Initiation of First-in-Human Gene Therapy for Rare Neurological Diseases

Steven J. Gray

Dept of Ophthalmology
Gene Therapy Center
University of North Carolina

Received patent royalties from Asklepios Biopharma and Abeona
The promise of gene therapy is to fix a genetic disease at the source. If you fix the DNA, you’ve solved the problem permanently.
Adeno-associated virus (AAV) characteristics

- single-stranded DNA human parvovirus
- non-pathogenic, requires helper virus for lytic infection
- able to transduce non-dividing cells and confer long-term transgene expression
- can package up to 4.6 kb in place of viral Rep and Cap genes
- dozens of naturally-occurring serotypes identified with differing tissue tropism
- Over 100 clinical trials initiated using rAAV, no serious adverse effects related to vector. In 2012, the first gene therapy product (Glybera) received full regulatory approval in Europe.
Gene therapy for aromatic L-amino acid decarboxylase deficiency.

Hwu WL, Muramatsu S, Tseng SH, Tzen KY, Lee NC, Chien YH, Snyder RO, Byrne BJ, Tai CH, Wu RM.

Targeting AAV to the CNS

- Direct injection into brain
- i.v. injection and transcytosis of vector
- Intrathecal injection into CSF
I.V. $1 \times 10^{13}$ vg/kg AAV9/C Bh-GFP

4 weeks post-injection

Gray et al, Mol. Ther., 2011
Intrathecal Administration
(inject vector into CSF)
Intrathecal Delivery, AAV9

1.25x10^9 vg injected IT, 10 wk time point
CONCLUSIONS:

- Intrathecal injection of AAV9 in adult pigs resulted in 50-100% of spinal cord motor neuron transduction across the entire spinal cord.
Intrathecal injection in pigs leads to brain delivery and extensive cerebellum transduction

- Collaboration with Nick Boulis at Emory University
- ~15 kg pigs were injected with $3 \times 10^{12}$ vg scAAV9/CBh-GFP ($2 \times 10^{11}$ vg/kg) [n=6]
- Pigs were euthanized after 4 weeks and fixed tissue subjected to IHC against GFP

Note: There was minimal or no delivery to peripheral tissues.
CONCLUSIONS:
• IT administration of AAV9 leads to global vector distribution and transgene expression to the CNS.
• IT administration overcomes many of the barriers associated with IV administration, including a lower dose, avoidance of NAbs, and reduced peripheral organ biodistribution.
Giant Axonal Neuropathy (GAN)

- Sensory and Motor Peripheral Neuropathy, “ALS in kids”
- Cognition is mostly unaffected
- 3-4 yrs old: clumsiness, loss of coordination
- ~10 yrs old: unable to walk
- Late teens: highly reduced coordination and use of arms/hands
- ~20 yrs old: Fatal
- Ultra-rare
"Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has."

- Margaret Mead
GAN Therapeutic Approach

self-complementary genome

**Targets:**
- Primary targets will be spinal cord and brainstem motor neurons, DRG (to treat peripheral motor and sensory disease)
- Secondary targets will be the brain (to address white matter abnormalities and suspected protein aggregations/ inclusion bodies)
The Road to an IND

- IND = Investigational New Drug

Good lab results (proof of concept) ➔ FDA preIND ➔ toxicology ➔ Clinical trial design ➔ PK/PD ➔ RAC ➔ IRB ➔ FDA ➔ Phase I Trial


Funded 100% from Hannah’s Hope fund up to the Phase I trial.
Intrathecal Administration of scAAV9/JeT-GAN for the Treatment of Giant Axonal Neuropathy

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 2014 by National Institutes of Health Clinical Center (CC)

Sponsor:
National Institute of Neurological Disorders and Stroke (NINDS)

Information provided by (Responsible Party):
National Institutes of Health Clinical Center (CC) (National Institute of Neurological Disorders and Stroke (NINDS))

ClinicalTrials.gov Identifier: NCT02362438
First received: February 12, 2015
Last updated: NA
Last verified: December 2014
History: No changes posted

Purpose

Background:
- The Gigaxonin gene lets the body make a protein chemical called Gigaxonin. Nerves need Gigaxonin to work properly. Giant Axonal Neuropathy (GAN) is a genetic disease that prevents the body from making Gigaxonin properly. As a result, Nerves do not work properly and nerves grow abnormally in people with GAN. This causes problems with walking and sometimes with eating, breathing, and many other activities. GAN has no cure. Overall, gene transfer treatment may help people with GAN.

Objectives:
- To see if a gene transfer is safe and shows potential to help people with GAN.

Eligibility:
MILESTONE: May 2015
First-in-human intrathecal gene transfer to broadly treat a CNS disorder

Pictured: Diana Bharucha, Lori Sames, Carsten Bonnemann, Steven Gray
Other trials with AAV9 vectors

- SMA (IV, started in 2014)
- GAN (intrathecal, started in 2015)
- CLN6 (intrathecal, started in 2016)
- MPS IIIA (IV, started in 2016)
- **MPS IIIB** (IV, anticipated 2017)
Disease Applications Within My Lab (intrathecal or IV gene transfer using AAV9)

- Giant Axonal Neuropathy
- Rett Syndrome
- Krabbe Disease
- Tay-Sachs Disease
- Batten Disease, Infantile (INCL)
- Batten Disease, Late Infantile (LINCL)
- Aspartylglucosaminuria (AGU)

Clinical Trial: Giant Axonal Neuropathy
Discovery: Rett Syndrome, Krabbe Disease, Tay-Sachs Disease, Batten Disease, Infantile (INCL), Batten Disease, Late Infantile (LINCL), Aspartylglucosaminuria (AGU)
IND-enabling: Advanced preclinical
Improved Survival and Reduced Phenotypic Severity Following AAV9/MECP2 Gene Transfer to

Intrathecal Administration of AAV/GALC Vectors in 10–11-Day-Old Twitcher Mice

Restoration of Cytoskeleton Homeostasis After Gigaxonin Gene Transfer for Giant Axonal Neuropathy

Novel Vector Design and Hexosaminidase Variant Enabling Self-Complementary Adeno-Associated Virus for the Treatment of Tay-Sachs Disease

Subha Karumuthil-Melethil, Sahana Nagabhushan Kalburgi, Patrick Thompson, Michael Tropak, Michael D. Kaytor, John G. Keimel, Brian L. Mark, Don Mahuran, Jagdeep S. Walia, and Steven J. Gray
Supporting via External Collaborations

Charcot-marie Tooth 4j

Batten (cln7)

Pitt-hopkins

Charcot-marie Tooth 6
Batten (cln6)

Batten (cln5)

GM2A deficiency
Niemann-pick C

Mucolipidosis Type 1/III

Spastic Paraplegia Type 7
Retinitis Pigmentosa (impg2)
Cost Estimate?

- Proof-of-Concept preclinical: ~$0.4-1 million
- Toxicology Studies: ~$1 million
- Vector Manufacture: ~$1 million
- Small Phase I clinical trial: ~$1-2 million
Not pictured: Dr. Emma Hoffman, Dr. Kenton Woodard, Dr. Charles Shyng, Dr. Erik Lykken, Dr. Sarah Snaouadj-Verber
Acknowledgements

Past contributing lab members
Swati Yadav       Lavanya Bachaboina
Huijing Sun        Sophia Shih
Clay Fox
Sahana Nagabhushan Kalburgi

Jude Samulski Lab (UNC)
Thomas McCown Lab (UNC)
Diane Armao (UNC)
Carston Bonnemann (NIH/NINDS)
Diana Bharucha (NIH/NINDS)

CIDD (UNC)
Sheryl Moy (Mouse behavioral studies)

NIH UL1RR025747, (NC TraCS)
NIH/NINDS 1R01NS087175
Jasper Against Batten