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National Tay-Sachs & Allied Diseases Association, Inc.

Friday, AUGUST 19, 2016

NTSAD Monthly Research Review

A NOVEL THERAPY: AN OVERVIEW

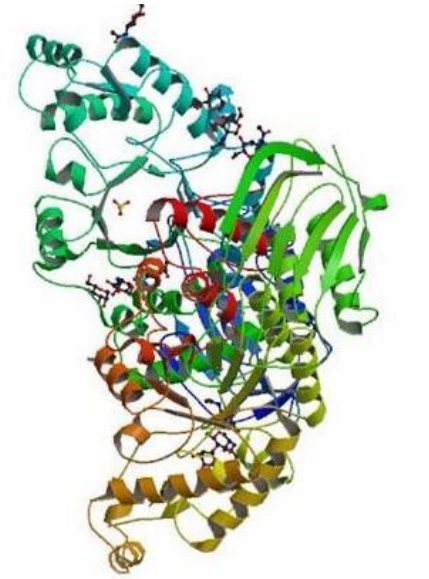
One of the challenges of treating GM2 gangliosidosis by gene therapy is finding a means to deliver the two necessary genes, HEXA and HEXB. A new approach to overcoming this hurdle was introduced in two publications recently detailing a novel variant of hexosaminidase called HexM.

So, what is the issue with HexA?

Hexosaminidase A (HexA), the enzyme responsible for the degradation of GM2 ganglioside, exists as a heterodimer meaning that it is composed of 2 different subunits: α and β, which are both required for maximum stability and functionality of the protein. The two subunits are encoded by 2 different genes, HEXA and HEXB. For gene therapy approaches it would be best to deliver the HEXA and HEXB genes in the same viral vector; however, the small packaging capacity of adeno-associated viral (AAV) vectors does not afford simultaneous delivery of these 2 genes because of their size (together sized ~3.2 kb). Alternatively, to date a 2 vector system has been utilized in which 1 vector has been used to deliver the HEXA gene and a separate vector to deliver the HEXB gene (AAV-HEXA + AAV-HEXB).

And what is HexM?

A hybrid subunit, named μ, was created to combine only the key portions the α and β subunits necessary for degrading GM2 ganglioside. A μ - μ homodimer forms a steady enzyme called HexM. The smaller size, ~1.6 kb, allows the HEXM gene to fit inside of an AAV vector.



Crystallographic structure of human beta-hexosaminidase A: interpretation of Tay-Sachs mutation and loss of GM2 ganglioside hydrolysis. Lemiux MJ et al. J Mol Biol. June 2006, 359(4): 913-929.

Rally & Raise Funds for Research

What did these two new studies find?

Novel Vector Design and Hexosaminidase Variant Enabling Self-Complementary Adeno-Associated Virus for the Treatment of Tay-Sachs Disease.
Published in Human Gene Therapy. July 2016, 27(7): 509-521. *Karumuthil-Melethil Subha, Nagabhushan Kalburgi Sahana, Thompson Patrick, Tropak Michael, Kaytor Michael D., Keimel John G., Mark Brian L., Mahuran Don, Walia Jagdeep S., and Gray Steven J.*

* An AAV vector encoding the HEXM gene (AAV-HEXM) was injected into the brain of 15-month-old Tay-Sachs mice and brains were analyzed 4 weeks post injection.
* AAV-HEXM was capable of clearing GM2 ganglioside storage in the regions that were injected; however, complete widespread clearance of GM2 was not achieved.
* Intravenous delivery of AAV-HEXM to neonatal (day 0-2) Tay-Sachs mice showed that the hind (caudal) brain had more complete reduction of GM2 ganglioside storage than the forebrain (rostral) 15 months after injection.

Due to an alternative ganglioside degradation pathway in mice that is not present in humans, the mouse model of Tay-Sachs disease does not replicate the biochemical, pathological, or clinical signs seen in human patients. For this reason Sandhoff disease mice are primarily used as the murine model of GM2 gangliosidosis. Therefore, a companion article was published detailing efficacy studies of AAV-HEXM gene therapy in the Sandhoff mouse model.

Systemic Gene Therapy Transfer of a Hexosaminidase Variant Using an scAAV9.47 Vector Corrects GM2 Gangliosidosis in Sandhoff Mice.
Published in Human Gene Therapy. July 2016, 27(7): 497-508. *Osmon Karlaina J.L., Woodley Evan, Thompson Patrick, Ong Katalina, Karumuthil-Melethil Subha, Keimel John G., Mark Brian L., Mahuran Don, Gray Steven J., and Walia Jagdeep S.*

* Neonatal (day 0-1) Sandhoff mice were treated with intravenous (IV) delivery (through superficial temporal vein) of AAV-HEXM.
* Sandhoff mice treated with IV delivery of AAV-HEXM had a mean survival of 42 weeks of age (range 36-49 weeks, n=6), compared to untreated Sandhoff mice which live to ~15 weeks of age.
* Gene therapy treated Sandhoff mice showed behavior improvements including superior performance on open

The field of rare disease research is expanding. New technologies are developing. Really smart people are dedicated to hurdling the neurological roadblock so we can have treatments for these diseases. **All of these efforts need funds to keep moving forward to the finish line!**

All events held for **Day of Hope** go to NTSAD's Research Initiative Fund which allows NTSAD to make grants to those really smart people. To see if an event is happening near you, click **here** for HOPE.

DAY OF HOPE NTSAD 9.17.2016

So...let's make this a big year. Contact Joan at NTSAD to make things happen at **joan@ntsad.org**.

MILLION DOLLAR BIKE RIDE
Request for Proposals

The 2016 MDBR Grant Program is now open!

The Request for Applications (RFA) on the Orphan Disease Center website, **here.**

First step is the Letters of Intent (LOI) and they are due no later than 8:00pm on Friday, September 16, 2016.

These grants are open to the international community (not limited to UPenn and CHOP). *Only academic institutions and nonprofit organizations are*

field test and rotarod assessments when compared to untreated Sandhoff mice.
* There was no significant increase in the hexosaminidase enzyme activity in the brain of Sandhoff mice after IV gene therapy at 8 weeks of age or long-term when compared to untreated Sandhoff mice.
* The authors noted that while this study demonstrated improvements in survival and behavior, future studies will be required to look at 1) the effect of increasing the dose of the gene therapy and 2) investigate the ability of this vector to cross the blood-brain barrier.

Studies assessing intravenous delivery to older (6 weeks old) Sandhoff mice as well as CSF delivery of AAV-HEXM are ongoing.

A Summary from the New Hope Research Foundation and Jack Keimel, Founder

The key to successful gene therapy for treatment of CNS neurodegenerative diseases is the development of methods to deliver the gene vector broadly and evenly throughout the brain and spinal cord. The New Hope Research Foundation has focused their research on using safe methods for injecting the gene vector to achieve broad distribution. For these methods to be effective, a new enzyme was developed, called HexM, which can be packaged within a small viral capsid (adeno-associated virus, AAV). Their recent research publications have shown that this new enzyme is twice as effective as the natural HexA enzyme in degrading GM2 ganglioside and that gene vectors using the genetic code for HexM can be effectively delivered broadly to the brain and spinal cord of Sandhoff and Tay-Sachs mice using minimally invasive injection methods. The research is now transitioning to establish the efficacy of these methods in larger animal models.

Jack Keimel, Founder
New Hope Research Foundation

In order to foster collaborations in the rapidly advancing field of gene therapy, the **Tay-Sachs Gene Therapy Consortium** was established in 2007. Since its inception, the Consortium, comprised of scientists from an international coalition of institutions, has striven to perform the preclinical safety and efficacy studies needed

eligible.

NTSAD CORPORATE ADVISORY COUNCIL

We'd like to introduce two of our newest Corporate Advisory Council (CAC) members.

Laura Cohen is a team leader at Health Advances, a strategy consulting firm and hopes to bring her new product commercialization expertise to bring new products to the families who need them most.

John Gordon has moved from the board to the CAC and will continue to advise NTSAD about advancing their research based on his knowledge gained working in biotech and pharma consulting.

Read more about them and NTSAD's Corporate Advisory Council **here**.

The CAC advises NTSAD about its efforts to direct, fund and promote the development of treatments and cures for the NTSAD family of diseases. It counsels NTSAD in expanding its evolving partnership model, recommend research strategies and assists NTSAD in leveraging its full range of capabilities.

for the first in-human clinical trials of gene therapy for Tay-Sachs and Sandhoff diseases.

Review of previous findings with two vector systems

Effective gene therapy in an authentic model of Tay-Sachs-related diseases. PNAS. July 2006, 103(27): 10373-10378. Cachon-Gonzalez Begona, Wang Susan, Lynch Andrew, Ziegler Robin, Cheng Seng, Cox Timothy.

* In 2006 Begona Cachon-Gonzalez and Tim Cox published a study in which 4 week old Sandhoff mice were treated by either a single or 4 direct brain injections of a 2 vector system AAV-HEXA + AAV-HEXB.
* Sandhoff mice that received a single brain injection had a mean survival of 199 ± 17 days (n=6) while mice that received 4 brain injections had a mean survival of 261 ± 89 days (n=10), compared to untreated Sandhoff mice which had a mean survival of 121 ± 6 days.
* Enzyme activity was greatest near injection sites but was distributed reaching both the forebrain and spinal cord and GM2 ganglioside storage was reduced in all parts of the brain.

Long term survival after gene therapy in a feline model of Sandhoff disease. Molecular Genetics and Metabolism. Feburary 2016, 117(2): S52. *Gray-Edwards Heather, McCurdy Victoria, Hwang Misako, Randle Ashley, Johnson Aime, Hudson Judith, Sena-Esteves Miguel, Martin Douglas.*

* Sandhoff disease cats treated with AAV-HEXA + AAV-HEXB by direct brain injection to the thalamus and cerebellum had a mean survival of 19.1 ± 8.6 moths of age compared to untreated Sandhoff cats which had a mean survival of 4.4 ± 0.6 months.
* To reduce surgical risks associated with directly injecting the cerebellum, a second group of Sandhoff cats received AAV-HEXA + AAV-HEXB gene therapy by direct brain injection to the thalamus in combination with injection to the lateral ventricle (CSF filled space), also known as intracerebroventricular (ICV) injection. These cats had a mean survival of 21.4 ± 6.8 moths of age.
* Gene therapy treated cats showed normalization of brain disease on MRI and had widespread distribution of hexosaminidase enzyme throughout

CONFERENCE ON CLINICAL RESEARCH FOR RARE DISEASES: November 3, 2016

For more information about the conference, including details about the program, applying for travel awards, and conference logistics and registration, visit the conference website **here**.

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the central nervous system.

The success of the two-vector gene therapy approach in animal models led to initiation of the pre-Investigational New Drug (IND) process with the FDA. Required safety and toxicity studies were completed in non-human primates; however, the therapy was found to be toxic to the animals. The researchers then made multiple new iterations of the vector and are now completing IND-enabling efficacy and safety studies.

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