RETINA INTERNATIONAL

Seeking A Cure For
Retinitis Pigmentosa, Macular Degeneration,
Usher Syndrome and Allied Retinal Dystrophies

Retina International Special Interest Group (SIG) on Usher Syndrome – RI USH SIG Newsletter – Gene Therapy for Usher Syndrome in or close to clinical trials – an Update (Aug/Sep 2019)

Within Retina International we have recently established the Special Interest Group for Usher Syndrome, and one of our main goals is to inform all individuals and families with Usher Syndrome - aligned or not to any organisation or group - about reliable up-to-date research news to ensure that they do not lose out on any opportunity for involvement in research, clinical trials, and ultimate access to therapy.
We start with an update of gene therapy for Usher Syndrome in or close to clinical trials:

USH1B:
UshStat – SAR421869

https://clinicaltrials.gov/ct2/show/record/NCT01505062?cond=Usher+Syndrome%2C+Type+1B&rank=3

UshStat is now called SAR421869, and the clinical trials are taking place in Paris (Hôpital National 15-20) and Portland (Casey Eye institute), Oregon, US. It is a gene replacement therapy where a correct copy of Myosin7A is injected into the retina via a vector called lentivirus, which has the capacity to carry a gene of the enormous size of MYO7A. UshStat has been on hold in Phase1/2 since December 2018 after Sanofi removed it from their pipeline. In their press release in February 2019, they announced that they were seeking an out-licensing partner and/or co-sponsor. We will keep you updated as soon as there is any news from their side.

USHther AAV8-MYO7A

A consortium around Alberto Auricchio (TIGEM Theleton Institute of Genetics and Medicine, Naples, Italy) has worked on dual AAV vectors for non-clinical studies and a clinical trial. Currently the safety, biodistribution, and expression of dual AAV vectors is being assessed in primates, and the multicentre phase1/2 clinical trial to investigate the safety and efficacy of dual AAV-MYO7A vectors in humans has been

designed. They are currently recruiting for a natural history study with a cohort of USH1b patients in Naples, Italy, in Madrid, Spain, and in Rotterdam, Netherlands. For details see: https://clinicaltrials.gov/ct2/show/NCT03814499?cond=Usher+Syndrome%2C+Type+1B&rank=1

USH1B Pre-Clinical Research

The Californian charitable organisation SaveSightNow has partnered with the US based Foundation Fighting Blindness to raise funding for leading medical research in USH1B related treatments. Candidates for support include USH1B Gene Augmentation Therapy Development, Creation and Characterisation of a Non-Human Primate USH1B model, USH1B Protein/Cellular Function Linked to Clinical Outcome Measures and USH1B HITI-Based Gene Editing Therapy Development.
www.savesightnow.com

USH1C

Gwanaëlle Géléoc and her team at Boston Children's Hospital could restore hearing and balance in a mouse model with USH1C by introducing a healthy copy of the protein Harmonin with the help of an AAV vector.

Jennifer Lentz has shown that a different approach called Antisense oligonucleotide (ASO or AON) treatment of mice with the human Usher mutation *Ush1c* c.216G>A (prevalent in Arcadian communities) corrects gene expression and significantly improves hearing. She compares skipping of the entire exon 3, which could be used on multiple USH1C mutations, to smaller sequence directed for the 216 mutation. She also is conducting a natural history study of vision loss in USH1C patients.

Kerstin & Uwe Wolfrum and their teams developed a transgenic USH1C pig model and investigated translational read-through inducing drugs in mouse and pig models with USH1C (p.R31X). This approach could serve as a treatment option for nonsense mutations in inherited retinal dystrophies.

USH1D

An Italian team (Naples) tested retinal gene transfer in mouse and pig retinas by using triple AAV vectors to maximise the transfer capacity for larger genes involved in Inherited Retinal Dystrophies such as USH1D.

Translation was sufficient, triple AAV vectors could enable gene therapy for USH1D.

USH1F

Multiple researchers are working on developing gene therapy for Usher 1F using three different approaches, split gene dual vector, mini-gene, and base editing. Research teams include Monte Westerfield, PhD, University of Oregon, Zubair Ahmed, PhD, University of Maryland, Livia Carvalho, PhD, Lions Eye Institute, University of Western Australia, Leah Byrne, PhD, University of Pittsburgh, David Corey, PhD, Harvard Medical School with Artur Indzhykulian, PhD, Massachusetts Eye and Ear, and Alex Hewitt, MD, PhD, Centre for Eye Research Australia. Currently in testing in mouse and zebrafish models are the split gene dual vector and mini gene approaches.

USH1G

Christine Petit and her team partially restored inner ear function and removed almost completely the balance defect in a mouse model of USH1G by viral transfer of the wild-type cDNA to the inner ear of mutant mice shortly after birth. The results provide a basis for future clinical trials in humans.

USH2A

STELLAR:

STELLAR, or PQ-421a-001, is a first-in-human study that will initially include approximately 18 adults who have vision loss due to mutations in exon 13 of the USH2A gene and will be conducted at about seven expert sites in North America and Europe. QR-421a is designed to exclude exon 13 from the USH2A mRNA, thereby removing the mutation in exon 13. This approach is also known as exon skipping. RNA is the "blueprint" for protein synthesis. Skipping of exon 13 in the "blueprint" is expected to lead to a shortened but functional Usherin protein.

The trial is currently ongoing and more information about this can be obtained on this link
https://clinicaltrials.gov/ct2/show/NCT03780257?term=proqr&rank=1

Pre-clinic:
Carla Fuster Garcia (Valencia, Spain) and her team successfully investigated CRISPR/Cas9 gene editing in USH2A c.2299delG mutation on fibroblasts. Successful in vitro mutation repair was demonstrated. The proven effectiveness and specificity of these correction tools indicates that the CRISPR system should be considered to further explore a potential treatment of USH.

USH3A
Dr. Dinculescu and her team from University of Florida have been working on developing therapeutic approaches for USH3A, which is caused by mutations in a small gene: Clarin-1 (CLRN1). Perinatal transfection of hair cells in mice with a single injection of AAV-Clrn1-UTR vector showed preservation of the hair bundle structure and hearing through adult life. They are also investigating on optimized AAV-vector designs to develop a gene therapy treatment for the vision loss in USH3A with the potential to provide a basis for future clinical trials in humans.

Kumar Alagramam is working with Case Western Reserve and University Hospitals (Cleveland, US) on a technology that allows to develop a more precise animal model of hearing loss associated with USH3A and that has the potential to preserve the hearing through gene therapy and to serve as a basis for development of gene therapies for other subtypes of Usher Syndrome.

We hope you enjoyed our inaugural newsletter. We are very committed to making our communications accessible. If you wish to receive this newsletter in an alternative format, please let us know by emailing usher@retina-international.org and we will endeavour to issue future newsletters in your preferred format.

We will come back to you with interesting news very soon. To make sure not to miss out any important news about USH research, clinical trials and surveys subscribe here: http://www.retina-international.org/updates-from-the-ri-ush-special-interest-group/

This newsletter has been written thanks to Dominique Sturz, Melissa Chaikof, Carol Brill, Isabelle Audo.