Demonstration of Durable Anti-VEGF Protein Expression and Otic Tolerability Following Intracochlear Delivery of AK-antiVEGF (AAVAnc80-antiVEGF Vector) Across Multiple Doses in Non-human Primates

AKOUOS

A Wholly Owned Subsidiary of Eli Lilly and Company

Shimon P. Francis*, Yuan Gao, Michael J. McKenna, Jean Phillips, Kathleen Lennon, Brian Lin, John Connelly, Pascal Schamber, Junaid Syed, Jenna Soper, Aaron D. Tward, Ann E. Hickox, Emmanuel J. Simons, Eva Andres-Mateos, Jennifer A. Wellman, Michelle D. Valero

Disclosures

Shimon Francis is an employee of Akouos, Inc., a wholly owned subsidiary of Eli Lilly and Company, and has received and is receiving compensation from Akouos, Inc.

SAFE HARBOR PROVISION

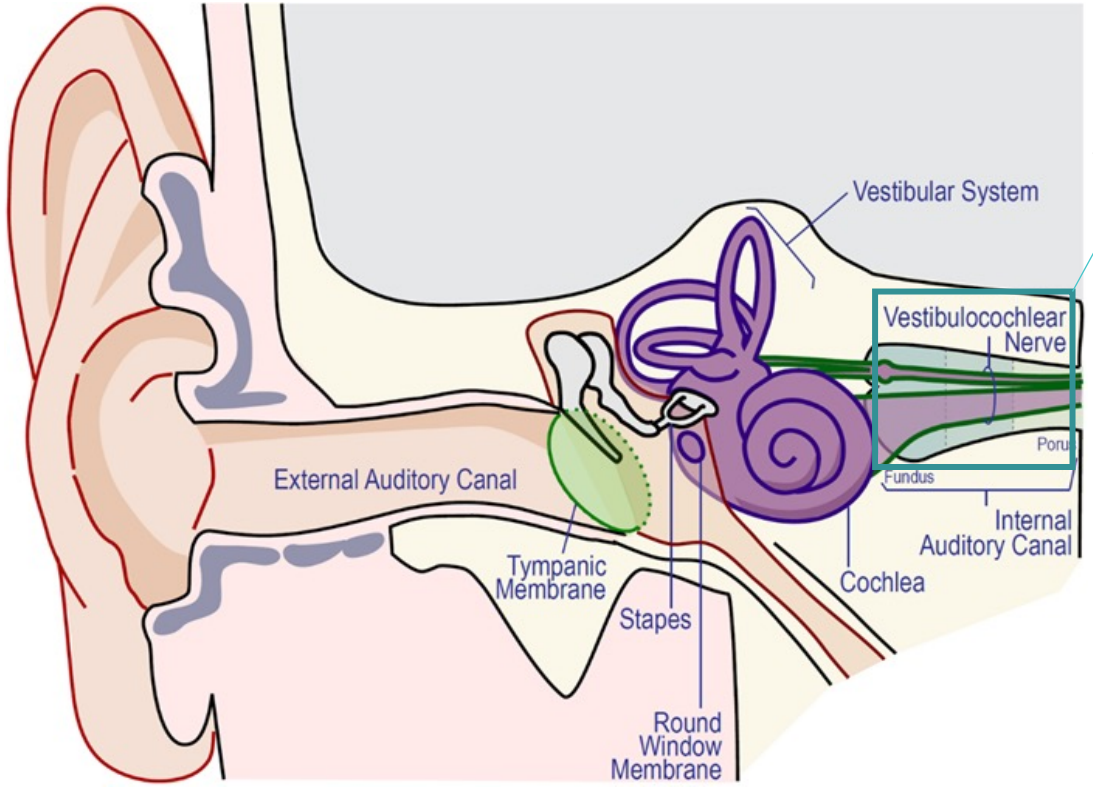
This presentation contains forward-looking statements that are based on management's current expectations, but actual results may differ materially due to various factors. The company's results may be affected by factors including, but not limited to, the risks and uncertainties in pharmaceutical research and development; competitive developments; regulatory actions; the extent and duration of the effects of the COVID-19 pandemic; litigation and investigations; business development transactions; economic conditions; and changes in laws and regulations, including health care reform.

For additional information about the factors that affect the company's business, please see Eli Lilly's latest Forms 10-K,10-Q, and any 8-Ks filed with the Securities and Exchange Commission.

The company undertakes no duty to update forward-looking statements except as required by applicable law

Vestibular Schwannoma

- Vestibular schwannomas (VSs) are tumors arising from Schwann cells that ensheathe the vestibulocochlear nerve
- VS is estimated to affect approximately 200,000 individuals in the US and Europe[1,2,3]
- VS symptoms include hearing loss, tinnitus, headaches, and impaired balance, and could progress to additional co-morbidities
- Current standard of care is observation, surgical resection, and/or radiation therapy
- Vascular endothelial growth factor (VEGF) is upregulated in VS, including sporadic tumors[3]



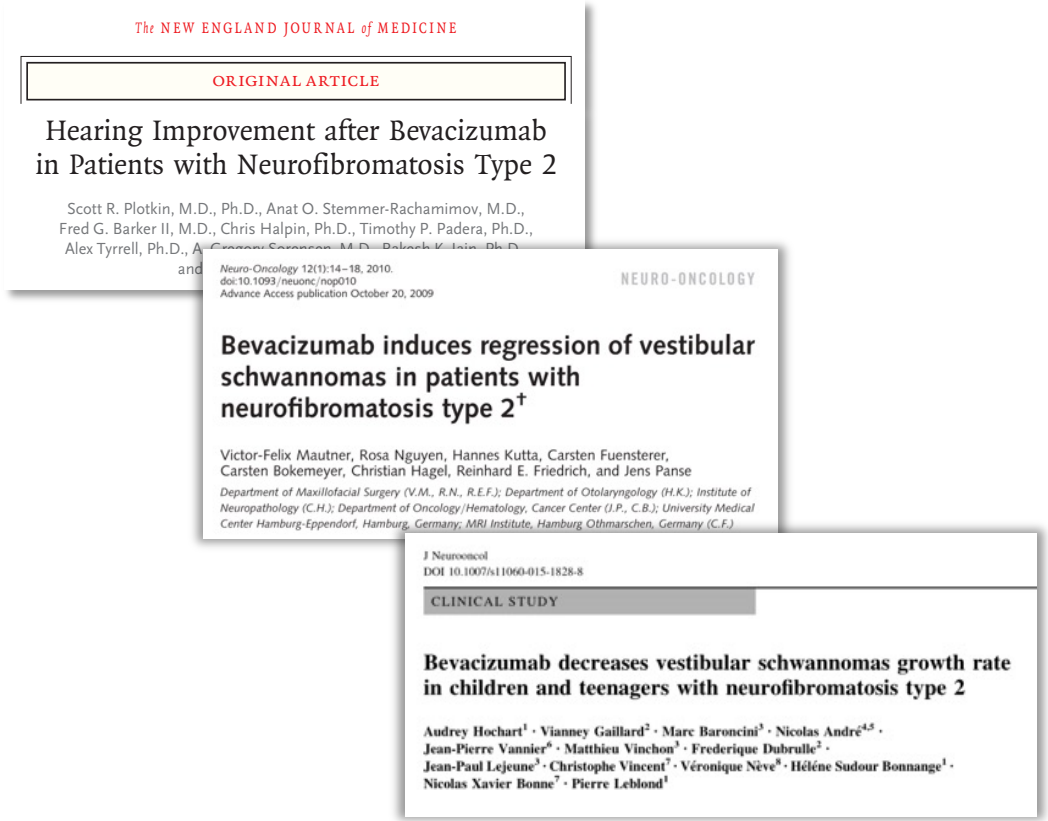
VS most commonly occurs along the vestibulocochlear nerve as it courses through the internal auditory canal (IAC) to the brainstem. The majority of small, intracanalicular tumors (less than 5 mm width) arise within the lateral third of the IAC, nearest to the cochlea[4]. Larger tumors may extend beyond the IAC into the cerebellopontine angle. Image modified from: https://commons.wikimedia.org/wiki/File:Anatomy_of_the_Human_Ear.svg

Abbreviations: IAC= internal auditory canal; VEGF = vascular endothelial growth factor; VS(s) = vestibular schwannoma(s).

References: [1]Lin 2005 *Arch Otolaryngol Head Neck Surg;* [2]Schmidt 2012 *Neurosurg Focus*; [3]Marinelli 2018 *Otolaryngol Head Neck Surg;* [4]Koutsimpelas 2012 *ORL J Otorhinolaryngol Relat Spec;* [5]Koen 2020 *Otolaryngol Head Neck Surg.*

VEGF Inhibition Shows Promise in *NF2*-related VS, but Systemic Administration Can Result in Toxicity

Clinical Trial Data Demonstrate Ability of Systemic VEGF Inhibitor to Improve Hearing and Reduce Tumor Volume in Some Patients With VS



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hearing Improvement after Bevacizumab in Patients with Neurofibromatosis Type 2

Scott R. Plotkin, M.D., Ph.D., Anat O. Stemmer-Rachamimov, M.D., Fred G. Barker II, M.D., Chris Halpin, Ph.D., Timothy P. Padera, Ph.D., Alex Tyrrell, Ph.D., A

Neuro-Oncology 12(1):14–18, 2010.
doi:10.1093/neuonc/nop010
Advance Access publication October 20, 2009

NEURO-ONCOLOGY

Bevacizumab induces regression of vestibular schwannomas in patients with neurofibromatosis type 2†

Victor-Felix Mautner, Rosa Nguyen, Hannes Kutta, Carsten Fuensterer, Carsten Bokemeyer, Christian Hagel, Reinhard E. Friedrich, and Jens Panse

Department of Maxillofacial Surgery (V.M., R.N., R.E.F.); Department of Otolaryngology (H.K.); Institute of Neuropathology (C.H.); Department of Oncology/Hematology, Cancer Center (J.P., C.B.); University Medical Center Hamburg-Eppendorf, Hamburg, Germany; MRI Institute, Hamburg Othmarschen, Germany (C.F.)

J Neurooncol
DOI 10.1007/s11060-015-1828-8

CLINICAL STUDY

Bevacizumab decreases vestibular schwannomas growth rate in children and teenagers with neurofibromatosis type 2

Audrey Hochart[1] · Vianney Gaillard[2] · Marc Baroncini[3] · Nicolas André[4,5] · Jean-Pierre Vannier[6] · Matthieu Vinchon[3] · Frederique Dubrulle[2] · Jean-Paul Lejeune[3] · Christophe Vincent[7] · Véronique Nève[8] · Hélène Sudour Bonnange[1] · Nicolas Xavier Bonne[7] · Pierre Leblond[1]

Meta-analysis: Clinical Trials of Efficacy and Safety of Bevacizumab in Patients With *NF2*-related VS

Journal of Neuro-Oncology (2019) 144:239–248
https://doi.org/10.1007/s11060-019-03234-8

TOPIC REVIEW

Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: a systematic review and meta-analysis of treatment outcomes

Victor M. Lu[1] · Krishnan Ravindran[1] · Christopher S. Graffeo[1] · Avital Perry[1] · Jamie J. Van Gompel[1] · David J. Daniels[1] · Michael J. Link[1]

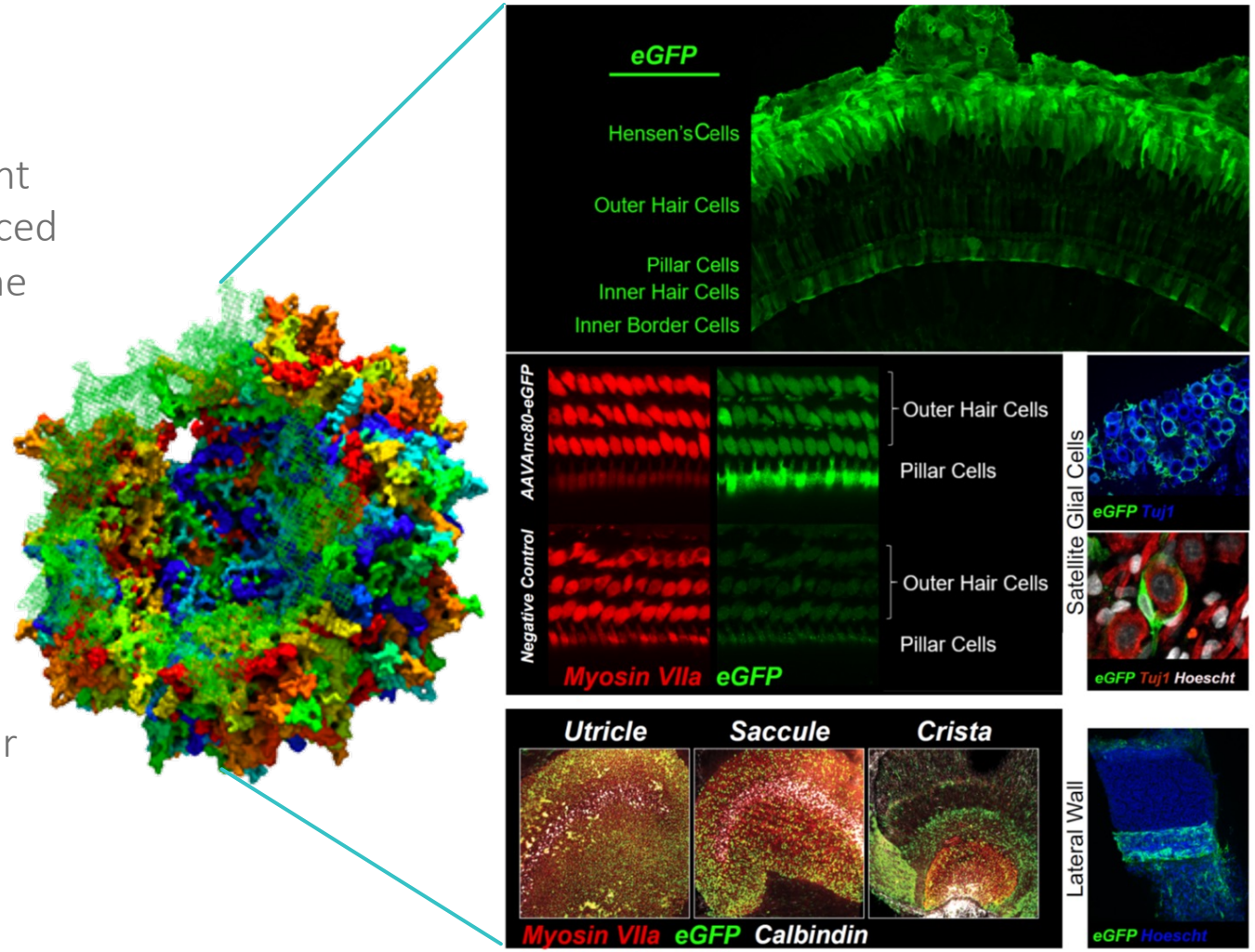
Outcome	Pooled incidence (95% CI)
Radiographic response	
Partial regression	41% (31–51%)
Stable	47% (39–55%)
Progression	7% (1–15%)
Hearing outcome	
Improvement	20% (9–33%)
Stable	69% (51–85%)
Worsening	6% (1–15%)

Outcome	Pooled incidence (95% CI)
Complications	
Serious toxicity	15% (10–26%)
Hypertension	33% (20–45%)
Proteinuria	43% (23–64%)
Amenorrhea	70% (51–87%)
Other	
Surgical intervention	11% (2–20%)

Abbreviations: *NF2* = neurofibromatosis type 2 gene; VEGF = vascular endothelial growth factor; VS = vestibular schwannoma.

AAVAnc80 Efficiently Transduces Multiple Cell Types in the Inner Ear

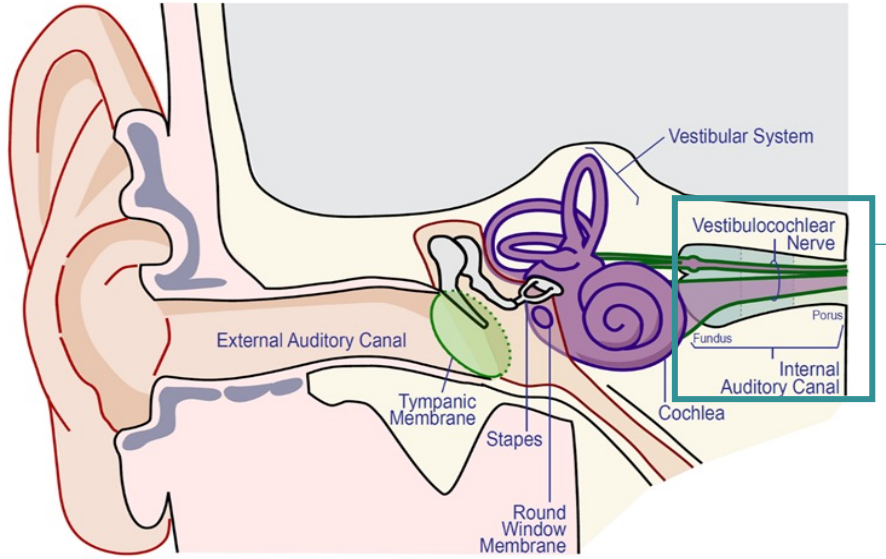
- ✓ Conducted nonclinical studies across three different species of non-human primate (NHP) using enhanced green fluorescent protein (eGFP) as a reporter gene delivered by AAVAnc80
- ✓ AAVAnc80 can efficiently transduce multiple target cell populations throughout the primate inner ear
- ✓ In the planned approach, after administration of AK-antiVEGF, an AAVAnc80 vector utilizing a ubiquitous promoter, the cochlear and vestibular cells are expected to produce and secrete anti-VEGF protein into the perilymph



All micrographs are from Study AK-007, with the exception of Satellite Glial Cells from Study AK-011

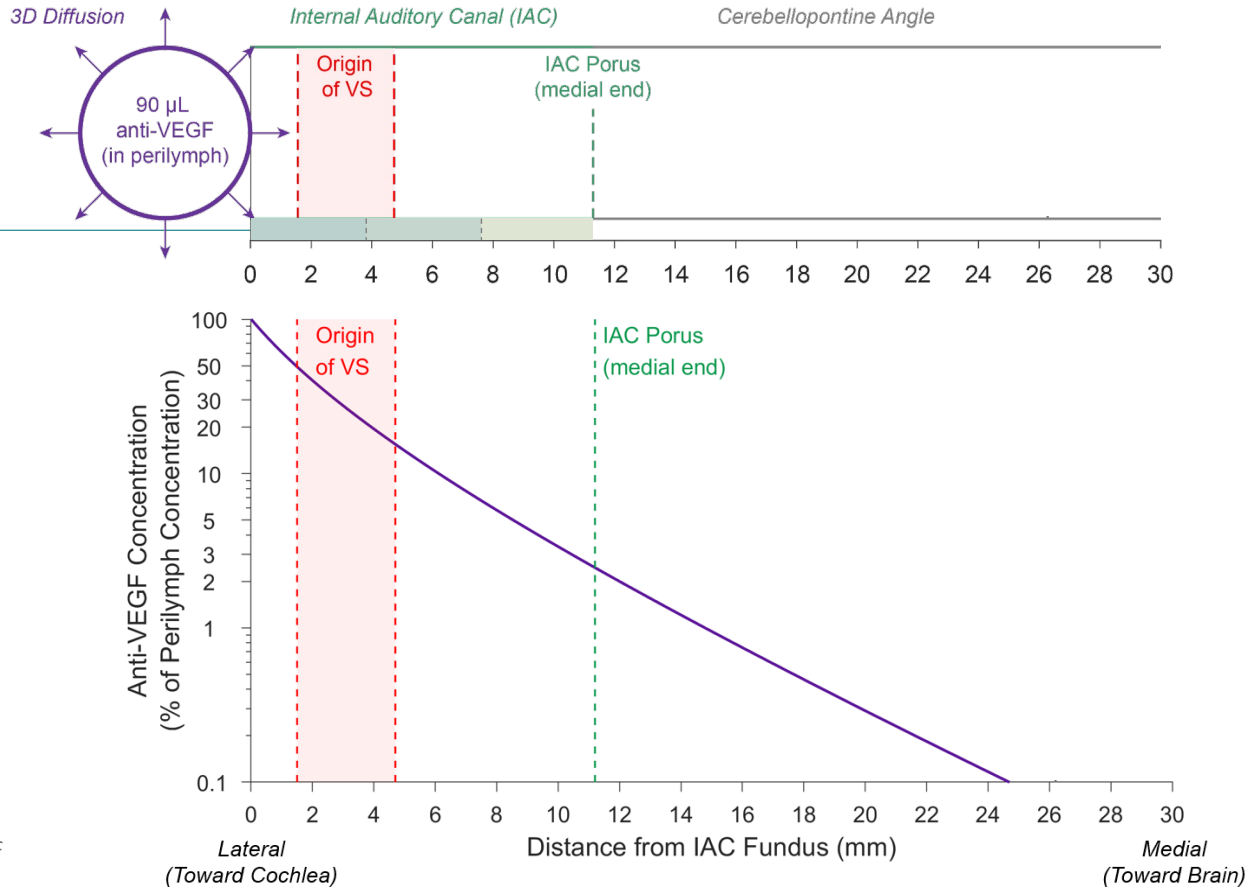
Abbreviations: AAVAnc80 = adeno-associated viral vector variant Anc80; eGFP = enhanced green fluorescent protein; NHP = non-human primate; Tuj1 = beta-tubulin III; VEGF = vascular endothelial growth factor.

Intracochlear Administration of AK-antiVEGF is Expected to Achieve Local Anti-VEGF Protein Exposure



- The majority of VS tumors originate in the lateral third (nearest the cochlea) of the internal auditory canal (IAC)[1]
- A computational model was used to estimate the concentration of diffused anti-VEGF protein as a function of distance from perilymph relative to the concentration of anti-VEGF protein in the perilymph
- The model simulation shows the rate at which anti-VEGF concentration decreases as a function of diffusion distance from the perilymph; diffused anti-VEGF concentration is expressed as a percentage of the concentration of anti-VEGF in perilymph

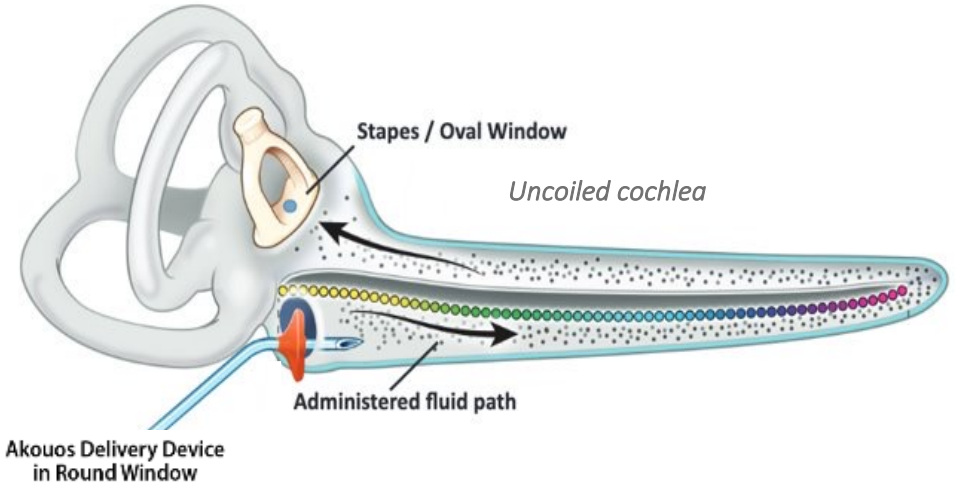
Secreted Anti-VEGF Protein is Predicted to Diffuse from Perilymph Through the IAC and Into the CPA



Abbreviations: CPA = cerebellopontine angle; IAC = internal auditory canal; VEGF = vascular endothelial growth factor; VS = vestibular schwannoma.

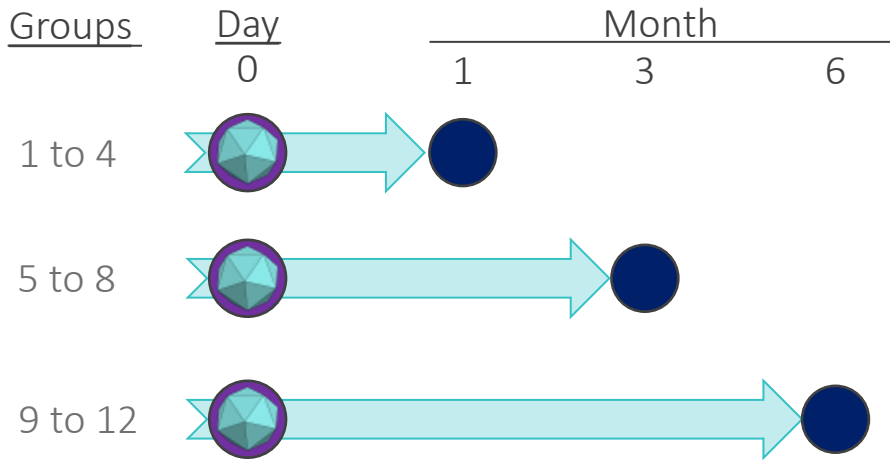
References: [1]Koen 2020 *Otolaryngol Head Neck Surg.*

Evaluating Potential for Durable and Tolerable Anti-VEGF Protein Expression in the NHP Inner Ear (AK-048)



Intracochlear administration of AK-antiVEGF or vehicle

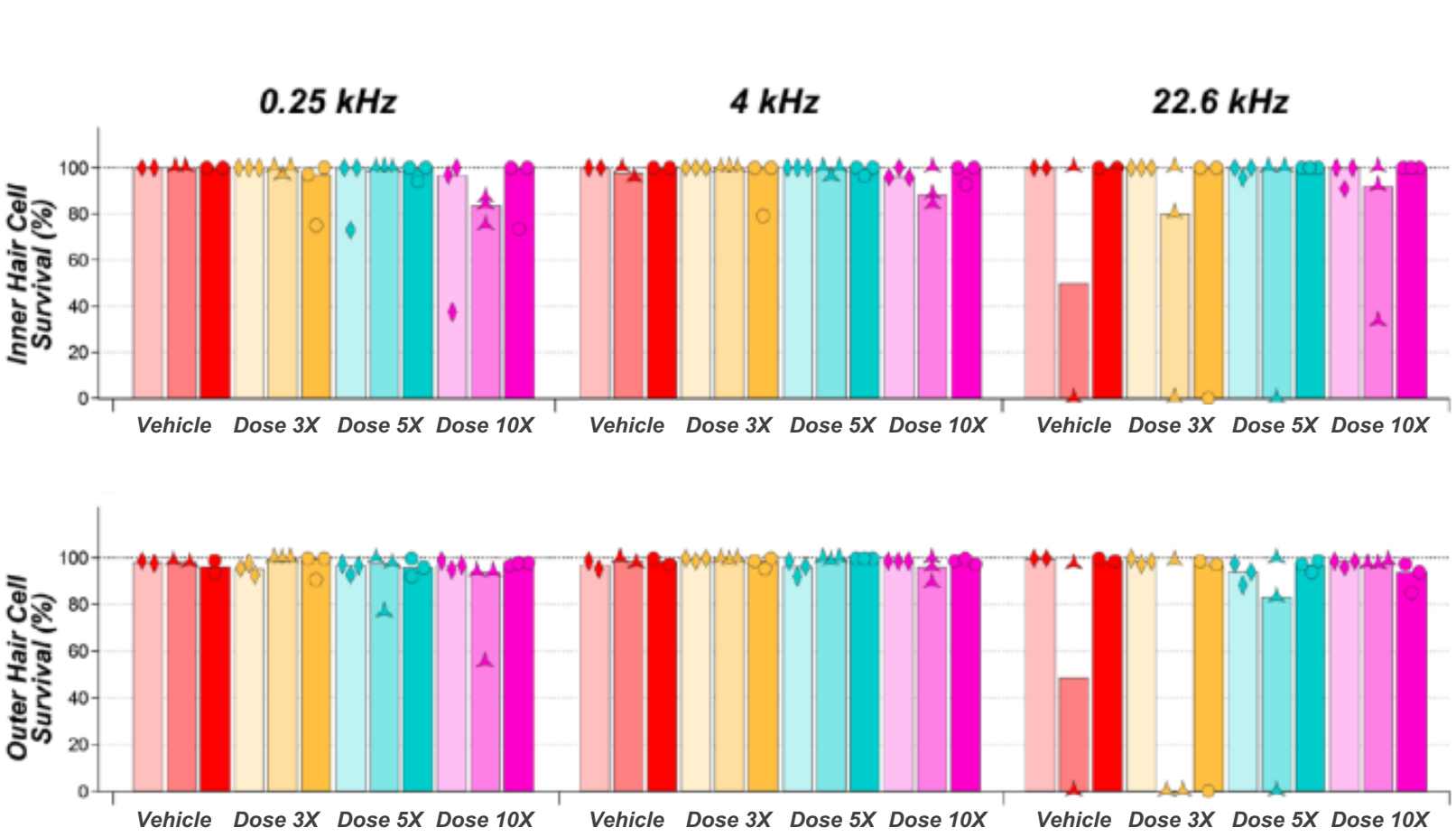
- Vehicle (n = 2 per group):
  - Groups 1, 5, and 9
- AK-antiVEGF (n = 3 per group):
  - Dose 3X: Groups 2, 6, and 10
  - Dose 5X: Groups 3, 7, and 11
  - Dose 10X: Groups 4, 8, and 12

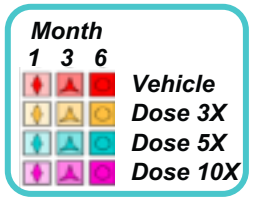


Dissection and immunostaining of left cochleae for evaluation of hair cell survival and detection of anti-VEGF protein

Abbreviations: NHP = non-human primate; VEGF = vascular endothelial growth factor.

Overall, Hair Cell Survival was Robust in NHP Cochleae Across All Study Groups





- Hair cell survival was robust in most ears
- There was no systematic loss of hair cells as a function of dose or survival duration
- Loss of hair cells in the basal 22.6 kHz region suggests damage specific to the NHP surgical approach / intracochlear administration procedure

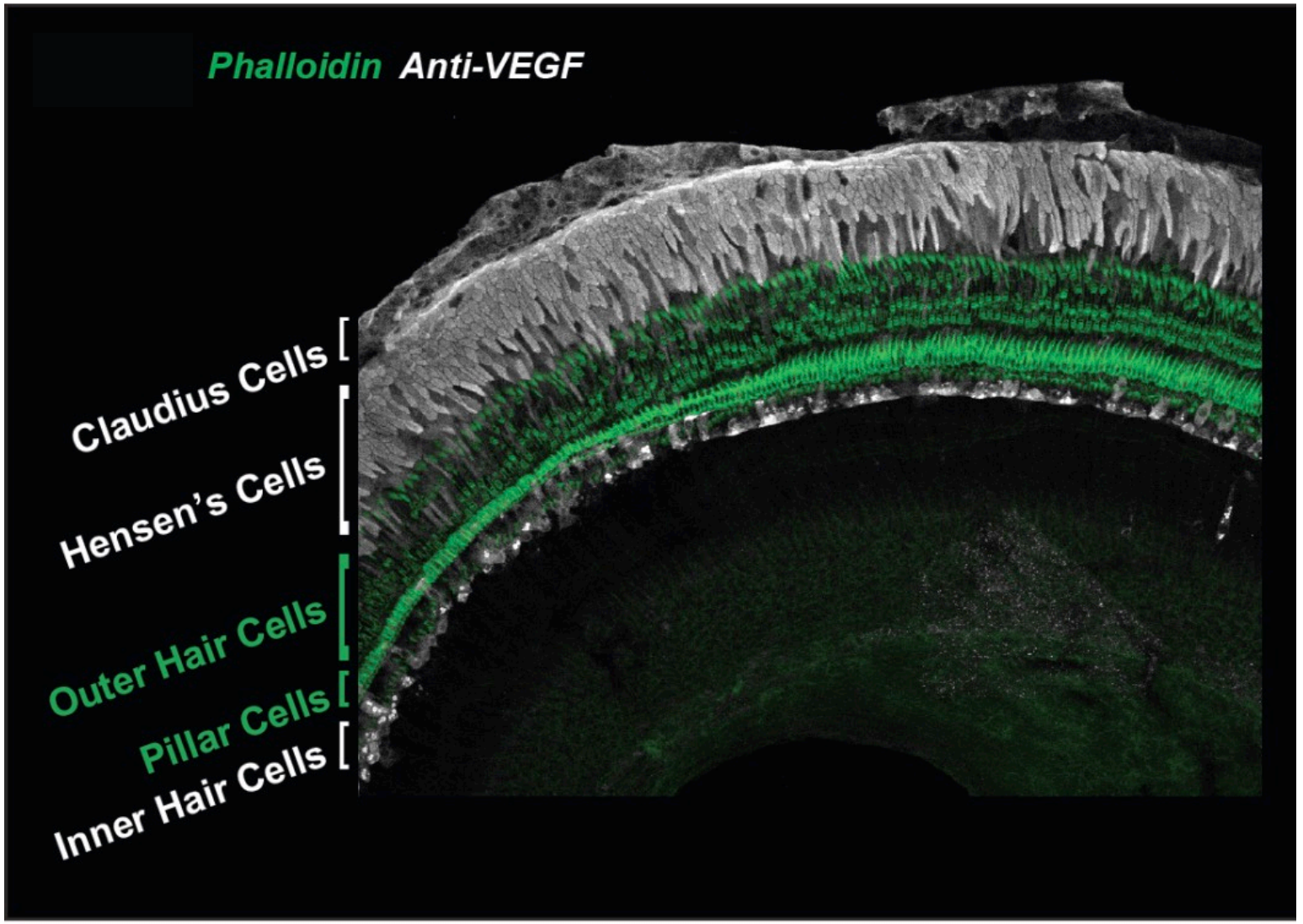
Individual data (markers) and median data are shown

Abbreviations: kHz = kilohertz; NHP = non-human primate.

Anti-VEGF Protein was Detected in Multiple Cell Types in the NHP Inner Ear

Cochlear cell types with anti-VEGF protein include:

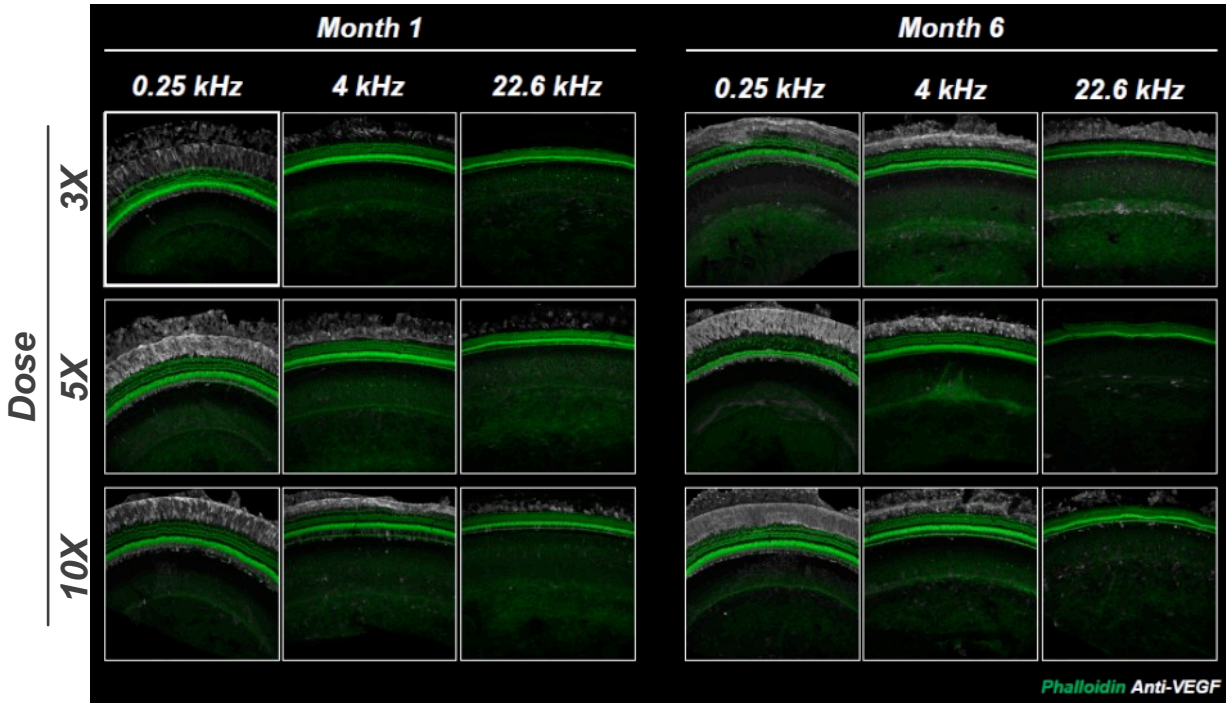
- Claudius cells
- Hensen's cells
- Inner hair cells
- Inner border cells
- Cells in Reissner's membrane



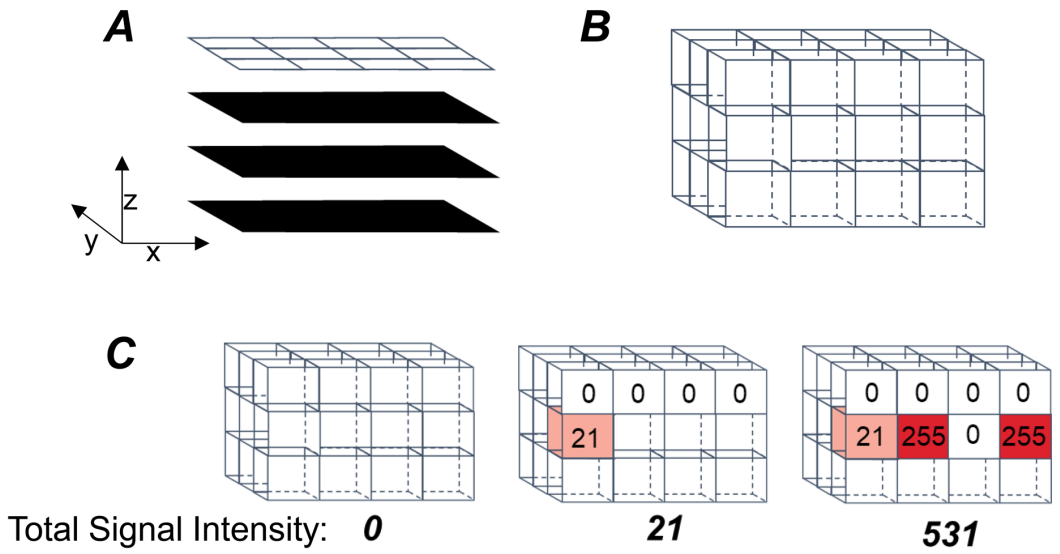
Abbreviations: NHP = non-human primate; VEGF = vascular endothelial growth factor.

Method to Quantify Anti-VEGF Protein Signal in Cochlear Micrographs

Cochleae were evaluated at three frequency positions for detection of anti-VEGF protein (shown in grayscale below, with phalloidin in green)

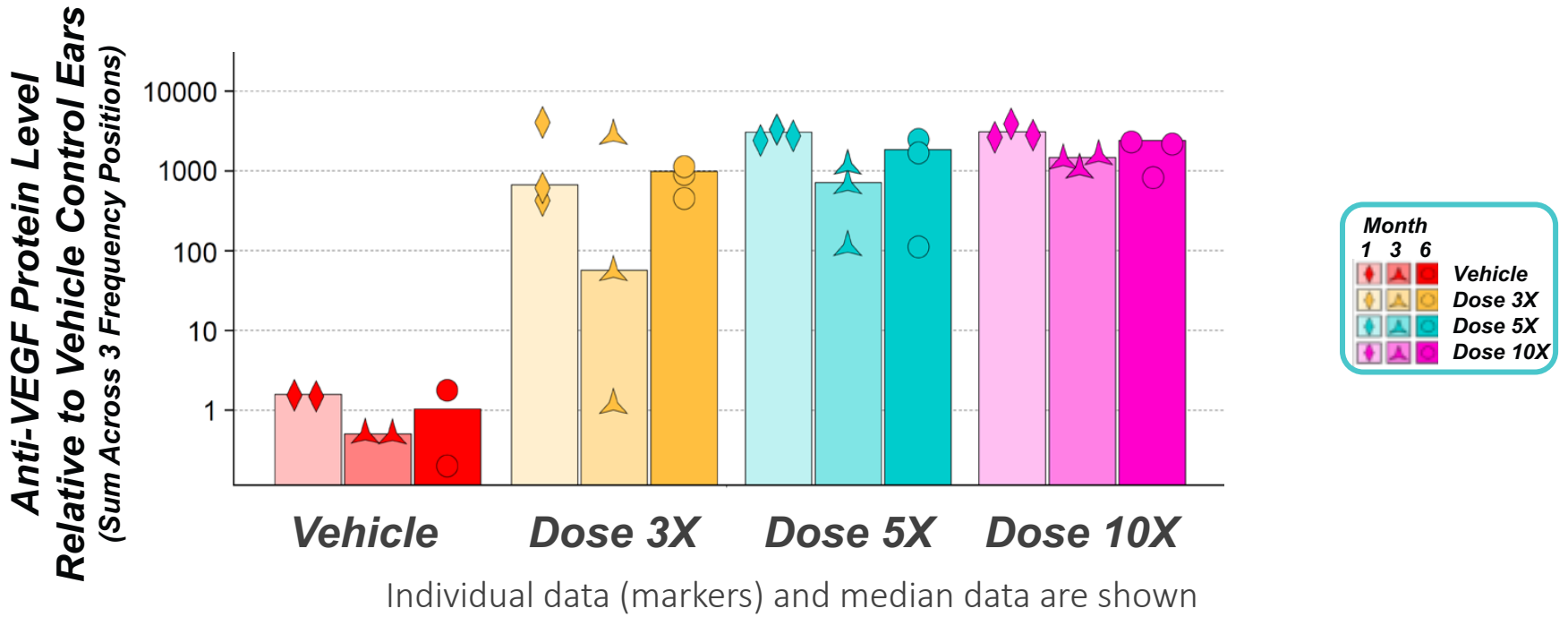


Fluorescence intensity in the anti-VEGF image acquisition channel was summed across the three representative frequency positions



Abbreviations: kHz = kilohertz; VEGF = vascular endothelial growth factor.

High Anti-VEGF Protein Expression Levels were Observed in NHP Cochleae Across All Doses and Survival Durations



Individual data (markers) and median data are shown

Relative anti-VEGF protein expression levels were overall robust and similar across AK-antiVEGF doses and survival durations, suggesting both durable expression through the longest in-life duration evaluated (6 months) and a lack of a dose-response effect within the dose range evaluated.

Abbreviations: NHP = non-human primate; VEGF = vascular endothelial growth factor.

Summary

- There remains a high unmet need for alternative treatments for patients with VS
- Previously published clinical trial data support the potential for systemically administered VEGF inhibitors to be efficacious in treating *NF2*-related VS
    - However, associated toxicity can limit the chronic systemic administration of VEGF inhibitors as a viable treatment option for VS
- Computational modelling supports the potential for diffusion of biologically active anti-VEGF protein levels to site of tumor following administration of AK-antiVEGF
- Local expression of anti-VEGF protein following intracochlear administration of AK-antiVEGF is robust, durable through at least 6 months post-administration, and well tolerated in NHPs
- Together, these data support the future clinical development of AK-antiVEGF for the potential treatment of VS
- Investigational New Drug (IND) application for AK-antiVEGF is planned for 2023

Abbreviations: IND = Investigational New Drug; *NF2* = neurofibromatosis type 2 gene; VEGF = vascular endothelial growth factor; VS = vestibular schwannoma.

Thank you!

Thank you!

Thank you!

Thank you!

Thank you!

Thank you!