



## Gene therapy for CNS diseases – Krabbe disease

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### Summary

This is a brief report of the 19th Annual Meeting of the American Society of Gene and Cell Therapy that took place from May 4th through May 7th, 2016 in Washington, DC, USA. While the meeting provided many symposiums, lectures, and scientific sessions this report mainly focuses on one of the sessions on the “Gene Therapy for central nervous system (CNS) Diseases” and specifically on the “Gene Therapy for the globoid cell leukodystrophy or Krabbe disease. Two presentations focused on this subject utilizing two animal models of this disease: mice and dog models. Different serotypes of adeno-associate viral vectors (AAV) alone or in combination with bone marrow transplantations were used in these research projects. The Meeting of the ASGCT reflected continuous growth in the fields of gene and cell therapy and brighter forecast for efficient treatment options for variety of human diseases.

### Author Biosketch

Mohammad Rafi received his PhD in Animal Biology from the University of Montpellier, France, in 1970. He taught Cell and Molecular Biology for over 17 years at the School of Science, Tabriz University, Iran, where he also served as Chair of the Department



of Animal Biology. He is currently a Professor of Neurology in the Department of Neurology with a joint appointment in the Department of Neurosciences at Thomas Jefferson University in Philadelphia, USA. Though he has worked on several lysosomal storage diseases, his main research interest is gene therapy of neurodegenerative disorders using animal models of globoid cell leukodystrophy (Krabbe disease). With successful AAVrh10-mediated treatment of murine and canine models, his research is moving towards the treatment trials of human patients.

The 19<sup>th</sup> Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) took place from May 4<sup>th</sup> through May 7<sup>th</sup>, 2016 at the Marriott Wardman Park Hotel in Washington, DC, USA. The meeting featured news about groundbreaking results from clinical trials and cutting edge technology advancements, as well as opportunities for social networking. According to Dr. Cynthia Dunbar, ASGCT President, the meeting attracted 2,393 attendees, which was about a 20% increase over last year's meeting and constituted the highest Annual Meeting attendance since 2002. Scientists represented 32 countries around the world, totaling 462 speakers. Scientific exchanges and technological updates were presented in the form of 775 abstracts and 63 exhibitors. For the first time, through a grant from the University of Massachusetts Medical School, meeting attendees could download a mobile app featuring the most updated speaker information, session schedules, oral and poster abstracts, and the ability to set a personal itinerary. The program offered a special half-day symposium, which included coverage of the concepts and clinical applications of “Genome Editing,” as well as “Scientific Symposiums” on different subjects, numerous “Educational Sessions,” and multiple “Oral Presentations.” The meeting also offered several specific lectures and symposiums:

1. Presidential Symposium, where Dr. Alain Fisher from Hôpital des Enfants malades, Paris, France, spoke on the topic of “*Sixteen Years of Gene Therapy for Primary Immunodeficiencies*,” and Dr. Theodore Friedmann from UCSD School of Medicine, La Jolla, CA, USA spoke on the topic of “*Purine Dysregulation, Neuropathology and Gene Therapy*”;
2. George Stamatoyannopoulos Lecture, in honor of Dr. Stamatoyannopoulos, the founding President of the American Society of Gene Therapy, where Dr. David Liu from Harvard University, Cambridge, MA, USA spoke on the topic of “*A New Approach to Genome Editing*”;
3. Outstanding Achievement Award Lecture, during which Dr. Seppo Yla-Herthuala from Finland was pronounced the recipient of the Outstanding Achievement Award and Dr. Katherine Ponder was pronounced the recipient of the Sonia Skarlatos Public Service Award; and
4. Outstanding New Investigator Symposium, where Dr. Jordan Green, Dr. Marcin Kortylewski, Dr. Eirini Papapetrou, and Dr. Jughae Suh were acknowledged for their pioneering works on various gene therapy subjects.

Our own research on gene therapy of Krabbe disease in



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the canine model was presented in the “Gene Therapy for CNS Diseases” session. In addition to two presentations on gene therapy of Krabbe disease, including our own, this session consisted of the following presentations:

- *A Neuro-Specific Gene Therapy Approach to Treat Cognitive Impairment in Down Syndrome by RNA Interference*, presented by **Andrea Contestabile** from Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia (IIT), Genova, Italy
- *Prevention of Sensory Ataxia in a Novel Mouse Model of Friedreich Ataxia Using Gene Therapy Approach* presented by **Françoise Piguet** from IGBMC, Illkirch, France
- *Aquaporins and CSF Flux Are Critical Determinants of AAV Mediated CNS Gene Transfer*, presented by **Giridhar Murlidharan** from Gene Therapy Center, University of North Carolina, Chapel Hill, NC, USA
- *Pushing the Limits for Canavan Gene Therapy into Adulthood: Is There an Age Limit for Gene Therapy in CNS Disorders?*, presented by **Dominic J. Gessler** from Gene Therapy Center, UMass, Worcester, MA, USA
- *APPs<sub>α</sub> Gene Therapy for Alzheimer's Disease*, presented by **Nathalie Cartier-Lacave** from INSERM U1169/MIRCen CEA, Fontenay aux Roses, France
- *Engineering AAV Vector for the Delivery of Human BuChE to Protect Against Exposure to Organophosphates*, presented by **Omua Ahokhai** from Gene Therapy Program, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Our research in collaboration with the University of Pennsylvania was presented by **Allison Bradbury**. The title of the presentation was “*Intracerebroventricular and Intravenous AAV Gene Therapy in Canine Globoid Cell Leukodystrophy*.” After a brief introduction on Krabbe disease, or globoid cell leukodystrophy (GLD), which is caused by the deficiency of one of the lysosomal enzyme called galactocerebrosidase (GALC), the outcomes of the research were outlined. The introduction also contained the symptoms and pathological characteristics of affected individuals in the human and in the canine models.

Next, the results from the combination of the intracerebroventricular (ICV) and intravenous (IV) injection of AAV vector encoding canine GALC that was packaged in AAVrh10 capsid (AAVrh10-cGALC) were compared with untreated affected dogs. According to the data presented, two affected dogs had received a low dose of AAVrh10-cGALC, 1.2E12, by combination IV and ICV injection routes and displayed a modest increase in survival to 17.9 and 22.1 weeks of age, respectively. This was compared to 15.9 ± 4.6 weeks of age in untreated affected dogs.

Two additional affected dogs were treated with a higher dose of AAVrh10-cGALC, 1.9E13. Their survival was further increased to 30.3 and 43.1 weeks, respectively. Both low and high dose combination IV and ICV therapy delayed the onset of neurological signs and prevented the onset of tremors, one of the debilitating neurological signs

in affected untreated dogs. High dose AAVrh10-cGALC resulted in complete normalization of pelvic and thoracic limb nerve conduction velocity (NCV) and near normal sensory NCV. Combination therapy of either dose had a negligible effect on the auditory system, as treated animals showed little to no improvement in distance between wave form peaks or hearing threshold over untreated animals. After high dose treatment with AAVrh10-cGALC, GALC activity reached near normal levels in the cerebellum and sciatic nerve, with levels decreasing in more distal brain regions. GALC levels in the liver and heart were between affected untreated GLD and normal control dogs. Interestingly, the highest GALC activity was found in the quadriceps muscle.

Efficacy of hematopoietic stem cell transplant (HSCT) alone and in combination with IV AAVrh10-cGALC is currently being evaluated in dogs affected with GLD. Ongoing studies suggest that addition of IV infusion of AAVrh10-cGALC substantially increases survival, as compared to HSCT alone. This research is based on the studies done on twitcher mice by Rafi et al [1 & 2].

The other presentation on gene therapy of Krabbe disease was delivered by **Subha Karumuthil-Melethil** from the University of North Carolina, Chapel Hill, NC, USA. The title of the presentation was “*Intrathecal Administration of AAV/GALC Vectors in Juvenile Twitcher Mice Improves Survival and Is Enhanced by Bone Marrow Transplant*.” This presentation compared multiple vector designs along with a combination treatment of AAV plus bone marrow transplant (BMT) in twitcher mice. The serotypes tested were comprised of AAV9, AAVrh10, and an engineered AAV with oligodendrocyte tropism (AAV-Oligo001). All vectors encoding mouse GALC were delivered via a lumbar intrathecal route. Results demonstrated a significant extension of life span of the twitcher mice for all three serotypes, compared to the untreated affected mice. The treatment produced similar survival benefit regardless of which capsid was used.

This group also tested a novel self-complementary AAV vector with a minimal synthetic promoter. While the overall level of GALC expression from this vector was weaker compared to the single stranded AAV vectors, preliminary results indicate that this vector design provides a survival advantage over the single stranded designs.

The 19<sup>th</sup> Annual Meeting of the ASGCT strongly reflected continuous development in the fields of gene and cell therapy and provided outstanding educational and networking opportunities.

#### References

1. Rafi MA, Rao HZ, Luzi P, Curtis MT, Wenger DA. Intravenous injection of AAVrh10-GALC after the neonatal period in twitcher mice results in significant expression in the central and peripheral nervous systems and improvement of clinical features. *Mol Genet Metab.* **2015**;114(3):459-66. doi: 10.1016/j.ymgme.2014.12.300.
2. Rafi MA, Rao H-Z, Luzi P, and Wenger DA. Long-term improvements in lifespan and pathology in CNS and PNS after BMT plus one intravenous injection of AAVrh10-GALC in twitcher mice. *Mol Ther.* **2015**;23(11):1681-90. doi: 10.1038/mt.2015.145.