Selected Notes from the
22nd Annual Research Research
Symposium on ALS/MND
Sydney, Australia

Robert A. Goldstein
1/11/2012

This document contains notes taken during these proceedings. This are not meant to replace any medical information received by a person living with any disease – nor are they meant to be a complete recap of any presentations made. ALS TDI does not endorse these as its opinion on any level of understanding nor make any claims to their accuracy.
## Contents

<table>
<thead>
<tr>
<th>Session</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1 – Joint Opening Session</td>
<td>3-4</td>
</tr>
<tr>
<td>Session 2A – Pathobiology of ALS</td>
<td>5-7</td>
</tr>
<tr>
<td>Session 3B – Translating Evidence into Practice</td>
<td>8-10</td>
</tr>
<tr>
<td>Session 4A – RNA and Protein Processing</td>
<td>11</td>
</tr>
<tr>
<td>Session 6B – Epidemiology</td>
<td>12-14</td>
</tr>
<tr>
<td>Session 8B – International Perspectives on Care Practice</td>
<td>15</td>
</tr>
<tr>
<td>Session 8C – Surrogate Markers</td>
<td>16</td>
</tr>
<tr>
<td>Session 9C – Neuroimaging</td>
<td>17</td>
</tr>
<tr>
<td>Session 10B – Clinical Trials</td>
<td>18-20</td>
</tr>
<tr>
<td>Session 11A – Disease Models</td>
<td>21-22</td>
</tr>
<tr>
<td>Session 11B – Respiratory Management</td>
<td>23</td>
</tr>
</tbody>
</table>
**Session 1 – Joint Opening Session**

Aboriginal welcome with didgeridoo music, song and dance.

*What heterogeneity of ALS phenotype may be telling us about pathobiology?*

**John Ravits (University of California, San Diego, CA, USA)**

(jravits@ucsd.edu)

- Heterogeneity of the disease. Spoke about focality of disease and the trends of it "spreading" from limb to limb and from bulbar to limbs, etc.

*The contribution of genetic factors to sporadic ALS/MND*

**Garth Nicholson (University of Sydney, Sydney, Australia)**

(garth.nicholson@sydney.edu.au)

Sporadic ALS
- Have we have likely found all of the high-penetrance genes? Are future ones going to be low penetrance and therefore account for much of SALS.
- TDP43 - is it the cause of the results? - found in spinal neurons in SALS & FALS
  - what triggers ALS?
  - What is the amplification mechanism?
  - does ALS spread cell by cell?
  - is TDP the common pathway to cell death?
  - can we slow it cascade?
  - can we get there to treatments?
- mentioned NAA work of Benatar "is this the set-up ping-pong table or are we already there? we just don't know yet"
- TDP mutation AND overexpression cause aggregation in cytosol. However, recent work shows that aggregation may not occur if you don't "seed" the cell first (according to recent paper)
  - We have villains (too many)
  - We have mechanism (too many)
  - We need to look at cell environment

**Forbes Norris Award**

Given to Orla Hardiman of Ireland. Made by Dee Norris. Acknowledged Merit Cudkowicz, Bob Brown, Pam Shaw

**Paulo Gontijo Young Investigator Award**

Went to Aaron Gitler

Gitler Talk:
Uses yeast models to study protein aggregation
41 genes in yeast verified TDP 43 enhancers or suppressors
One of them, PBP1 overexpression enhances TDP43 toxicity. PBP1 is the homolog of human Ataxin2 gene. Did a cross with TDP43 and Ataxin2 fruit flies. Leads to massive eye degeneration. Then looked in PALS spinal cord samples and found some overexpression on Ataxin2 as well. Number of polyQ repeats 22-23 normal. 34+ causes SCA2. Determined that between 27-33 likely linked to ALS by looking at PALS samples.
Microglia T-Cell motoneuron dialogues influence disease progression

Stan Appel (Methodist Neurological Institute, Houston, Texas, USA)

(SAppel@tmhs.org)

- increased inflammation present in most cell types in the CNS and in periphery
- M1 microglia are pro-inflammatory
- M2 neuroprotective microglia
- You can convert microglia type back and forth using various cytokines
- More M2 (neuroprotective) than M1 (cytotoxic) during stable phase of disease in PALS samples looked at, it switched during the progressive/end stage of disease in those PALS
- In the mSOD1 cross with PU1 mouse, when they transplanted the WTmSOD1 bone marrow survival improved (2006 study)
- T Cell markers in blood and spinal cord samples from PALS
  - Example, FoxP3 up in the stable/early phase of disease. Are T-Cells cytotoxic or neuroprotective in ALS?
- Crossed mSOD1 with RAG2 mice (RAG2 mice don’t have functional T or B cells)
  - Animals died earlier. Therefore, the T Cells were relatively protective, not toxic.
  - CD4 T Cells are neuroprotective, especially in experiments in transplanting cells collected late stage into animals in early stage of disease
- Obvious questions - do these marker indicated progression rate?
  - FoxP3, IL-4 TGF-beta levels in blood high early on in disease seem to correlate with a slower form of ALS. May be predictive.

Elimination of innate immune system adaptor TRIF significantly accelerates disease progression of ALS mice

Koji Yamanaka (RIKEN Brain Science Institute, Wako, Saitama, Japan)

(kyamanaka@brain.riken.jp)

- Microarray analysis on spinal cord of mSOD1 mice (one active, one inactive SOD1)
- Innate immunity is first line defense of invading pathogens
  - Toll-like receptors are major sensor for pathogen derived components
  - Microglia (or astrocyte) elicits the response of innate immunity in CNS
- TLR receptors are over active in SOD1 mediated disease
  - MyD88 and TRIF inhibition experiments to see
  - removing TRIF cut survival time 28 days (same as if they removed both genes)
  - They further showed using a knockout experiment that TRIF Is determinant
- Down regulation of some chemokines seems to be associated to SOD1/TRIF cross mouse rapid progression
- TRIF expression seems to be associated from microglia, not astrocytes
- blocking innate immune signaling (TRIF) accelerated disease progression in SOD1 mouse models
- suppressing CCL5 (RANTES) and CXCL10 (IP-10) was correlated in accelerated disease progression in TRIF/SOD1 mice, indicating these chemokines may have neuroprotective action (they are also implicated in sporadic ALS)
- Microglia is responsible cell type for TRIF-dependent production of CCL5 and CXCL10

**Aggregated wild-type SOD1 increases serum levels of cytokines in patients w/ALS**
Martina Wiedau-Pazos (UCLA, Los Angeles, CA, USA)
(mwiedau@medmet.ucla.edu)

- Expression of cytokines in SOD1 stimulated PBMCs
- Macrophages express IL-1b in spinal cord sections of the ALS spinal cord
- showed that macrophage and neurons co-localize
- Plan is to look at a longitudinal study in PALS of the cytokines in the blood cells

**Abnormal axoglial communication in the corticospinal tracts could underlie upper motor neuron degeneration in sporadic ALS**
F. Song (Wayne State University, Detroit, MI, USA)
(fsong@med.wayne.edu)

- NRG1 mediated microglia activated in ALS disease. MRG1 is a potential common therapeutic target.
- Seems to be associated with UMN Dominant ALS cases and associated with demyelination and axonal die-back
- developed a novel NRG1 agonist in collaboration with David Bennet to block the microglial activation.

**Neuropathological findings of six Scandinavian patients homozygous for the D90A SOD1 mutation**
Karin Korsberg (Umea University, Sweden)
Karin.forseberg@medbio.umu.se

- D90 genetic mutation of SOD1 is the focus. D90 is one of the most common adult onset mutation found in SOD1 cases. It is found in both autosomal dominant and recessive cases of ALS.
- Survival mean of D90A patients is 14 years
- D90A patients’ extreme loss of MN in spinal cord

**Prominent redistribution of TDP43 and FUS/TLS under conditions of cellular insult in primary neurons**
Anthony White (University of Melbourne, AUS)
(arwhite@unimelb.edu.au)

- TDP43 and FUS talk
- They are both components of stress granules
- SGs are thought to be a response to stress in the cell
Session 3B - translating evidence into practice

Treating MND: Does the evidence lead us or lag behind us?
Jeffrey Rosenfeld (UCSF, Fresno, CA, USA)
(jrosenfeld@fresno.ucsf.edu)

- Multidisciplinary centers - lack of evidence base, which is a problem
- Combination of evidence and experience is important in discussing the care of PALS
- Evidence based standards good for - instructing less experienced practitioners, provide min standards of excellence and challenge the field on where to focus research
- Barriers to evidence: cost of trials is high; # of available patients is low, disease heterogeneity, ethics of withholding care, limited power of endpoints
- Future directions?
  - A role for consensus?
  - Pooled experience?
  - Periodic surveys?
  - Collective database
  - Etc

Cochran Collaboration - Robert Miller - 15 treatment reviews already

Does rigorous control of exercise intensity affect survival and functional outcomes in ALS?
Anabela Pinto (Santa Maria Hospital, Lisbon, Portugal)
(jsanches.apinto@mail.telepac.pt)

- Exercise in ALS is the topic, which has been controversial for a number of years
- Exercise is generally recommended to the able bodied population
- Exercise related neurotoxicity has yet to be clarified
- Main question has become not whether to prescribe exercise to ALS patients, but what kind, how much and to which patients
- High-intensity exercise and weight training not recommended for neuromuscular diseases
- Conducted a clinical trial with 20 control and 20 experimental PALS
  - Design was to determine if a training program would have an effect (training program included a program 2-3 times a week vs. a more casual exercise program asking PALS in control group to simply exercise until exhausted by walking at home
  - Outcome: moderate progressive exercise is possible
  - Outcome: apparently positive impact on functional and survival outcome
  - Conclusion: moderate exercise should be prescribed
  - Conclusion: health professionals may become more proactive in support of moderate strengthening exercise
  - Future work: earlier referral to exercise? Increase resistance level?
Implementation of AAN ALS guideline as performance measures in the joint commission disease specific certification program at Carolinas Neuromuscular/ALS-MDA Center
Benjamin Brooks (Carolinas Medical Center, Charlotte, NC, USA) (benjamin.brooks@carolinashealthcare.org)

- AAN Guidelines as Measure of Performance
  - "measurement leads to improvement"
  - focused on cognition and depression
  - looked at AAN guidelines for standards of care and choose the quickest and most insightful ones
    - Hospitals are accreditation - macro system
    - Hospitals are certification - micro system
  - "measurement leads to adherence leads to improvement"

Evidence-based guidelines for power wheelchair prescription for persons w/ALS
Amber Ward (Carolinas Neuromuscular ALS/MND Center, Charlotte, NC, USA) (amber.ward@carolinashealthcare.org)

- Wheelchair prescription to ALS patients
- 40 people responded to the surveys
  - 44% thought they should have started power wheelchair process earlier
  - Majority said that clinical therapists brought up need for a PWC, not the neurologist or doctor
    - What influenced their choice was primarily the ability to go in and out on their own and easier to move around
      - 100% thought it met their expectations
      - 87% felt good value for cost
      - Some of the negative outcomes were that it was too big, destructive to home, unable to visit places, among others
        - 92% said their quality of life improved once they got the PWC
        - 88% said their mobility improved
  - take home messages
    - PWCs should have tilt, recline, elevating legs and seat
    - upgraded electronics (about to move without only a joystick)
    - Etc

A systematic review of ALS service users’ perceptions of services and decision making in care
Ger Foley (Beaumont Hospital ALS Clinic, Dublin, Ireland) (gefolet@o2.ie)

- Service users’ perspective and decision making in care
- looked at data from 1988-March 2011 for data from journals that had articles about ALS+care, MND+ services, etc...And it must have included service users’ perspective
  - found 47 papers (43 studies)
    - 16 overall views and experiences of care
    - 7 assistive devices
    - 6 communicating the diagnosis
    - 18 on life sustaining treatment and assisted suicide
    - Mostly they were European and US based
    - Majority of data was descriptive
    - Small sample sizes
    - No control arms in most of the studies
  - Perceptions IDed from study
    - services users wanted: dignified care, MD clinics, info to make choices, dissatisfied with delays, though provided were detached, dissatisfied with QOS, satisfaction with assistive devices
  - Decision making from study
    - Personal values, control, QOL, care burden, conflicting feelings, etc
- Conclusions
  - Dignity, autonomy and control are crucial to providing care
4A - RNA and Protein Processing

**Altered RNA function in ALS: Lessons from genetics**  
Robert Brown (University of Massachusetts Med. School, Worcester, MA, USA)  
(robert.brown@umassmed.edu)

- 95% of the human genome is transcripted into RNA  
- TDP43 and FUS are present at nearly every step of gene expression  
- Dendritic spiny architecture seems to be abnormal in FUS.....also in TPD43  
- FUS and TDP43 stress granule formation present with mutant form, not wild-type  
- 40k sites in the human genome that TDP43 binds, in 6000 genes  
- Nonsense mediated decay of TDP43 caused in part by extra "molecular graffiti" during splicing process.  
- 12 different strains of TDP43 rodent models created to date (many different promoters, transgene and host type....so difficult to compare)  
  - Loss of TDP43 levels can also lead to pathological disease  
- FUS mice (there are several of them)  
  - Larry Hayward at umass - 11 different lines of FUS mice have been created. 14 months of age thus far. No motor neuron phenotype, but there is truncated FUS packing the cytosol  
  - There is likely an additional stressor causing the disease pathology he suggests  
VCP - more than 20 mutations in the gene known to date

**Identification of FUS/TLS-mediated RNA processing alterations**  
Magdalini Polymenidou (UCSD, San Diego, CA, USA)  
(mpoldmen@ucsd.edu)

- FUS binds with about half the mouse genome.  
- looked a human brain to find binding sites as well. Similar findings. 90 of the sites that it binds to are intron. FUS binds into own site on opposite. Also, binds to long, non-coding sites.  
- used ISIS oligo-mediated knockdown stratum. About 90% knockdown achieved.  
- Most of the downregulated genes upon TDP43 or FUS depletion have exceptionally long introns and multiple binding sites.  
- 55 genes downregulated in both with long introns and multiple binding sites  
- Splicing changes - 83 common between TDP43 and FUS
**6B - Epidemiology**

*Exogenous risk factor in ALS: a population based case control study*

M.H.B. Huisman (University Medical Center, Utrecht, The Netherlands)

(m.h.b.huisman-3@umcutrecht.nl)

- 22-62% of sporadic cases have an environmental link it is hypothesized, however, smoking is the only confirmed risk factor
- Increased pre-symptomatic energy expenditure, suggests better metabolism before disease onset
- Data suggests increased risk with saturated fat and/or trans-fat intake being higher
- Data suggested may be risk with increased leisure time and ALS, but very small yet statistically significant
- Vigorous physical activity is not a risk factor of ALS
- Identified 20 different job exposures to study
  - Diesel motor exhaust exposure may be risk factor, statistically significant results from their study (also, they found a correlation to survival of those exposed to diesel exhaust had shorter survival with ALS)
  - Electromagnetic field exposure may also be a risk, however, lifetime vs. just prior confounding
  - Exposure to pesticides related to increased risk
  - Alcohol found to be protective factor against ALS
- Power of their study may have been too small to justify hard results
- Have set up an international consortium to increase power, have three countries involved now

*Permorbid cardiovascular fitness is a risk factor for ALS: evidence from record linkage studies*

Martin Turner (Oxford University, Oxford, UK)

(martin.turner@clneuro.ox.ac.uk)

- Conflicting past reports on whether or not physical activity related to ALS developing in any way
- The challenge has always been if exercise is the cause or whether people that develop ALS are just more inclined to exercise
- Prospective study not practical for rare disease
- Spoke about the +/- between case study and hospital admission studies
- ALS arises in a population with relatively higher levels of cardiovascular fitness
- His data shows that a person is more likely to get ALS is you aren't treated for coronary heart disease
- Diabetes is slightly higher in their ALS population research in England national health databases
May the ALS phenotype be explained as part of the spectrum of paraneoplastic diseases?

Adriano Chio (University of Torino, Torino, Italy)
(achio@usa.net)

- Cancer related relationships with ALS risk
- Controversial still
- looked at 1260 patients in Piemonte and Valle d'Aosta from 1995-2004
- Only included patients that had cancer occur 6 months +/- ALS DX
- 46 patients (3.7%) had cancer in these criteria
  - Lung, breast and GI tract are the highest
  - No gender preference - about 50/50
- Survival of patients with Cancer and ALS was lower, as expected
- Data suggests, cancer, predominantly lung and breast cancer, has an incidence significantly higher than expected in ALS population.
- Still need bigger numbers to review and determine the actual likely risk or associated factors.

Epidemiology of ALS is the island of Ireland from 1995-2010

S. Byrne (Beaumont Hospital, Dublin, Ireland)
(suabyrne@hotmail.com)

- Epidemiology of ALS in the island of Ireland + Northern Ireland
- 2005-2010 data
- using data from the Irish registry was established in 1995 by orla hardiman
- using northern Irish registry started in 2005 by victor Patterson
- looked at prevalent ALS cases as of December 31, 2010
- 511 Irish people with ALS from 2005-2010
- 208 northern Irish PALS during same period
- Incidence oppurtunity does seem to be about the same by looking at age demographics
  - Average age of DX is 65 for both
  - Northern Ireland women seem to get it later on average though
  - Site of onset is about the same - 35 bulbar, rest lumbar
- Prevalence
  - 6.8 per 100,000 people about 15 years old - Ireland
  - 6.4 per 100,000 people about 15 years old - Northern Ireland
- FALS
  - 7.8% in Ireland
  - 6.7% in Northern Ireland
- Riluzole
  - >90% usage in both
- Some differences in NIV, gastro
- Survival difference seems to be there with
  - 45 months in Ireland from symptom onset
- 31 months in n.ireland from symptom onset
- is there a clinic effect?
  - discussed the multidisciplinary approach used in Ireland at orla's clinic
    - conducted an analysis to see if there was an effect on survival of this approach
    - MDT shows a 9 month survival advantage among PALS in Ireland
- Ireland hasn't seen an increase in incidence rate since 1995
- Prevalent data shows while it is the same, the number of PALS living at any given time has gone up, which is important information to have for government funding
- However, overall, there hasn’t been an increase in survival over the time period outside of the minor overall effect from the MDT clinic work in Beaumont
- However, bulbar onset patients did have a trend toward survival improvement in Beaumont over the 1995-2010 survey...however, only about a 3 month gain
- have started to use gastronomy and NIV earlier today than a few years ago
Computer accessibility: recommending healthcare professionals as a resource for individuals with ALS

Sarah Feldman (Drexel University, Philadelphia, PA, USA)

(sfeldman@drexelmed.edu)

- Survey of 41 PALS on their use of computers, ease of use, knowledge of accessibility programs on the devices they have
- 27 males and 14 females with average age of 56yo and FRS of 30
- 56% used computers for pleasure only, 32% use for both work and pleasure
- On average use a computer a few times a week
- 63% said their use was limited due to accessibility issues
- 93% said they had some difficulty using a keyboard and/or a mouse
- 73% said they were unaware of accessibility options on their home computer
- 63% said they were limited but wanted to use more
- suggested that there is a lack of discussion of accessibility options between PALS and their healthcare professionals and commented that nurses and therapists should try and make it part of their regular rounds.

Self-assessed online symptom monitoring in ALS

Andre Maier (Charite University Hospital, Berlin, Germany)

(andre.maier@charite.de)

Talked about their first ever self-report clinical trial (127 self test reports)
50 PALS enrolled in Feb 2011 in a trial of anakinra (IL-1 agonist). They have to self-report every week over a period of 12 months. It is an open label trial.
Neurophysiological testing: steps towards earlier diagnosis
David Burke (University of Sydney, Sydney, AUS)
(david.burke@sydney.edu.au)

- F waver averages reflexes below, peripheral dysfunction
- (short interval intra-cortical inhibition)SICI response may be useful for cortical hyper excitability (significant reduction)
  - Challenge is that there are many potential neurodegenerative or neuromuscular diseases that this can suggest as result (Kennedys, etc)
- H Reflex tests used rarely outside Oz, but may hold promise as assistive diagnostic tool

Cortical hyperexcitability appears intrinsic to ALS
Steve Vucic (Sydney Medical School Westmead, Sydney, NSW, AUS)
(s.vucic@neura.edu.au)

- Threshold Tracking Transcranial Magnetic Stimulation (TMS)
- Cortical hyper excitability is an early feature of SALS MND (Vuciv 2006)
- Cortical hyper excitability is an early feature of FALS MND (Vuciv 2008)
- Research found that SICI will distinguish diseases - Kennedys vs. ALS
- Suggested that TMS technique may eventually be able to help measure glutamate excitotoxicity
- Suggested that TMS may be quicker and easier to perform that the traditional stimulation techniques
- Seems to be some early instability n cortical stimulation, which pseudo-normallizes overtime so that
Session 9C - Neuroimaging

The past, present and future of neuroimaging in ALS/MND
Martin Turner (University of Oxford, Oxford, UK)
(martin.turner@clneuro.ox.ac.uk)

- NAA – reduced in ALS and others
- TI analysis
  - changes in grey matter small but while matter large
- DTI studies have revolutionized the research process
- Corpus Collisom involvement identified overtime
- MRI work in SOD1 mouse 7 years now
- Interested in looking at endothelial cell change
- Neuroimaging in ALS in Miami 2013
- Hypothesized that ALS brain is more “athletic” brain network that works faster, etc – different structural architecture in ALS vs. non-ALS brain

MRI evidence of disease in pre-symptomatic SOD1 positive individuals at risk for developing FALS
Michael Benatar (University of Miami, Miami, FL, USA)
(mbena.tar@med.miami.edu)

- Neurodegenerative disease process starts well before symptom onset
- Study: Cervical cord MRS
  - 29 controls
  - 21 SOD + preFALS
  - 23 ALS DX FALS
- Not ready for an individual scan, still a group study – result of interest
- Cervical Cord DTI
  - FA up (Control 5)
  - RD down (ALS DX 4)
  - Early unpublished data suggests FA up in preFALS

A longitudinal 4-T MRI study of the anterior cingulate
Jonathan Katz (California Pacific Medical Center, San Francisco, CA, UCA)
(woolles@sutterhealth.org)

- PALS have a change in apathetic behavior
- Study conducted to see if there were potential markers in brain to explain this
- 17 PALS (non-demented) examined using MRI over a series of months
- Found same pretty small changed in anterior cingulated
- Still, the finding was under significance according to Katz
10B – Clinical Trials

ALS Trial Design – can we do better?
Robert Miller (California Pacific Medical Center, San Francisco, CA, USA)
(millerrx@sutterhealth.org)

- Trial design
- Phase 2 is the crucial step
  - Futility design phase 2 trial becoming popular
    - predict the outcome (improvement) and reject drug if null
    - commented that 5 lithium trials may be too many, may need to focus on collaboration more
  - Selection trial
    - Multi-dose trial
    - Dose comparison stage 1, stage 2 is best dose only vs. placebo
  - Sequential design
    - Mortality is the endpoint (creatine, valproate, and lithium - van der berg)
    - lead in design
    - Baseline slope for each patient, proved to add little power and delays treatment
  - called the Dexpramipexole the "nearly ideal" phase 2 trial design
    - However, no biomarkers used in the trial
- Historical controls in trials?
  - Not appropriate for phase 3 trials
  - Key issue: is there a "drift" or systematic change, or is there bias knowing that all patients are getting drug
    - Parkinson’s trials tried this and abandoned it because there is systematic drift
    - Millers group looked at historical controls of about 660 patients
      - WALS lithium trial (published in neurology recently)
      - 107 pals treated vs. 249 matched controls
      - No effect
      - compared the outcome to NEALS and Chio lithium trials, which should no bias to positive effect
- If we are looking for a 30% effect in FRS (with 60 patients)
  - 30 in each group on 39% power
  - But with 60 on drug with historical controls, you get above 90% power to ID 30%
- need for more biomarkers in trials, suggests all trials should have them
- Early treatment more effective (patients in early part of the disease and more likely to show positive response than those later on in disease process)
- In 2004 only 8% of PALS enroll in clinical trials, down from 34% in 1999
- Bedlack found that 25% enrolled in 2009
- 2/PALS/Site/Month
- Compared to other diseases - 5-10% of adults in cancer trials
Lithium
- 6 different trials
  - Fornai 44 pals (Italy)
  - Aggarwai 84 (NEALS)
  - Chio 171 (Italy)
  - Wicks 596 (PLM)
  - Miller 107 (WALS)
  - Vestsrate 133 (Netherlands)

_A randomized, double blind dose ranging study of memantine in patients with ALS_
K. Ming Chan (University of Alberta, Alberta, Canada)
(ming.chan@ualberta.ca)

- Memantine trial in Canada (University of Alberta)
- Low affinity, non-competitive NMDA receptor antagonist (used in AD patients with moderate onset)
- Antiglutamatergic, inhibits and reverse hyperphosphorylation of tau
- SOD1 studies - 2 of them - pre-symptoms was 9 day difference, post-symptoms was 7 days
- Phase 2 study design
  - Randomized to 2 different doses (BID: 5 mg vs. 10 mg), no placebo control
  - Outcome measures - ALSFRS, FVC and muscle strength
  - 29 enrolled, 24 went into the study - 12 at each dose (3 deaths and 1 withdrawal)
    - All sporadic cases, 50% were on riluzole
- Findings from the trial:
  - No statistical significance to decline in FRS, FVC, etc - although there was a trend...thinks that the trial group was too small to ID an effect anyways
  - MUNE median thenar muscles, just shy of significance
  - In the high dose group it was though, the average screwed it up
- Other studies:
  - Saperstein (2010)
    - Open label pilot of 20 people at 10 mg, showed decline in progression
- Suggestions: 2 of 3 phase 1/2 trials showing potential benefit. Should pursue a larger definitive phase 3 trial.

_A first in human study in ALS with the anti-Nogo-A monoclonal antibody_
GSK1223249. Preliminary results.
Pierre Francois Pradat (AP-HP Groupe Hospitalier Pitie-Salpetriere, Paris, France)
pierre-francois.pradat@psl.aphp.fr

- GSK1223249 (anti-nogo-A-mab)
- Phase 1/2A studies
  - Nogo-A is over expressed in skeletal muscle of ALS patients and such correlates with ALS-FRS score
- Placebo controlled with 76 patients
  - 5 cohorts 1 dose, 3 cohorts 2 doses (.01mg/kg - 15mg/kg)
  - 75% males in trial
  - 93% completed the study
  - 3 PALS had total of 6 SAEs
    - 2 died of respiratory problem associated with ALS progression
    - 1 PALS had a head injury due to an accidental fall
    - judged not to be related to the investigational product
- estimated of half-life of the mab was 20 days
- Data showed that the decline of FRS was slower in the high dose, only a trend, small sample size, not significant statistically (48% difference)
- Also a trend in FVC, but not statistically significant
- MMT tests also showed same outcome - trend, not significant statistically (50% difference)
- End conclusion
  - No safety or tolerability problems
  - Higher dose showed trends in endpoints
  - Next step is to analyze muscle biopsies
  - seek to initiate a large multi-center phase 2 trial

**Effects of NP001 treatment on monocyte/macrophage activation in PALS**

Robert Miller (California Pacific Medical Center, San Francisco, CA, USA)

- Nearly a decade long project now
- Inflammatory biomarkers - CD16
- NP001 is blocking macrophages from releasing cytokines
- 16 animals in g93A 2 mg/kg 6x21 day cycles 5 days IV, 16 days off starting at 65 days
  - 20 day response
- phase 1 trial
  - 32 patients (6 in each dose level group)
  - confirmed that there was elevated CD16 and DR values were related to disease progression
  - After single dose, they saw that decline with greater effect with greater dose on CD 16 levels
- phase 2 trials
  - 17 sites, 136 subjects have been enrolled
  - 2 doses, placebo controlled
  - 6 months of infusions, 3 month follow-up
  - will report results of phase 2 at next years meeting in Chicago
**Session 11A – Disease Models**

*Optimising stem-cell derived models for ALS research*

Kevin Eggan (Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA) ([eggan@mcb.harvard.edu](mailto:eggan@mcb.harvard.edu))

- advantages propositions
  - Since they are made from humans, remove the "mouse or man" debate
  - can make a lot very quickly
  - No need to over express mutant proteins
  - do not necessarily need to know the genetic issues involved to model ALS
- How do they do it?
  - Day 0 heS Medium, day 4 N2 medium, Day 10 RA+SHH, Day 25 neurabased medium (29 day differentiation with Duel SMAD with patterning with Retonic Acid and Sonic Hedgehog pathway agonist)
  - depending on the particular experiment, between 10-40% of the resulting cells are motor neurons
  - become active following 7 days of culture
- showed data that confirmed that they were able to create motor neurons that would exist in both the brain (IL marker) and spinal cord (HoxA5, HoxC8)
- by 15 days there is a trend toward number of MN in SOD1 A4V iPS cells, 30 days the size goes now (or a deficit of large motor neurons)
  - this suggests a cellular phenotype of ALS
- No large scale aggregates of SOD1 occur over 30 days of MN culture in controls or SOD1A4V cases
- Next steps:
  - Next to get a good purification technology up and running to isolate only MN
  - start building other models and importantly compare their phenotype without genetic variants of disease.

*Neuronal expression of ALS-linked TDP43 in mice is sufficient to trigger adult-onset motor neuron disease*

Paul Wong (Johns Hopkins University, Baltimore, MD, US) ([wong@jhmi.edu](mailto:wong@jhmi.edu))

- TDP43 mice
- cytoplasmic inclusions are not immuno-positive for TDP
- Mitochondria in MNs is altered
- Modest expression of WT or mTDP43 contributes to risk in ALS
  - more in cyto leads to RNA splicing issues which cases mito transport issues which leads to cell death
- They have 3 lines; one is low-expressing others that are high-expressers die very quickly
Overexpression of human wild type FUS results in motor dysfunction and death in homozygous mice

Jacqueline Mitchell (Kings College, London, UK)
(Jacqueline.mitchell@kcl.ac.uk)

- FUS mouse model
- weighed and observed and scored, looked at brain and spinal cord pathology
- confirmed expression of the transgene using staining
- 2X heterozygous expression in western blot
- From 4 weeks old, they failed to gain any weight
- At end stage they lose weight quickly
- live on average 82 days +/- 12 days
- get shaky at 4 weeks old and some stilted gait
- 8 weeks old they have gait issues
- 11/12 weeks they are euthanized
- Rotor-rod results significant impairment from 4 weeks on
- FUS and Ubiquitin do not co-localize in spinal cord in the mouse, same as the findings in the human samples examined
- FUS profoundly regulates its own expression in vivo
- Phenotype is associated with a significant increase in cytoplasmic FUS levels
Session 11B – Respiratory Management

*Traditional ventilation monitoring may underestimate the ventilator requirements of MND Patients*

R. Angus (Walton Centre for Neurology & Neurosurgery, Liverpool, UK)  
(carolyn.young@thewaltoncenter.nhs.uk)

- Ventilator of PALS in UK (cheshire and mersey)  
- Followed 35 people into a long-term survey of their physiological and emotional impact of NIV (have a year of data on 12 of those people)  
- Question remain about what type of monitoring should we be doing of PALS on NIV  
- How do you put together a program for the benefit of the patient?  
- 10 people (ave/age is 62), 9 Males, 3 bulbar onset

*Current and practical utilization of diaphragm pacing in ALS/MND: from piolet trail experience to FDA humanitarian device approval indications for helping respiration*

Raymond Onders (University Hospitals Case Medical Center, Cleveland, OH, USA)  
(raymond.onders@uhhospitals.org)

- FDA approved it under strict guidelines  
  - FVC can’t be less than 45% predicted  
  - Full FDA report is now online H100006 (all the data is there)  
  - Safety data was the outcome measure of importance  
- breathing dysfunction involved both UMN and LMN issues  
- targeting here of the phrenic nerves  
- been working on this for 16 years  
- have implanted on ALS patients for the last 12 years  
- 66 PALS have been evaluation, 52 have actually been implanted  
- 88% get the PEG tube at the same time  
- Also 100% get information about the end of life issues that may arise  
- Why not allowed?  
  - No evidence of chronic hypoventilation  
  - No evidence of stimulatable diaphram  
  - A couple others