanding and predicting pk, understanding tissue distribution, ways of exploring target engagement and Pd effects
5. How design pivotal and use of controls
6. Unique safety issues
7. Patient group interactions

Session 6: Discussion Points for Animal Models
1. What advantage does the particular model bring to studying ALS pathophysiology?
2. Has it been, or how could it, be an effective tool for drug discovery
3. What are the pros of this model?
4. What are its disadvantages?
5. Where has it seen real success; where has it failed:
6. What would you do to improve it in the future?
7. Most importantly does it accurately recapitulate human disease- if so where, and where has it failed (for example- the mutant SOD1 mouse model beautifully shows a clinical disease— but if one is honest— it really does not meet classic ALS pathology or clinical phenotypes— is has huge protein aggregates and vacuoles, with “blown” mitochondria— which is never seen in real sporadic or familial ALS; it has dramatic lower motor neuron phenotype — but minimal – at best- upper motor neuron disease (and would not meet clinical criteria for for a “diagnosis” of classic ALS)