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Research News

Mapping the Landscape of ALS Precision Medicine Initiatives

The big data revolution in ALS has begun, bringing with it excitement and expectations for transforming diagnosis and patient care. Multiple large initiatives are currently underway to collect and analyze such data from ALS patients, all aimed at identifying causes of the disease, biomarkers, and treatments. In this article, we provide an overview of ongoing big data/precision medicine projects in ALS in order to map out the landscape of projects, the opportunities for collaboration and new resources that will become available to the research community.

Loss of C9ORF72 Impairs Macrophage and Microglial Function

Repeat expansions in the C9ORF72 gene, the most common cause of familial ALS and FTD, cause a decrease in C9ORF72 expression, suggesting that loss of function may play a role in pathogenic mechanisms of these diseases. In the March 18 Science, researchers describe two mouse models lacking the C9ORF72 gene. Intriguingly, the mice do not exhibit motor neuron degeneration, but rather inflammation and impaired immune responses in macrophages and microglia. Several of the dysregulated immune pathways were also found to be disrupted in human C9ORF72 expansion carriers. These findings suggest that C9ORF72 is necessary for myeloid cell function, and microglia may play an important role in C9-ALS.

The C9ORF72 Poly(GA) Dipeptide Repeat Impairs Nucleocytoplasmic Transport in Mice

Dipeptide repeat proteins (DPRs) translated from hexanucleotide repeat expansions in the C9ORF72 gene, have been implicated as mediators of neurotoxicity caused by this mutation. A new study, published in the March 21 Nature Neuroscience online, examined whether a specific DPR species, previously shown to form neurotoxic inclusions in culture, would be toxic in vivo. When aggregation-prone poly(GA) was

expressed in the mouse brain, it caused neuronal death in multiple brain regions and sequestered HR23 proteins, which transport proteins from the nucleus to the proteasome for degradation. Interestingly, TDP-43 inclusions, the pathological hallmark of ALS and FTD, were absent following poly(GA) expression, suggesting that poly(GA) alone is not sufficient to recapitulate all aspects of C9-ALS and FTD pathology.

Revving Up the Heat Shock Response Could Protect Neurons and Muscles
Two new studies suggest that revving up chaperone activity could protect degenerating motor neurons and muscles. In the March 23 Science Tranlsational Medicine, researchers demonstrate that the experimental drug arimoclomol (also in clinical testing for SOD1-ALS), which increases heat shock protein (HSP) expression, improved muscle function and reduced mislocalization of TDP-43 in the inflammatory and degenerative muscle disease inclusion body myositis (IBM). A Phase II trial in IBM is slated for later this year. A second study in the March 1 Brain reported that HSP activation could help clear TDP-43 aggregates in cell culture, providing additional evidence that activating HSPs could help in ALS and other neurodegenerative diseases.

Eisai Withdraws New Drug Application for Ultra-high Dose Mecobalamin for ALS in Japan
Japanese Pharmaceutical company Eisai Co. has withdrawn its New Drug Application for ultra-high dose mecobalamin (E0302) for ALS in Japan. Last May, the company submitted the New Drug Application for a form of the vitamin B12 that is already approved in Japan for treatment of other indications (see May 2015 news). However, recent meetings with the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory authority, clarified that the data was insufficient for approval and Eisai subsequently withdrew its application. It is unclear whether the company will continue its development efforts of mecobalamin in ALS.

Deals and Partnerships

ALS TDI and Denali Therapeutics Partner to Identify New ALS Clinical Trial Endpoints
The ALS Therapy Development Institute (ALS TDI) and startup company Denali Therapeutics have launched a new partnership to identify potential new ALS clinical trial endpoints, with the aim to improve tracking of disease progression and effects of therapeutic interventions in clinical trials. The partners will analyze data collected through ALS TDI's Precision Medicine Program (PMP), including disease progression data collected through accelerometers worn by PMP participants. Functional data from these devices could potentially reveal better endpoints for tracking ALS disease progression, and ultimately reduce the cost and time needed to determine drug efficacy in ALS clinical trials.

Origent and Cytokinetics Collaborate to Develop Predictive Analytics Model of ALS
Data analytics company Origent Data Sciences has launched a collaboration with biotechnology company Cytokinetics to test and validate its computational models on

ALS clinical trial data. Origent, a winner of the winner of the ALS Prediction Prize4Life Challenge (see Nov 2012 news), has developed algorithms for patient-level prediction of disease progression as a means to improve clinical trial design and efficiency. The collaboration with Cytokinetics will provide Origent with its first opportunity to prospectively validate its models, using clinical data derived from the ongoing Phase III trial of tirasemtiv in ALS (see July 2015 news). If validated, the results will be submitted to the FDA to potentially open the door to new models for ALS clinical trial design.

Funding Opportunities:

Department of Defense ALS Research Program (ALSRP) Therapeutic Development Award. Pre-application due April 14, 2016.

Department of Defense ALS Research Program (ALSRP) Therapeutic Idea Award. Pre-application due April 14, 2016.

FTD Biomarkers Initiative. Letter of Intent due April 15, 2016.

ALS Canada Discovery Grants. Full application due June 3, 2016.

Full List of Funding Opportunities >>

Upcoming Meetings:

April 2016

April 6-7, 2016: Boston, MA: Neurotech Investing and Partnering Conference.

April 15-21, 2016: Vancouver, BC: American Academy of Neurology Annual Meeting.

May 2016

May 9-11, 2016: Seoul, Korea: International Conference on Molecular Neurodegeneration.

May 16-19, 2016: Philadelphia, PA: Biomarkers and Diagnostics World Congress

June 2016

June 5-9, 2016: Whistler, BC: Keystone Symposium: Autophagy, Molecular and Physiological Mechanisms.

Full List of Upcoming Meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

TargetALS Cores

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