DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 87 **June 4, 2013**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. Please forward this e-newsletter to friends and colleagues who may be interested in learning more about ALS.

Resources:

Visit the PRO-ACT Database atwww.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

Funding News:

ALS Research Program Announcements Released: including Therapeutic Development Award and Therapeutic Idea Award.Deadline for pre-application is June 5.

Request for Proposals:Accelerating Drug Discovery for Frontotemporal Dementias. Letter of Intent due before August 22, 2013.

Upcoming Webinar:

The ALS Association's Research Update Webinar Series continues with Dr. Steven Burden of NYU Medical Center who will be discussing MusK agonists as a treatment for ALS. The webinar will be held on Tuesday, June 18, 2013 at 4pm EST. Click here to register.

Research News

The Power of Three: Genetic Trios Yield ALS Gene Candidates

A new study published in *Nature Neuroscience* on May 26, 2013 shows the "power of three" in genetics. First author Dr. Alessandra Chesi, along with senior co-author, Dr. Aaron Gitler of Stanford University in Palo Alto, California sequenced the exomes of 47 ALS patient-parent trios to see if they could identify new candidate genes associated with sporadic ALS. Their efforts led to the identification of 25 new genes that are potentially linked to ALS. Although there was no overlap between the 25 genes (each gene mutation identified only showed up in a single trio), several genes did group into similar functional categories, including five genes that are associated with chromatin remodeling. One gene in particular stood out from the rest as a potential ALS risk factor (the researchers even found that this gene associates with another well-known ALS-linked gene). Want to know the identity of this candidate ALS risk factor? Click here to read Dr. Amber Dance's coverage of this exciting story.

Scientists Create Human Stem Cells by Somatic Cell Nuclear Transfer

Researchers led by Dr. Shoukhrat Mitalipov from Oregon Health & Science University in Portland, Oregon have made a groundbreaking advance, using somatic cell nuclear transfer (SCNT) to generate human embryonic stem (ES) cells. These findings were published online on May 15, 2013 in*Cell*. The SCNT-derived ES cells have the ability to differentiate into any type of cell and become fully functional, for example the authors showed that cardiomyocytes generated from the SCNT-derived ES cells actually beat. One day this method could potentially be used to offer people with neurodegenerative diseases such as ALS sources of genetically-matched cells. Looks like the SCNT-derived ES cells are going to give iPS cells a run for their money. Click here to read the full story (and if you want, you can even watch the short video of the beating cardiomyocytes).

Although these results are exciting, they have not been without controversy. In fact, barely a week after publication, an anonymous poston PubPeer suggested that the *Cell* article reused some of the same images for different figures. The last group to publish findings suggesting they could use SCNT to create human ES cells was Woo Suk Hwang's laboratory in 2004. As it turns out, these earlier papers contained data that was completely fabricated. Is this a repeat situation? Click here to read the Nature News coverage of the story, and find out what Dr. Mitalipov claims really happened.

Upcoming Meetings:

June 10-11, 2013: Cambridge, MA: New Avenues for Brain Repair: Programming and Reprogramming the Central Nervous System

June 12-15, 2013: Boston, MA: International Society for Stem Cell Research

June 16-21, 2013: Les Diablerets, Switzerland:Inhibition in the CNS

June 18, 2013: Boston, MA:US-India BioPharma & Healthcare Summit

June 23-27, 2013: Boston, MA: DIA 49th Annual Meeting

June 29-30, 2013:Philadelphia, PA: The ALS Clinical Research Learning Institute

July 7-12, 2013: Smithfield, RI: Gordon Research Conference: Human Genetics & Genomics

August 10-16, 2013: Andover, NH: Gordon Research Conference: Cellular & Molecular Mechanisms of Toxicity

September 21-26, 2013: Vienna, Austria: XXIth World Congress of Neurology: Neurology in the Age of Globalization

Stem Cells Engineered to Express GDNF and VEGF Improve Survival in ALS Rats

In a study published in *Molecular Therapy* on May 28, researchers led by Dr. Masatoshi Suzuki, assistant professor of comparative biosciences at the University of Wisconsin-Madison School of Veterinary Medicine, showed that treating SOD1 rats with modified human mesenchymal stem cells (hMSCs) delayed disease onset and prolonged survival in the rats. The modified hMSCs were engineered to express one of four growth factors, including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor-I (IGF-I), or glial cell line-derived neurotrophic factor (GDNF). Intriguingly, the four factors did not have the same effects; hMSCs expressing IGF-I or BDNF had no observable effect, while treatment with hMSCs expressing VEGF or GDNF "prolonged survival and slowed the loss of motor function." However, the researchers unexpectedly observed the greatest effects when they treated the rats with both VEGF and GDNF.

SCA and ALS-linked Gene Ataxin-2 Also Regulates Circadian Clock

Dr. Ravi Allada, professor of neurobiology at Northwestern University, working with postdoctoral fellow, Dr. Chunghun Lim, recently discovered that the neurodegenerative disease-linked gene, ataxin-2, is responsible for helping to regulate the body's circadian clock. Polyglutamine expansions in ataxin-2 have long been linked to spinocerebellar ataxia type 2 (SCA2). In 2010, Dr. Aaron Gitler and Dr. Nancy Bonini discoveredthat intermediate glutamine expansions (more than 22 but less than 34) in ataxin-2 are also associated with a higher risk of ALS. In the recent study, using *Drosophila*, the researchers found that normal ataxin-2 helps regulate the translation of the protein period (or PER), which is an important regulator of an organism's circadian clock. Interestingly, people with SCA2 often have a disrupted circadian clock early on in their disease course, although we are unaware of any studies exploring such a link in ALS.

Drug News

Initial Results from Collaboration between ALS-TDI and to-BBB Appear Promising

Earlier this year, The ALS Therapy Development Institute (ALS TDI) and Dutch biotech company to-BBB announced their formal collaboration to test the pharmacokinetics of to-BBB's therapy, 2B3-201, in SOD1 mice. to-BBB is known for their development of a liposome-based drug delivery system capable of crossing the blood-brain barrier, called G-technology. The 2B3-201 therapy is G-technology encapsulated methylprednisolone, which enables delivery of methylprednisolone to the brain for the treatment of neuroinflammation. The results of ALS-TDI's initial pharmacokinetic studies looking at uptake of 2B3-201 in the spinal cords and brains of SOD1 mice were positive. Based on these exciting results, ALS-TDI has initiated a larger survival study in SOD1 mice. Going forward, ALS-TDI will continue to investigate 2B3-201, as well as other promising ALS therapeutics in the to-BBB pipeline. Read more about to-BBB's ALS initiatives here.

Genervon Receives FDA Approval for Their Phase II Trial in ALS

Genervon Biopharmaceuticals discovered GM6 over ten years ago when they were working to identify a "master regulator" of multiple cellular pathways that could "correct defects in the nervous system". GM6 (also called GM604) is a short peptide derived from motoneuronotrophic factor (MNTF), a protein involved in embryonic development. Genervon claims that GM6 regulates over 4,000 different genes, including modulating over 80 ALS-related genes. This past December,

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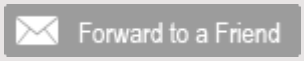

Genervon announced thatGM604 extends the life of SOD1 mice by 30%, and can delay the onset of ALS symptoms in these mice by 27%. Now, Genervon reports additional exciting news; they recently received FDA approval for testing GM604 in a Phase IIa clinical trial in ALS. Genervon will soon be recruiting 12 patients for its broadly inclusive Phase IIa trial at two different locations:Massachusetts General Hospital and Columbia Medical Center in New York. Genervon also recently received approval for a Phase II study of GM6 in Parkinson's disease, and they are currently recruiting patients for their Phase II study in Ischemic Stroke.

KineMed and MedImmune Partner to Study Prion Protein Dynamics
California biotech KineMed recently announced that they are partnering with MedImmune to investigate how an antibody directed against the cellular prion protein (PrP) will influence the "turnover and expression" of PrP. Although this research will primarily inform neurodegenerative diseases including Creutzfeldt-Jakob disease and potentially Alzheimer's disease (there is still a great deal of debate about whether PrP is involved in Alzheimer's), these studies could also yield information that could be beneficial for ALS. KineMed is already committed to developing therapeutics for ALS. Hopefully, positive results from the antibody-PrP study will convince KineMed and MedImmune to look into antibodies that target SOD1. Amorfix, Biogen Idec, and Neurimmune are already working to identify antibodies that target the misfolded pathogenic SOD1 proteins; read more about these initiatives here.

Neuralstem's NSI-566 Shows Promise in Rat Spinal Cord Injury Model
A recent study out of Dr. Martin Marsala's laboratory at the University of California, San Diego School of Medicine showed that Neuralstem's spinal cord-derived human neural stem cells, NSI-566, had positive benefits in a rat model of spinal cord injury. The rats were treated with the stem cell therapy three days post injury. Eight weeks post treatment, the rats showed significant improvements in motor function, including paw placement, and even showed "amelioration of spasticity." In April, Neuralstem announced that the FDA approved their Phase II study to inject NSI-566 directly into the spinal cord for the treatment of ALS. To learn more about this trial click here. Also, be sure to watch this informative presentation by Richard Garr, Neuralstem's CEO and President, from the 8th Annual World Stem Cells & Regenerative Medicine Congress 2013 held in London, UK from May 21-23, 2013. Garr discusses in detail Neuralstem's Phase I ALS trial results and their next initiatives in ALS.

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