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Tell us what interests you! As we explore ways to improve the ALS Research Forum, we would like to hear your input on what resources you would find most useful. Please respond to a brief, 5-question survey: https://www.surveymonkey.com/r/2016_ALSRF Thank you for your time and feedback!

Research News

ALS Rates Predicted to Soar

As the human life expectancy continues to increase in many regions of the world, so may the prevalence of chronic diseases associated with aging. But the number of ALS cases is predicted to increase at a startling rate - nearly 70% - over the next few decades, according to a study published in the August 11 Nature Communications. The investigators integrated data from 10 studies of ALS incidence across the globe, and then developed software to predict future ALS rates, based on projections of population growth and aging. Based on these models, they projected an increase from an estimated 220,000 ALS cases worldwide in 2015 to over 375,000 cases in 2040. Such numbers highlight the importance of increased ALS research funding and improved patient care.

Disrupted Mitophagy Pathway Links ALS and Childhood Neurodegenerative Disease

Heterozygous mutations in sequestome 1 (SQSTM1) have been implicated in ALS and FTD (Fecto et al., 2011; Rubino et al., 2012). The gene encodes for an autophagy adapter protein called p62, which helps target proteins and mitochondria to autophagosomes for disposal. A study published in the September 1 American Journal of Human Genetics describes a third neurodegenerative disease caused by mutations to SQSTM1, which is characterized by childhood onset and gait abnormalities, ataxia and cognitive decline. Fibroblasts from patients do not express p62 and show signs of impaired mitophagy, such as a reduced number of autophagosomes. The study

expands the scope of diseases associated with impaired autophagy, and further underscores the role of this pathway in neurodegenerative diseases.

Conserved Region of TDP-43 Ensures Phase Separation of RNA Granules
A pathological hallmark of ALS is the appearance of cytosolic aggregates of TDP-43 in structures known as RNA stress granules, cytosolic membrane-less organelles composed of RNA and RNA-binding proteins. Are the aggregates toxic or is a loss of TDP-43 function causing cellular toxicity? According to a paper in the August 18 Structure, ALS-causing mutations in a conserved, unstructured region of TDP-43 impair an important function of the protein: forming a liquid-liquid phase separation between RNA granules and the surrounding cytoplasm (see Oct 2015 news). In complementary studies published in August 2 Cell Reports, researchers found that in cell culture, deletion or mutations in this conserved domain impaired formation of phase-separated liquid droplets in the cell. These studies highlight this specific domain of TDP-43 as a potential target for therapeutic interventions.

New Brain Mapping Method Uses Sequencing, Not Microscopes
A new brain mapping method, called MAPseq (Multiplexed Analysis of Projections by Sequencing) can trace the axonal projections of individual neurons using sequencing technology rather than microscopy. In the September 7 Neuron, researchers describe a method to label neurons in the brain with an engineered virus that contains a large library of unique, 30-nucleotide RNA sequences, which serve as a barcode. Barcode mRNA is transported along axonal projections and accumulates at the axon terminals. Next, the RNA from target regions of interest is extracted and sequenced, and the RNA barcodes are with the neurons of origin. This novel technique can help decipher brain circuitry at the single neuron resolution, and may in the future yield insights about how these circuits are affected by disease.

Cognitive and Behavioral Changes in ALS Not Associated with End of Life Wishes, Study Finds
In 2015, California became the fourth state to permit terminally ill patients to end their lives with prescribed medications. ALS clinicians are striving to understand possible associations between the wish to die and cognitive, behavioral, or psychiatric changes, since ALS patients are up to 10 times more likely than cancer patients to request to end their lives. A recent study in 247 ALS patients, published August 5 in Neurology, found no association between desire to end life and behavioral or cognitive changes, based on questionnaires of psychiatric measures and the results of the Cognitive Behavioral Screen. Patients with behavioral deficits, but not cognitive impairment, were at highest risk of depression, suggesting the need for improvement management of these symptoms.

Drug News

Denali Embarks on New Partnerships and RIP1 Inhibitor Phase I Trial
Denali Therapeutics is expanding its portfolio and establishing partnerships to break

new ground in the treatment of neurodegenerative disease, including ALS (see May 2015 news). The company has announced the filing of its first clinical trial application for a Phase I clinical trial in Europe to test inhibitors of of receptor-interacting protein 1 (RIP1), kinases that have been implicated in neuroinflammation and glial dysfunction in the CNS (see Feb 2014 news). Data from this trial will help shape the design of future RIP1 clinical trials in ALS and Alzheimer's disease. Some additional programs include development of LRRK2 inhibitors for Parkinson's disease, bi-specific antibodies to cross the blood-brain barrier, and a previously announced collaboration with ALS TDI on ALS clinical trial endpoints (see March 2016 news).

Flex Pharma to Begin Phase II Efficacy Trial to Tackle Muscle Cramps in ALS
Flex Pharma, a biotechnology company developing treatments for neuromuscular disorders, has initiated a Phase II clinical trial of FLX-787 for treating muscle cramps and spasticity in ALS. FLX-787 is a small molecule transient receptor potential (TRP) ion channel activator, which prevents repetitive firing of the spinal motor neurons that control muscle contractions. The randomized, controlled and blinded trial will take place in Australia. Flex Pharma was co-founded by scientific leaders in the area of ion channels, including Roderick MacKinnon of Rockefeller University and Bruce Bean of Harvard Medical School.

Bell Biosystems is Developing Magnetic Organelles to Track Cell Therapies in ALS Â
Biotechnology startup company Bell Biosystems is developing a unique approach to improve in vivo tracking of cell therapies following transplantation, and they are targeting applications in ALS. Bell Bio's Magnelle contrast agents are derived from magnetotactic bacteria (MTB), a type of non-pathogenic bacteria that can be visualized on MRI. Cells labeled with Magnelles can be tracked longitudinally in vivo by MRI and provide information on migration, engraftment and survival of transplanted cells. Preclinical studies in rodents have demonstrated the utility of Magnelles in tracking transplanted stem cells for cardiovascular applications (Mahmoudi et al., 2016). The company has recently announced the award of a Phase II SBIR grant from the NIH to test applications of the technology to cell therapies in ALS in collaboration with Clive Svendsen from Cedars-Sinai Medical Center in Los Angeles.

Funding Opportunities:

September 2016

Frick Foundation for ALS Research Grants. Application due Sept 30, 2016.

October 2016

CIRM Accelerating Therapies: Public-Private Partnership Program (ATP3). Application due Oct 31, 2016.

December 2016

MDA Investigator-Initiated Research Grants. LOI due Dec 15, 2016.

MDA Young Investigator Development Grants. LOI due Dec 15, 2016.

Full List of Funding Opportunities >>

Job Opportunities:

Director, Neuroscience Research & Drug Discovery, Verge Genomics, San Francisco, CA.

NEW! Postdoctoral Position, Roger Sher Lab, Stony Brook University, Stony Brook, NY.

NEW! Postdoctoral Position, Joe Lewcock Lab, Denali Therapeutics, South San Francisco, CA.

Full List of Job Opportunities >>

Upcoming Meetings:

Please note the abstract submission deadline for AD/PD 2017 is Sep 29, 2016 and for AAN is Oct 24, 2016.

October 2016

Oct 16-18, 2016: Baltimore, MD: American Neurological Association Annual Meeting.

Oct 19-21, 2016: London, UK: The Lancet Neurology Conference: Preclinical Neurodegenerative Disease.

November 2016

Nov 10-11, 2016: San Diego, CA: RNA Metabolism in Neurological Disease.

Nov 12-16, 2016: San Diego, CA: Society for Neuroscience Meeting.

December 2016

December 7-9, 2016: Dublin, Ireland: International Symposium on ALS/MND.

March 2017

Mar 29-Apr 2, 2017: Vienna, Austria:International Conference on Alzheimer's and Parkinson's Diseases. **Abstracts due September 29, 2016.**

April 2017

April 22-28, 2017: Boston, MA. American Academy of Neurology Annual Meeting. **Abstracts due October 24, 2016.**

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

Target ALS Core Facilities