OTONOMY®

Targeted
Medicines
for the **Ear**

OTO-413 Program Review

November 5, 2018

Forward-Looking Statements

Safe Harbor Statement

These slides and the accompanying oral presentation (the "Presentation") contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements generally relate to future events or future financial or operating performance of Otonomy, Inc. ("Otonomy"). Forward-looking statements in this Presentation include, but are not limited to, the timing of the Phase 1/2 clinical trial for OTO-413, the potential market opportunity for OTO-413, and expectations regarding program advancement. Otonomy's expectations regarding these matters may not materialize, and actual results in future periods are subject to risks and uncertainties. Actual results may differ materially from those indicated by these forward-looking statements as a result of these risks and uncertainties, including but not limited to: Otonomy's limited operating history and its expectation that it will incur significant losses for the foreseeable future; Otonomy's ability to obtain additional financing; Otonomy's dependence on the regulatory success and advancement of product candidates, such as OTO-413; the uncertainties inherent in the drug development process, including, without limitation, Otonomy's ability to adequately demonstrate the safety and efficacy of its product candidates, the nonclinical and clinical results for its product candidates, which may not support further development, and challenges related to patient enrollment in clinical trials; the risk of the occurrence of any event; Otonomy's ability to obtain regulatory approval for its product candidates; side effects or adverse events associated with Otonomy's product candidates; Otonomy's ability to successfully commercialize its product candidates, if approved; competition in the biopharmaceutical industry; Otonomy's dependence on third parties to conduct nonclinical studies and clinical trials; Otonomy's dependence on third parties for the manufacture of its product candidates; Otonomy's dependence on a small number of suppliers for raw materials; Otonomy's ability to protect its intellectual property related to its product candidates in the United States and throughout the world; expectations regarding potential market size, opportunity and growth; Otonomy's ability to manage operating expenses; implementation of Otonomy's business model and strategic plans for its business, products and technology; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in Otonomy's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 5, 2018, and Otonomy's future reports to be filed with the SEC. This Presentation is dated as of November 5, 2018, and Otonomy undertakes no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Hearing Loss: Large and Growing Unmet Need

Hearing Loss is 4th Leading Cause of Disability Globally[1]

[1] *Lancet, July 2017*

Review

Global hearing health care: new findings and perspectives

Blake S Wilson, Debara L Tucci, Michael H Merson, Gerard M O'Donoghue

In 2015, approximately half a billion people had disabling hearing loss, about 6·8% of the world's population. These numbers are substantially higher than estimates published before 2013, and point to the growing importance of hearing loss and global hearing health care. In this Review, we describe the burden of hearing loss and offer our and others' recommendations for halting and then reversing the continuing increases in this burden. Low-cost possibilities exist for prevention of hearing loss, as do unprecedented opportunities to reduce the generally high treatment costs. These possibilities and opportunities could and should be exploited. Additionally, a comprehensive worldwide initiative like VISION 2020 but for hearing could provide a focus for support and also enable and facilitate the increased efforts that are needed to reduce the burden. Success would produce major personal and societal gains, including gains that would help to fulfil the "healthy lives" and "disability inclusive" goals in the UN's new 2030 Agenda for Sustainable Development.

Published Online July 10, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31073-5

Division of Head and Neck Surgery and Communication Sciences, Department of Surgery, Duke University Medical Center, Durham, NC, USA (Prof B S Wilson DSc, Prof D L Tucci MD); **Duke Global Health Institute** (Prof B S Wilson, Prof D L Tucci,

NEJM, Dec 2017

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Hearing Loss in Adults

Lisa L. Cunningham, Ph.D., and Debara L. Tucci, M.D., M.B.A.

HEARING LOSS IN ADULTS IS ENCOUNTERED IN ALL MEDICAL SETTINGS and frequently influences medical encounters. This disorder constitutes a substantial burden on the adult population in the United States, yet screening for hearing loss is not routine,[1] and treatments are often inaccessible because of the high cost or perceived ineffectiveness.

From the Section on Sensory Cell Biology, National Institute on Deafness and Other Communication Disorders, Bethesda, MD (L.L.C.); and the Division of Head and Neck Surgery and Communication Sciences, Duke University Medical Center, Durham, NC (D.L.T.). Address reprint requests to Dr. Tucci at the Division of

- Most prevalent neurologic health issue: > 360M people have disabling hearing loss[2]
- High economic burden: medical costs + impact of lower work productivity
- Leads to social isolation, lower QoL, and higher rates of dementia and depression
- Common causes: aging, noise, ototoxic drugs and genetics
- Established clinical outcome measures that are objective patients assessments

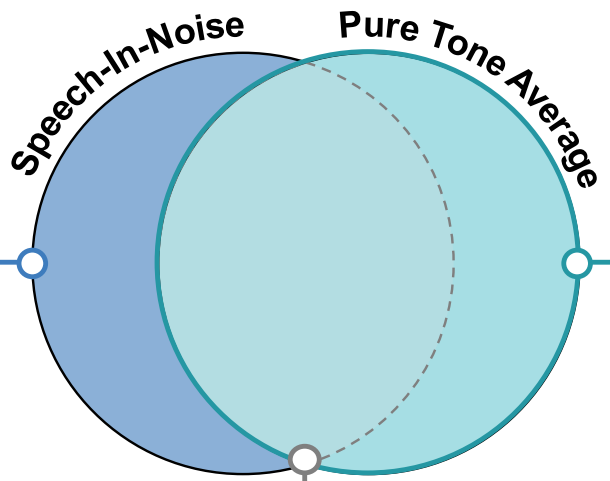
[2] World Health Organization, Global Estimates on Prevalence of Hearing Loss, 2012.

OTO-413 Addresses Significant Population with Cochlear Synaptopathy

Speech-in-Noise (SiN) Hearing Difficulty

- Problem hearing in presence of background noise
- U.S. prevalence[1] ≈ 9M with SiN only (no PTA changes)
- Loss/damage to cochlear synapses

ILLUSTRATIVE



PTA Hearing Deficit

- Hearing loss in standard test (soundproof booth)
- U.S. prevalence[2-5] ≈ 42M
- Loss/damage to hair cells and/or synapses

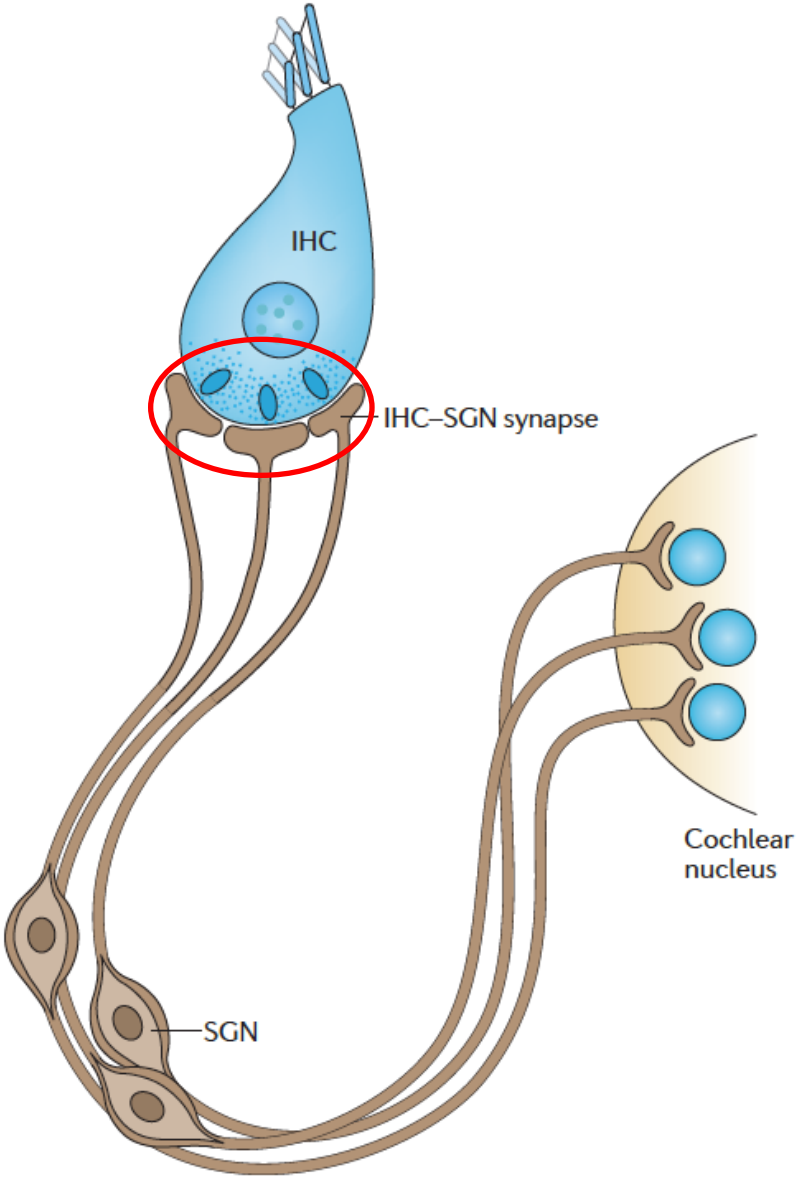
OTO-413 Target Patient Population

Mixed Pathology

- Includes patients with age-related and noise-induced hearing loss
- Prevalence ≈ ??

[1]Tremblay et al., Ear Hear, 2015
[2]Hoffman et al., JAMA Otolaryngol HNS, 2017
[3]Nash et al., Arch Otolaryngol HNS, 2011
[4]Morton et al., N Engl J Med, 2006
[5]Brooke et al., JAMA Otolaryngol HNS, 2017

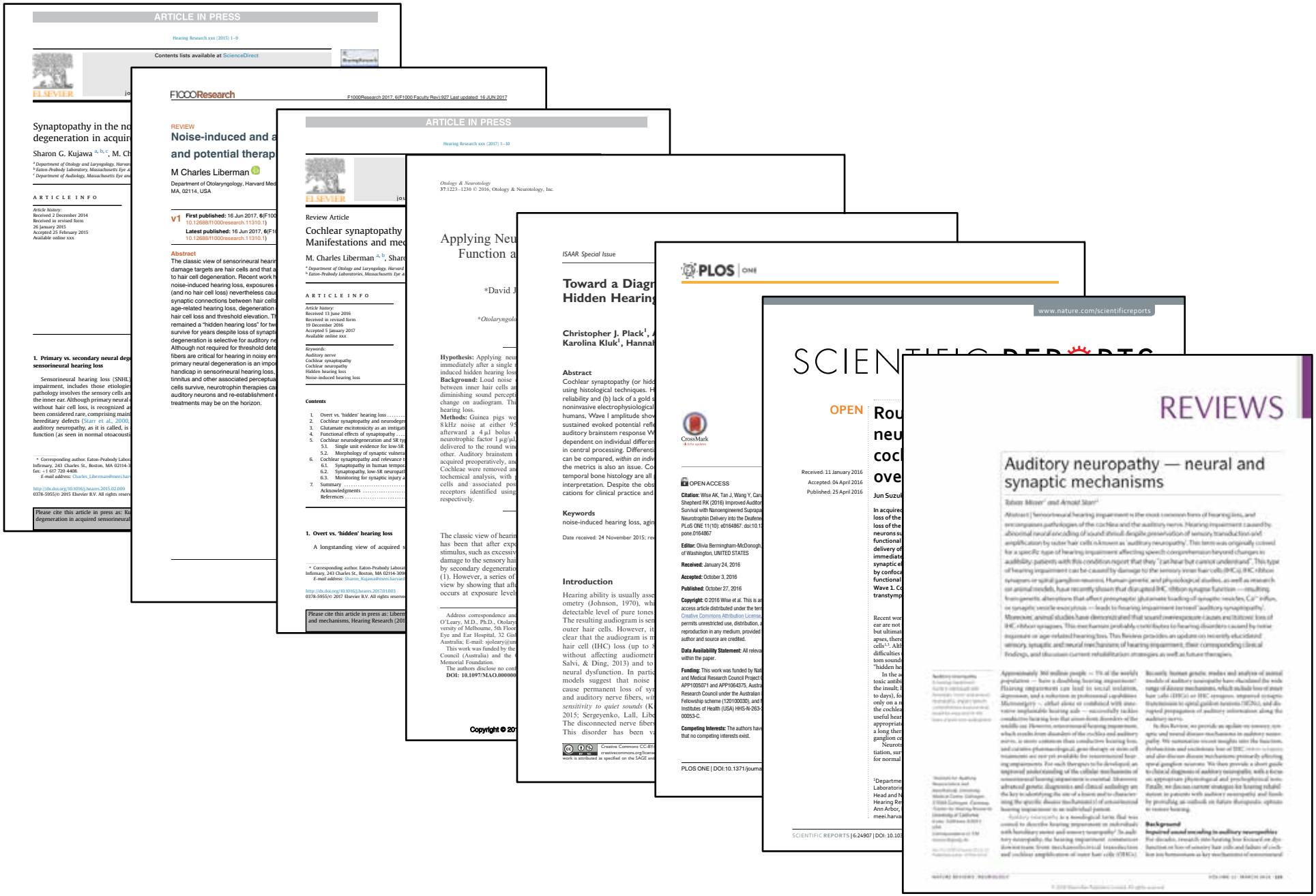
Cochlear Synaptopathy and Hearing Loss



- In the last decade, research has identified loss or dysfunction of synaptic connections between inner hair cells (IHC) and spiral ganglion neurons (SGN) as playing important role in hearing loss pathology
- Synapses can be damaged or lost due to loud noise, aging, and/or exposure to ototoxic chemicals
- "Cochlear synaptopathy" contributes to speech-in-noise difficulties as well as age-related and noise-induced hearing loss
- Potential to repair synaptopathy using neurotrophic factors

Figure from Moser and Starr, Nature Reviews: Neurology (2016)

Extensive Support for Synaptopathy and Repair by Neurotrophins



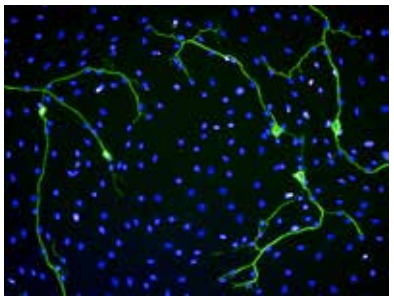
Background on OTO-413 Program

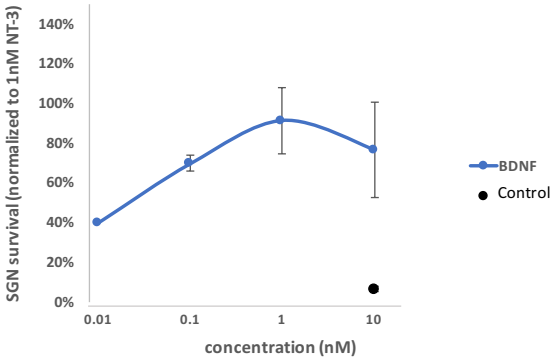
- Selected BDNF after extensive evaluation of multiple neurotrophic factors and Trk antibodies
  - Cochlear explant assay, *in vitro* testing and *in vivo* evaluations
- OTO-413 comprised of BDNF in thermosensitive polymer (same used for OTIPRIO® and OTIVIDEX™)
- IP covers proprietary formulation and manufacturing know-how
- Single intratympanic injection of OTO-413 provides sustained-exposure of BDNF to the inner ear
- Therapeutic potential of OTO-413 demonstrated in cochlear synaptopathy animal model – presentation selected as "Hot Topic" at 2018 Society for Neuroscience Annual Meeting (November 6)

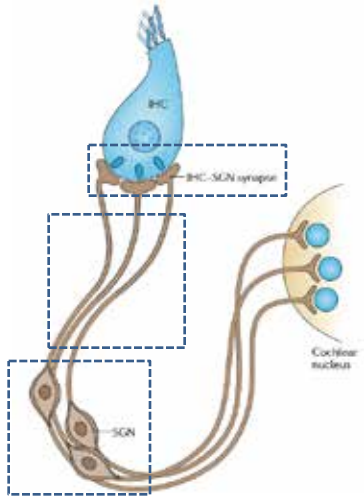
Therapeutic Effects of BDNF in the Cochlea

Brain-derived neutrophic factor (BDNF) activates TrkB receptors on SGNs to:

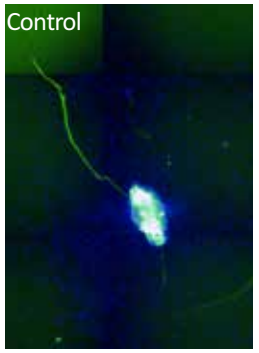
- Promote survival of SGNs

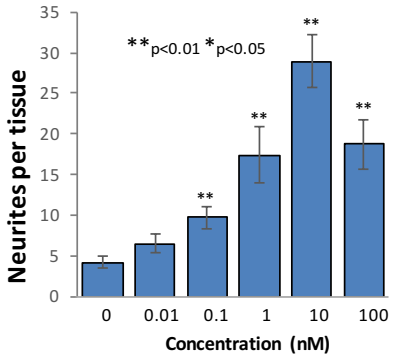




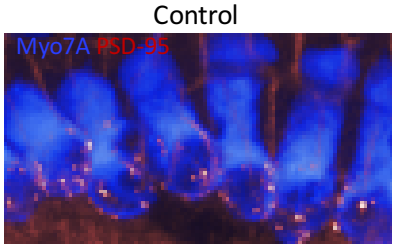


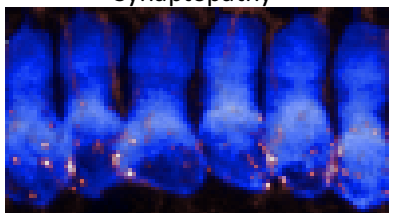
- Increase neurite outgrowth of SGNs

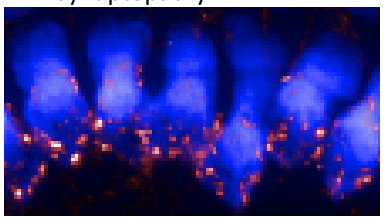


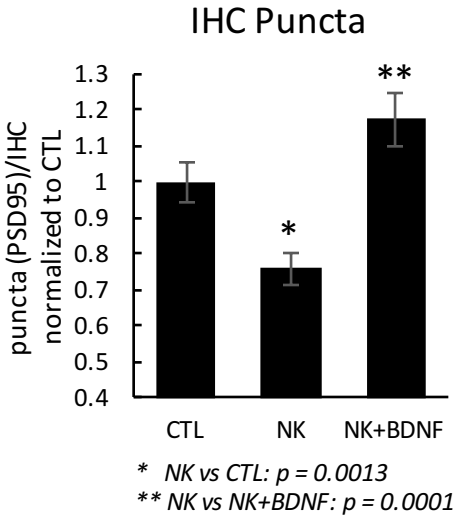


- Reconnect SGNs with hair cells after chemical synaptopathy







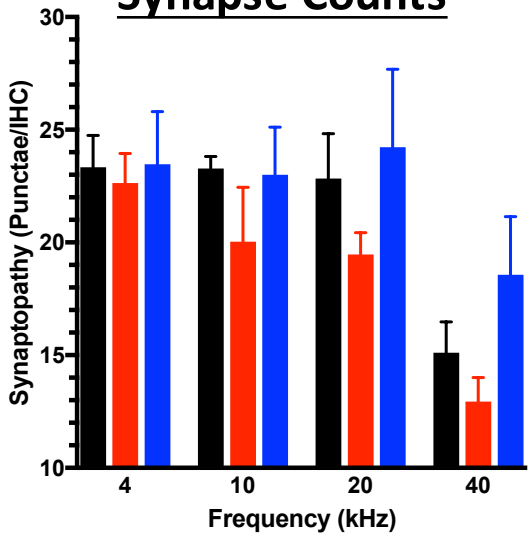


* NK vs CTL: p = 0.0013
** NK vs NK+BDNF: p = 0.0001

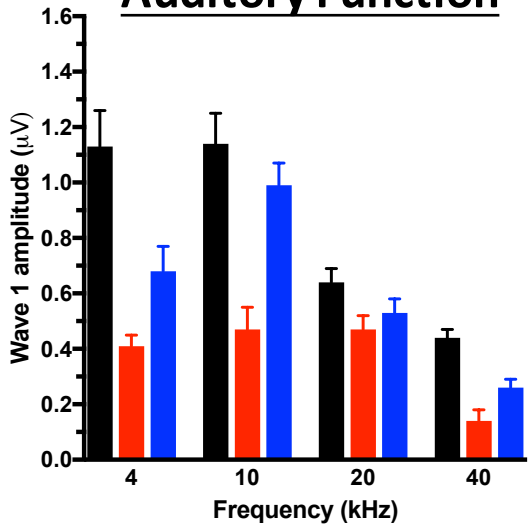
OTO-413 Proof-of-Concept in Synaptopathy Animal Model

Recovery of both synapse numbers and auditory function with OTO-413

Synapse Counts

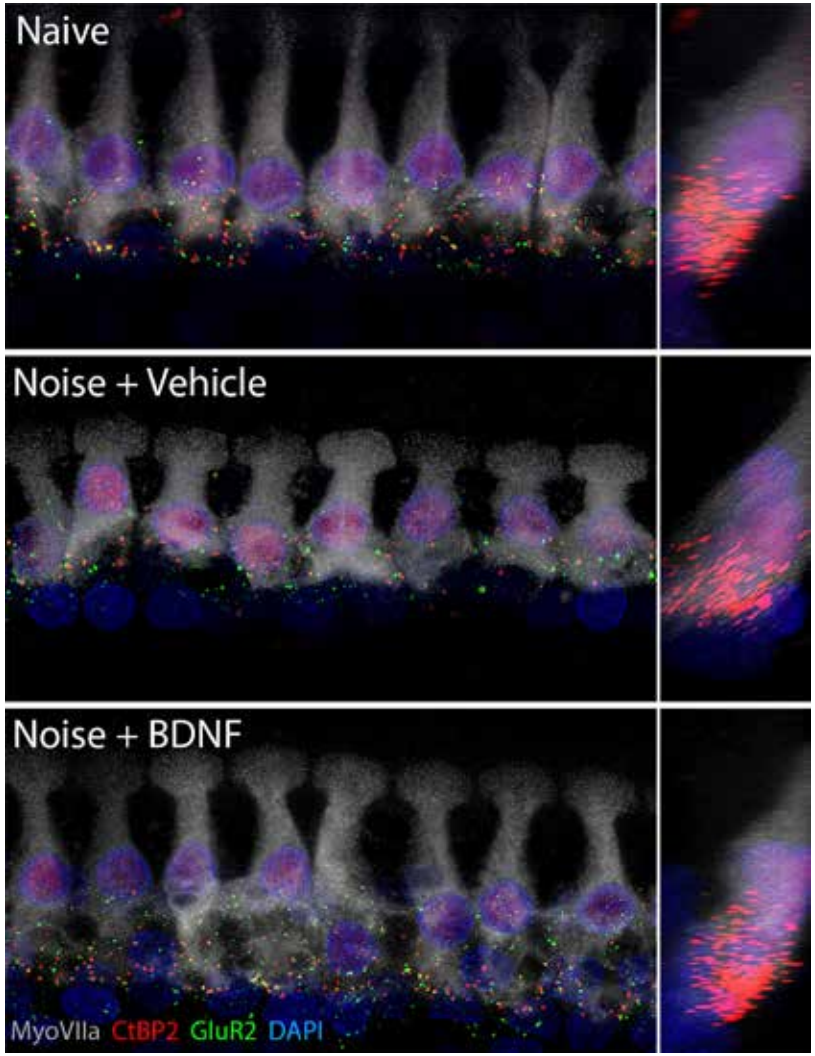


Auditory Function



Naïve
Noise + Vehicle
Noise + OTO-413

Visualization of Synapses on Hair Cells



OTO-413 Program Status and Plan

- Pre-IND meeting completed with FDA
- IND enabling activities ongoing
- Expect to initiate Phase 1/2 study in hearing loss patients in 1H19
- Initial study population: speech-in-noise hearing difficulty
  - Common and growing problem not improved by hearing aids
  - Objective clinical endpoints
  - Extensive discussions with KOLs about study design
- Will outline clinical trial plan and timing in January