

Cell Therapy Transplant for Hearing Loss

Auditory Neuron Progenitors (ANP1)
(*ReSonance*[™])

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Cell Cure Neurosciences

Forward-Looking Statements

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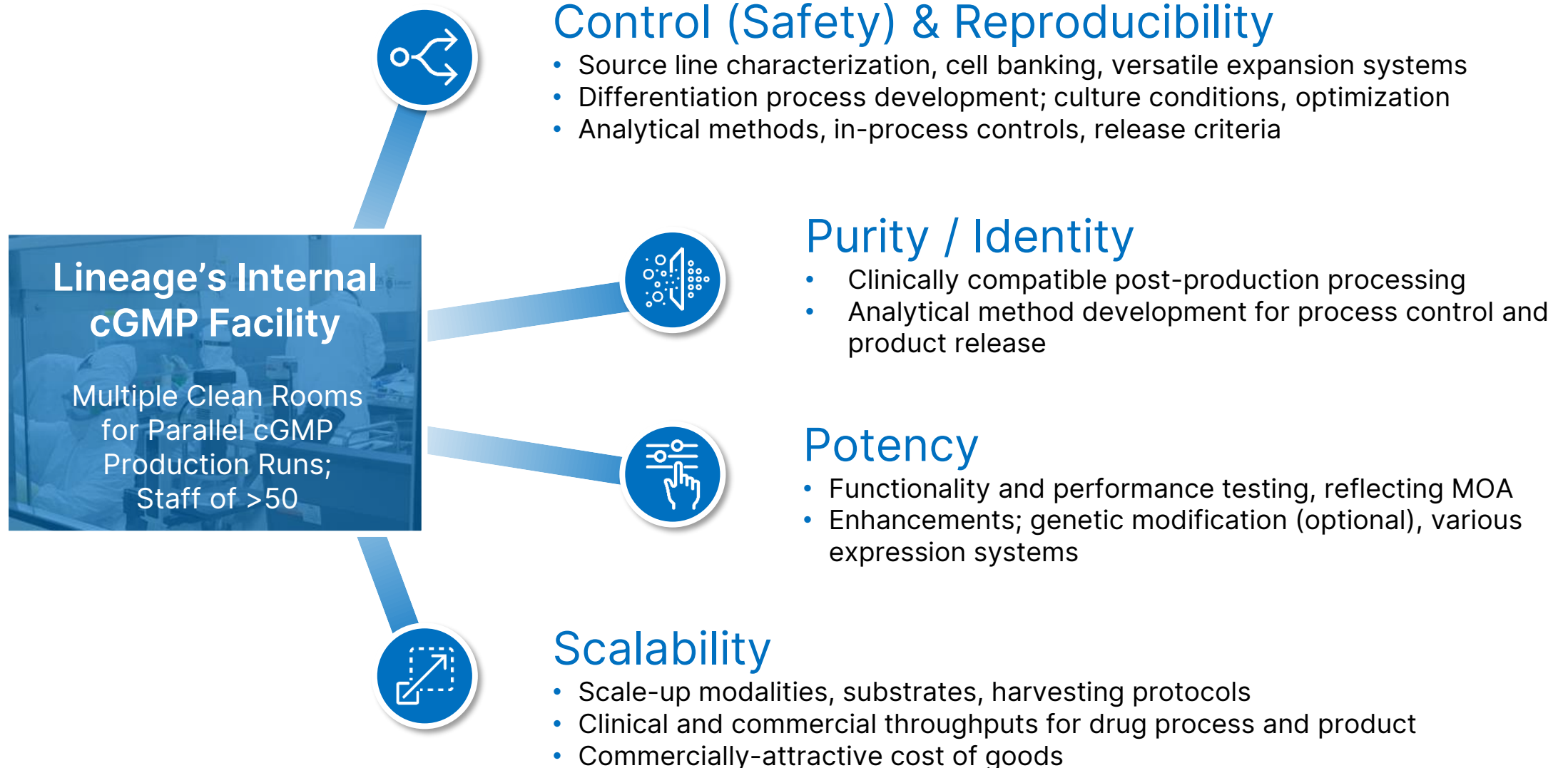
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Cell Cure Neurosciences

- An Israel-based subsidiary of Lineage Cell Therapeutics (LCTX), responsible for research, process development, and GMP production
- Development and production of unique allogeneic cell therapies from pluripotent stem cells
 - Versatile expansion and culturing systems of pluripotent stem cells
 - Process development, 2D, and 3D differentiation, for multiple lineages
 - Product release and qualification for clinical use (ready to inject)
- Infrastructure includes R&D, Analytical Labs and GMP production facilities
- Highly trained and skilled personnel (55)
- Validation
 - 2 clinical stage products, 3 pipeline products
 - \$670M global alliance with Roche/Genentech for lead program (“OpRegen”; an RPE cell transplant)

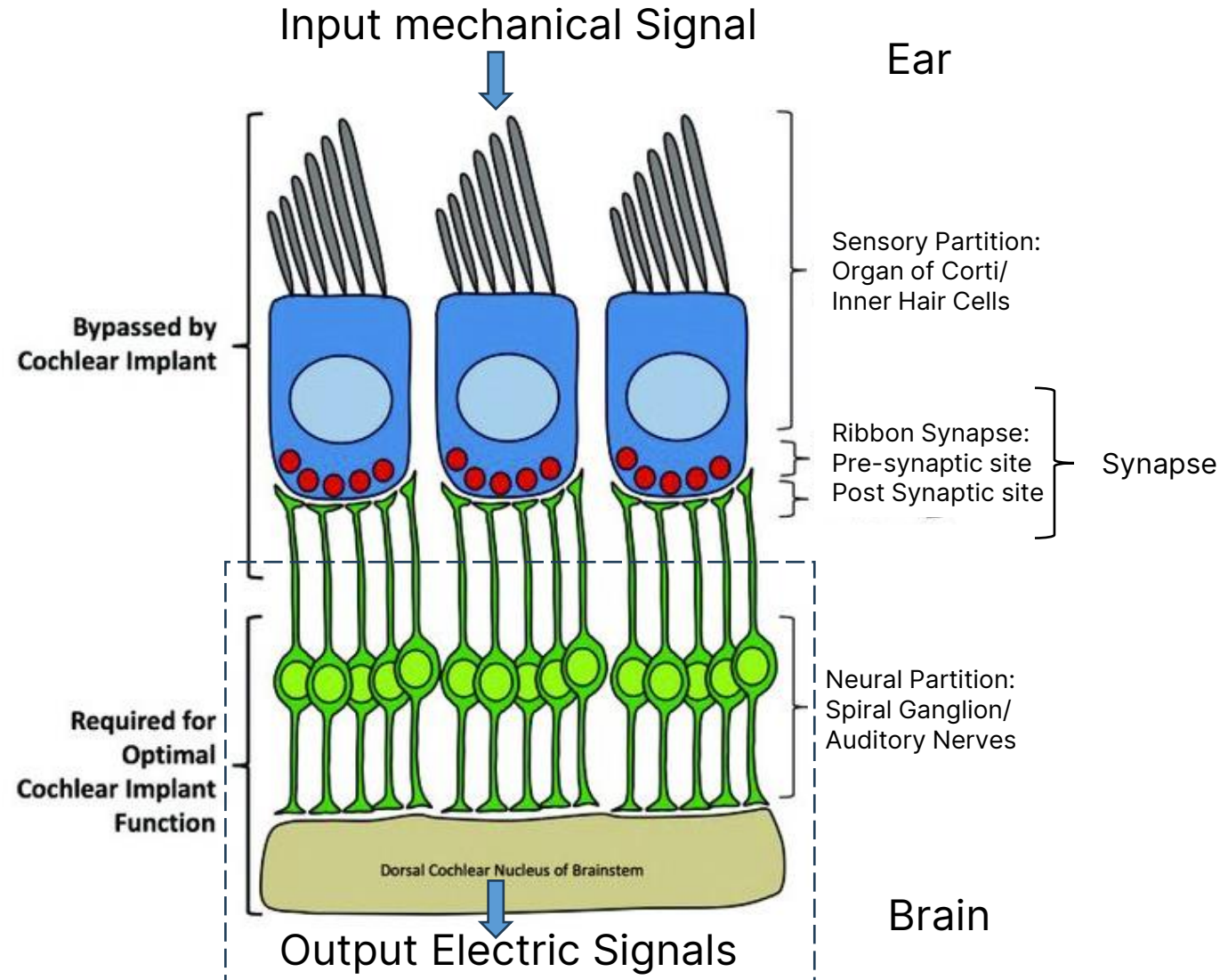


Requirements for a Successful Cell Therapy



Why Target Sensory Neuron Replacement?

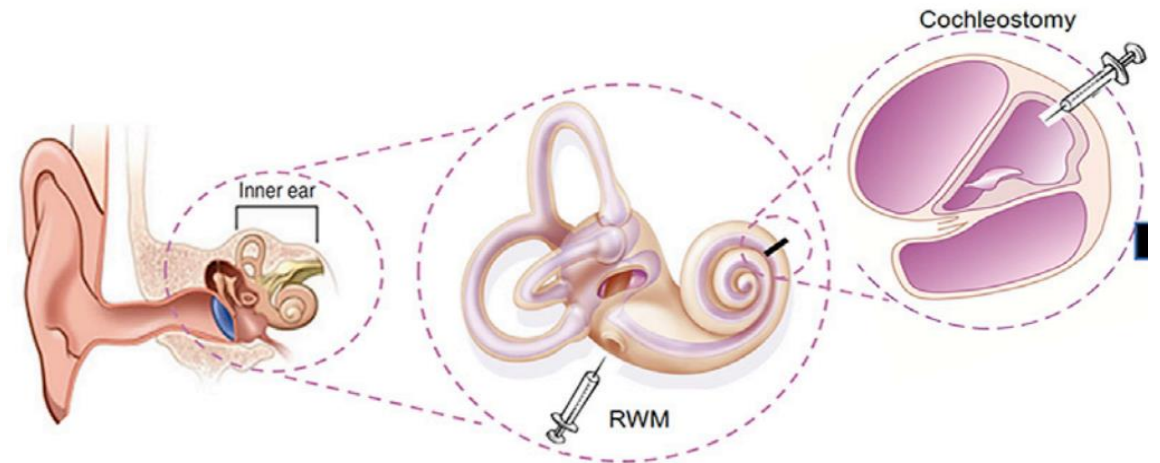
- Auditory Neuropathy Spectrum Disorder (ANSD) is a variety of diseases linked by the common trait of dysfunctional auditory nerve function
- ANSD could be treated by a single cell therapy by replacing damaged cells with healthy neuronal cells irrelevant of the pathology.
- Cell therapy may solve conditions where cochlear implants are non-functional due to neural deficiency



Adapted from: The Hearing Journal 73(6):p 32,33,34, June 2020.

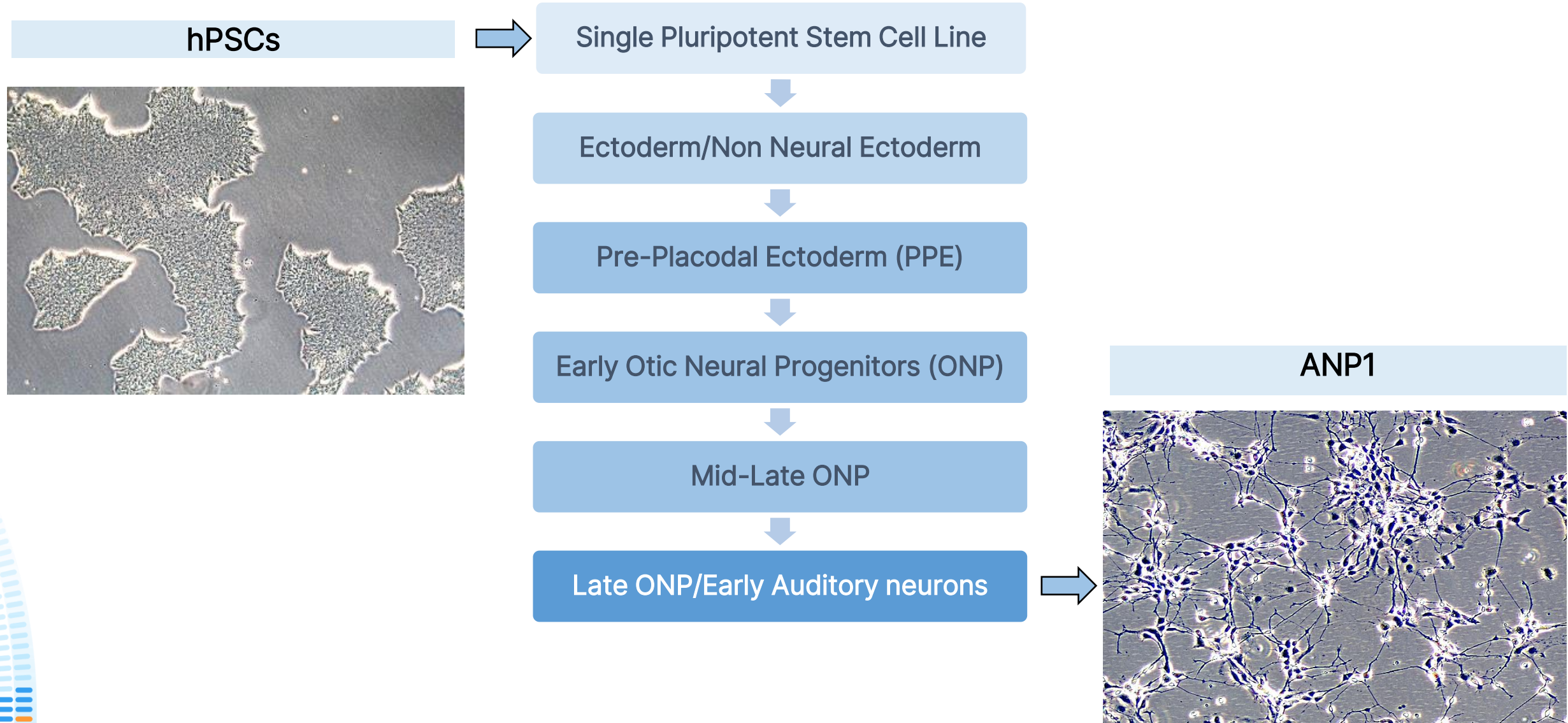
ANP1 Cell Therapy Product

- **ANP1** - Transplantable otic neural progenitors (ONP) derived from human pluripotent stem cells
 - Manufactured via a directed differentiation process that generates pure population of cells
 - Proprietary and protected manufacturing process based on in-house expertise, accompanied by in-process controls and batch release criteria using internally-developed analytical assays
- Transplanted ANP1 cells are permissible to further maturation into auditory neurons (AN)
- ANP1 is cryopreserved allogeneic off-the-shelf product, at clinical doses, ready to be thawed at clinical sites and injected into a patient's cochlea
- Potential ANP1 indications:
Auditory Neuropathy Spectrum Disorders
and/or in combination with cochlear implants.

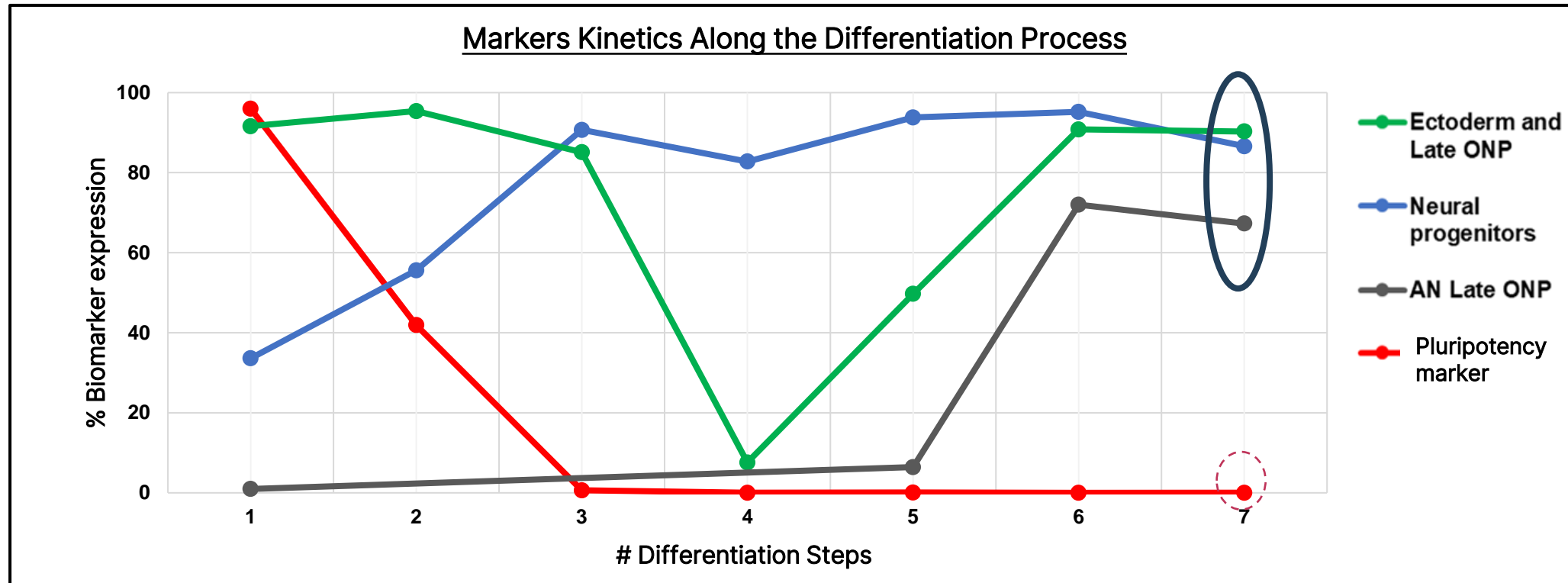
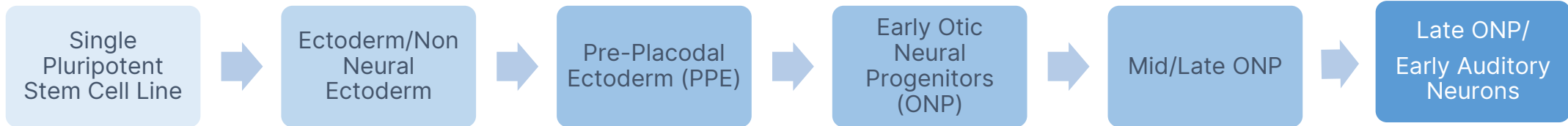


ANP1 Directed Differentiation Manufacturing Process

ANP1 differentiation follows natural otic development



Monitoring of ANP1 Differentiation Using In-Process Controls



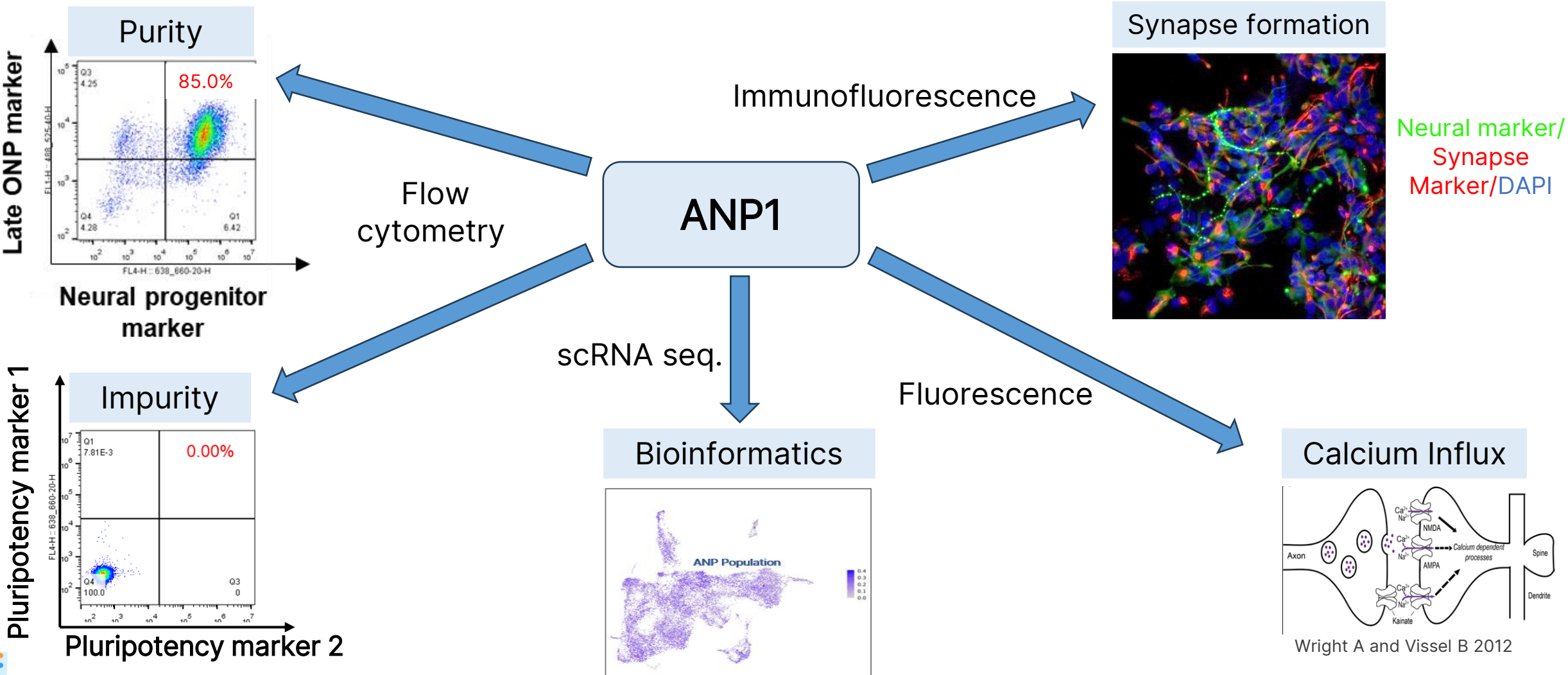
Induction of otic neural progenitor markers and Elimination of Pluripotency markers along differentiation timeline

Product Characterization To Assess Clinical Applicability

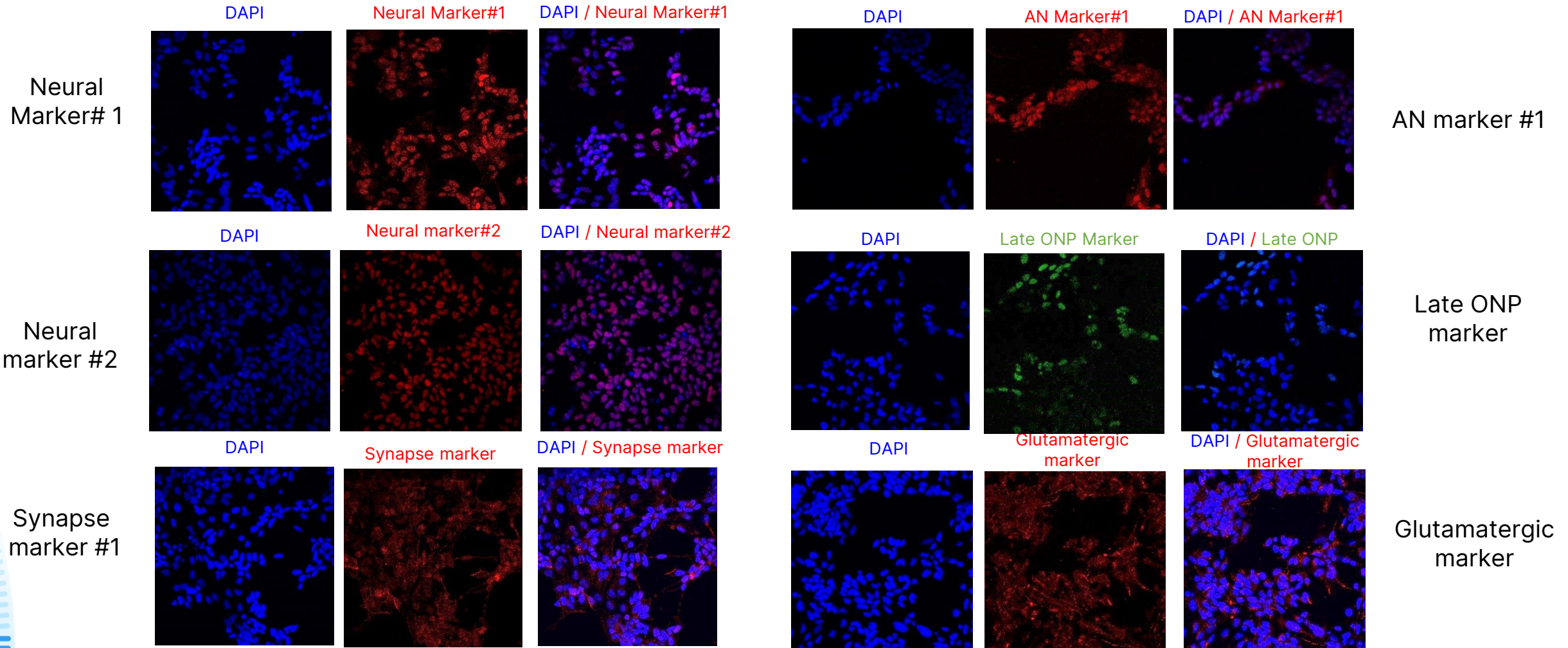
Snapshot of in-vitro analytical method development, designed to monitor the differentiation process and the final cell therapy product

Bio-Analytical Assessments

Functional Assessments

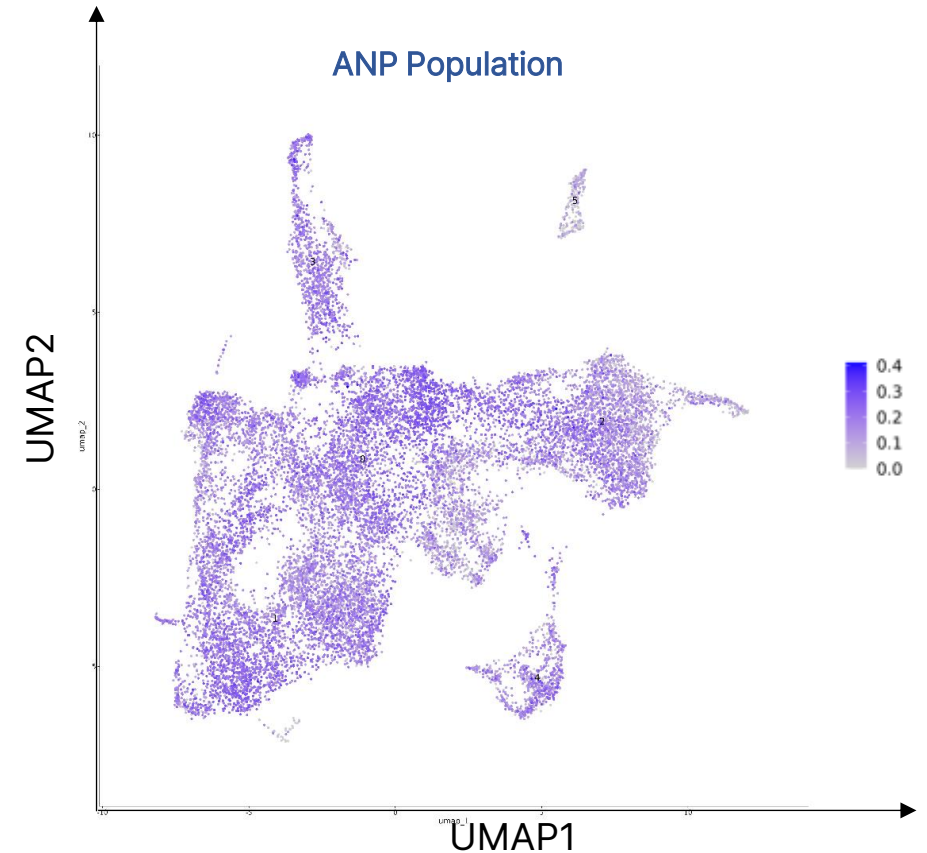


Advanced Characterization: ANP1 Expresses Otic Neural Progenitors and Neural Markers



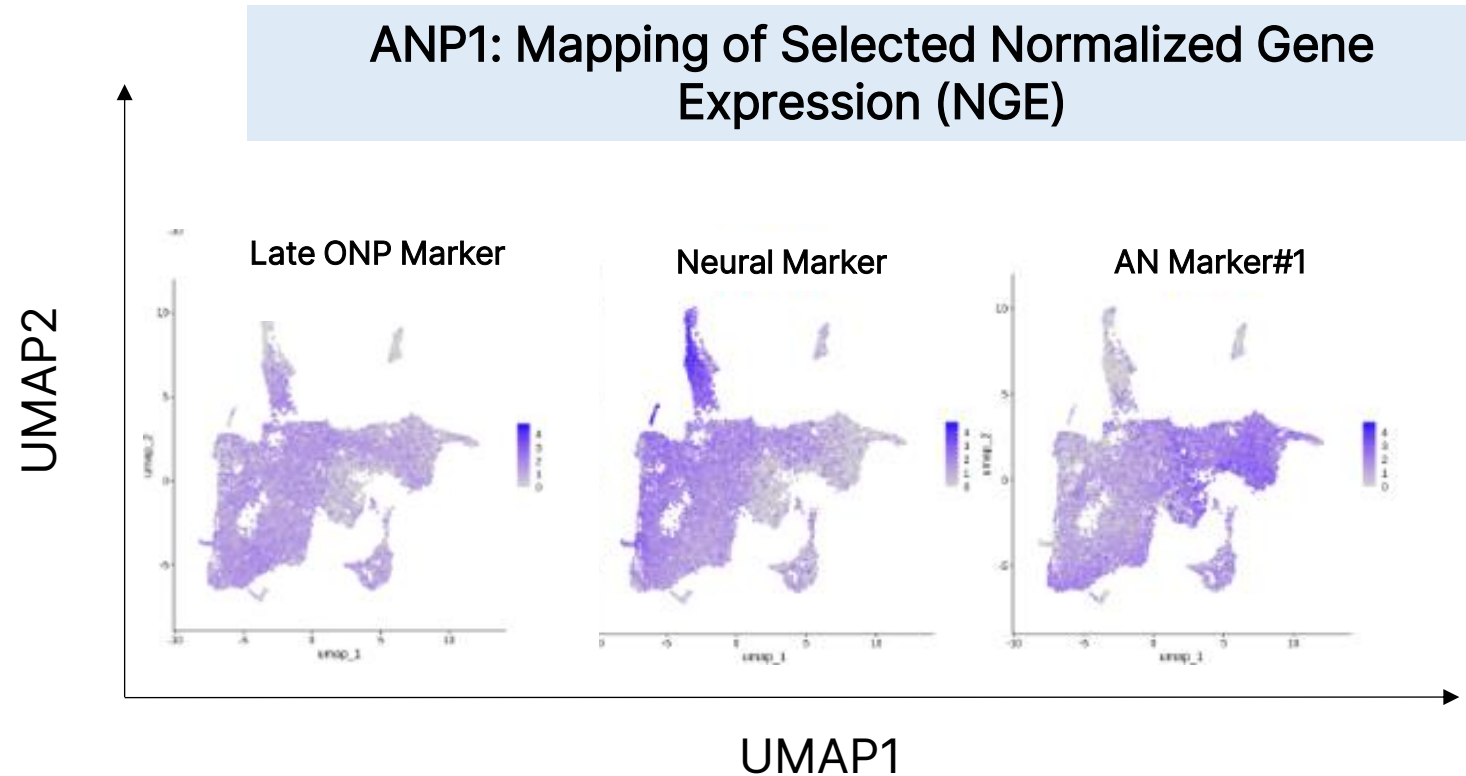
ANP1 Bioinformatics: Auditory Neuron-Related Gene Expression

- Bioinformatics is a computational approach that facilitates a deeper understanding of ANP1 cell function and differentiation
 - scRNA seq analysis was performed on the ready to inject ANP1 drug product
 - Bioinformatics using UMAP was created based on principle component analysis (PCA)
 - Generation of AN related Gene sets was based on available worldwide databases (such as MSigDB, Panglao and Cell Marker) and recently published scientific data.
- As a part of safety measures, an orthogonal analysis using a specific gene set did not detect any residual hPSC cells within the final product.



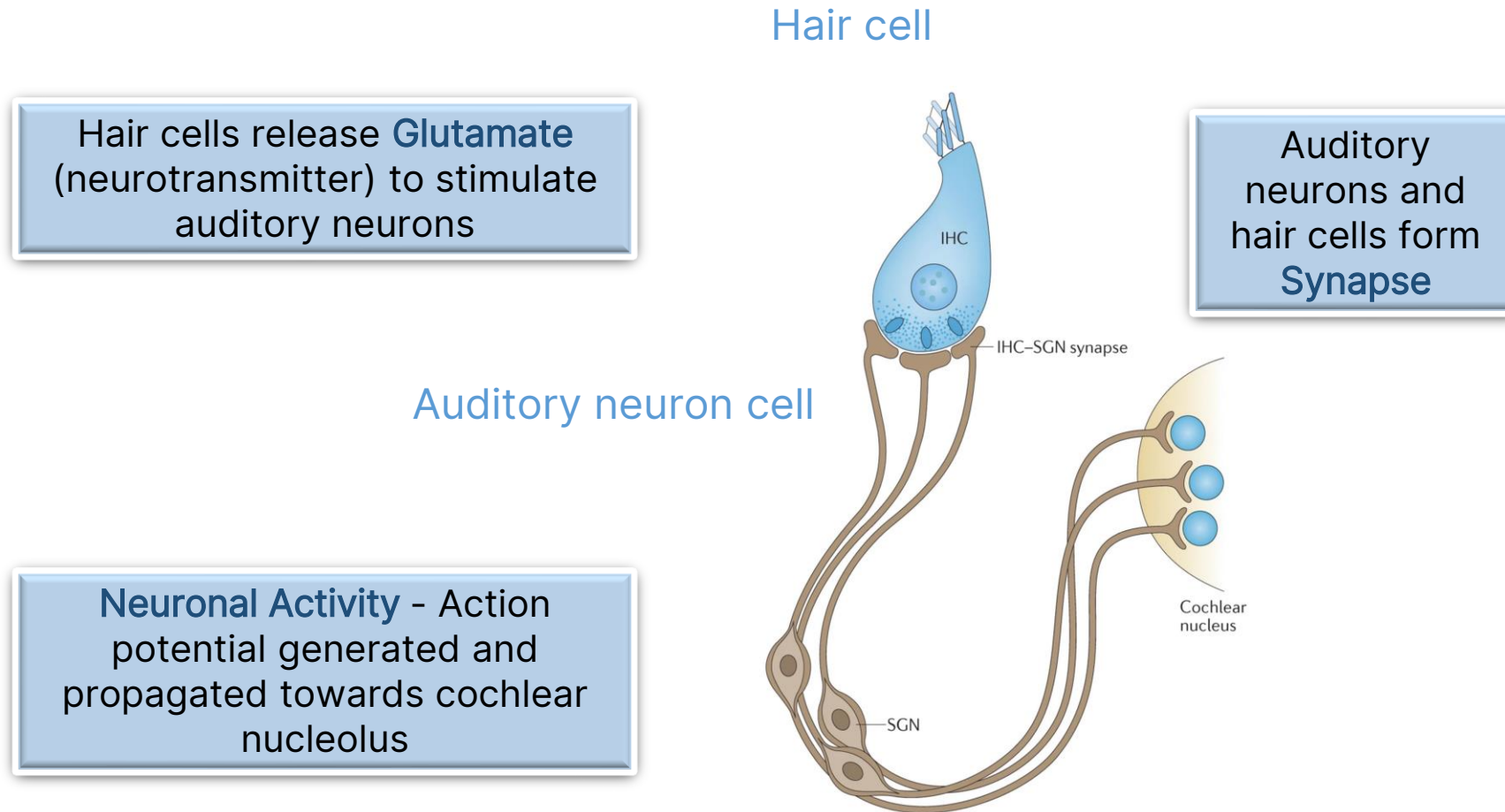
Color representation of cells expressing auditory neuron-defined gene set, based on literature review

ANP1 Bioinformatics: Auditory Neuron Genes Distribution



Bioinformatics reveals expression of key auditory neuron related genes distributed among ANP1 final product

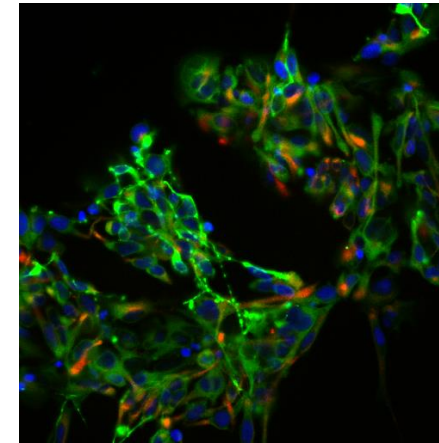
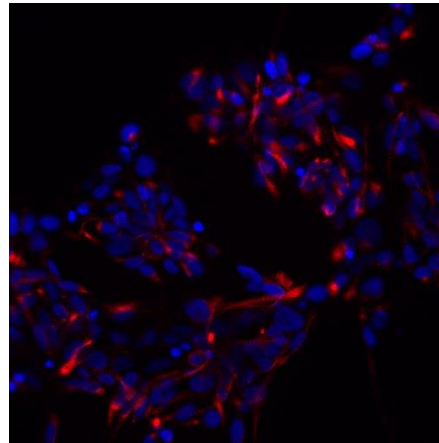
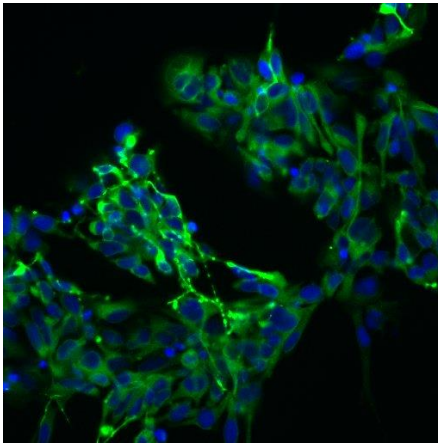
Developing Functional Assays for Auditory Neurons



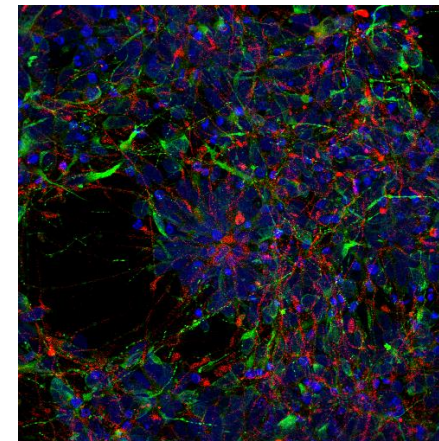
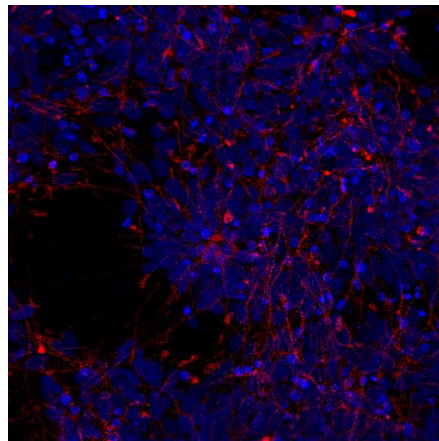
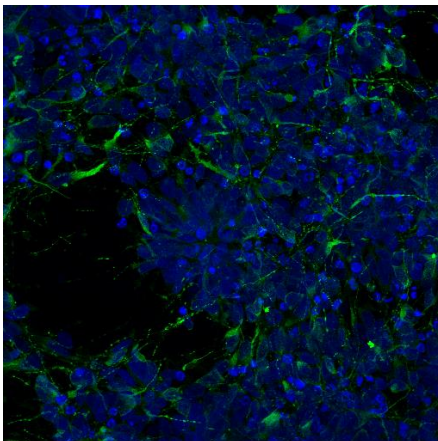
Adapted from Moser & Starr, Nat Rev Neurology, 2016

ANP1: Initial Assessment of Connectivity In-Vitro using a Synapse Marker

ANP1 morphological characterization is based on a combination of neural and synapse-related markers, showing a significant increase in expression with culture time



3 days maturation



3 weeks maturation

DAPI / Neural

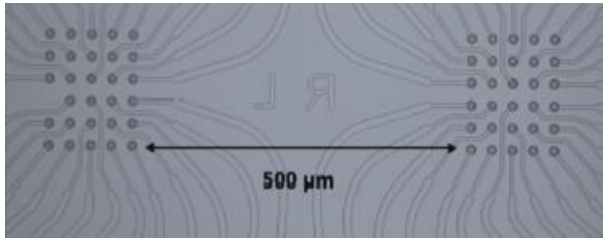
DAPI / Synapse

Neural / Synapse / DAPI

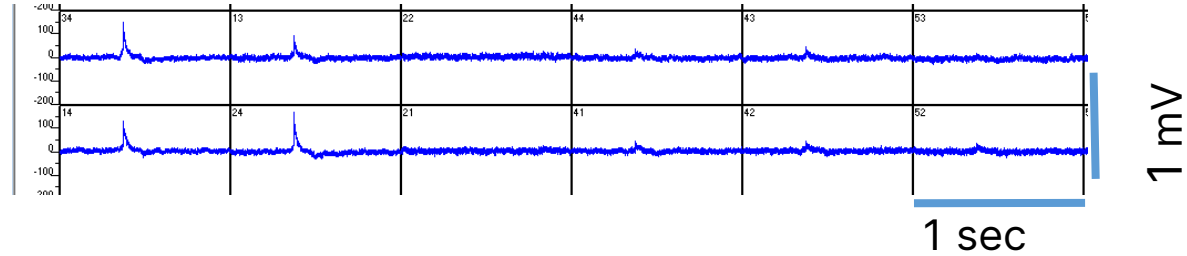
Auditory Neuronal Activity on Multi Electrode Array

Neuronal activity from multiple ANP1 cells was recorded simultaneously in the absence (basal activity) and presence (induced activity) of glutamate receptor agonist, using multi electrode array

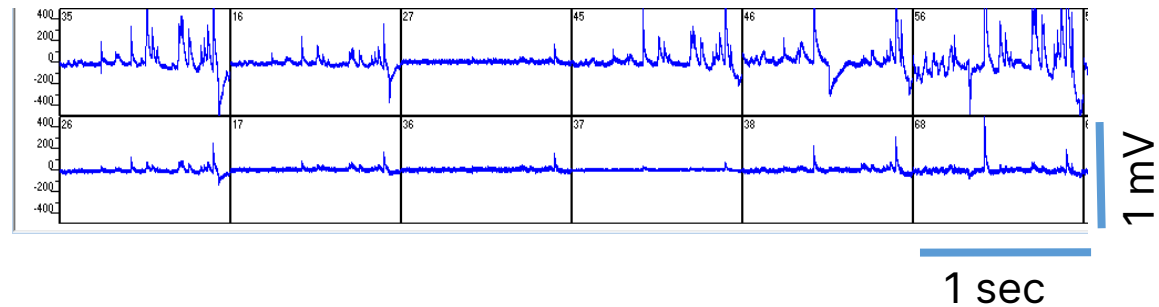
—Multi Electrode Array (MEA)



ANP1 Basal **Neuronal activity** without stimulant



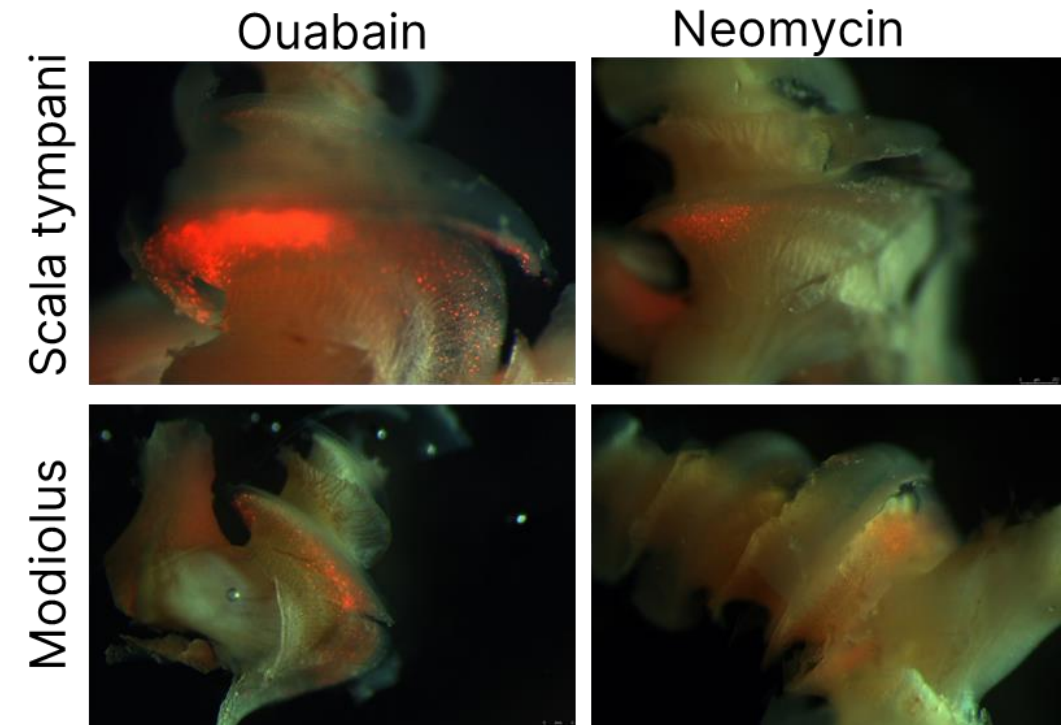
ANP1 induced activity using **Glutamate** Receptor Agonist



ANP1 showed auditory-specific glutamatergic neural response

ANP1 7-Day Preclinical Study Demonstrating Survival

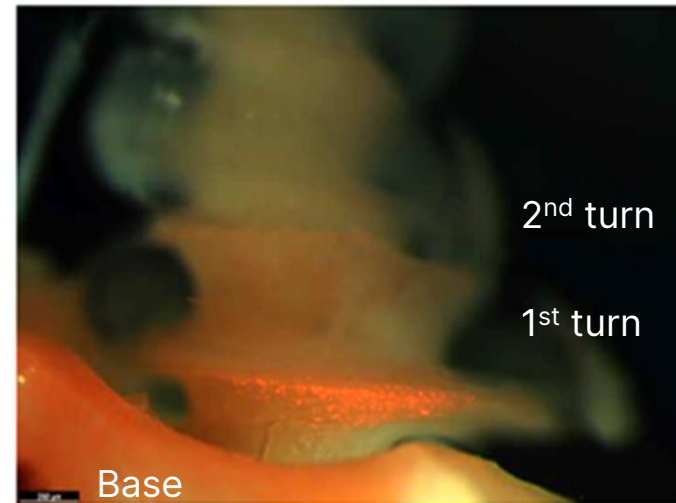
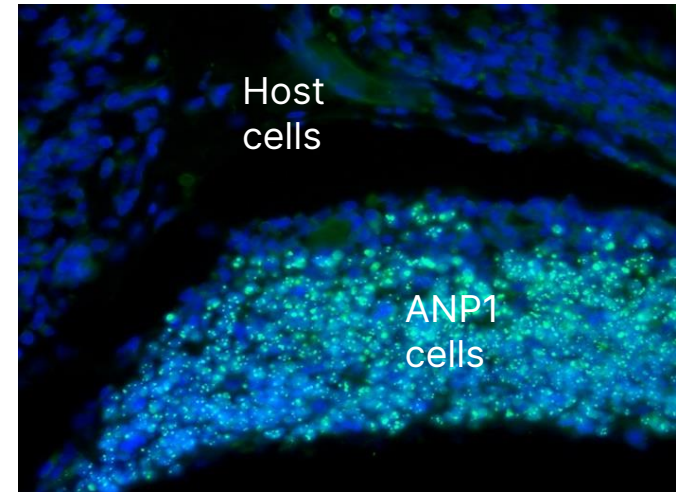
- Delivery and survival of ANP1 in preclinical models through collaboration with Prof. Yehoash Raphael and University of Michigan
- Comparison of multiple models of chemical deafness and routes of administration
 - Neomycin vs ouabain induced deafness
 - Modiolus vs scala tympani administration
- Conclusions
 - ANP1 cells observed 7 days post-administration
 - Ouabain model exhibited fewer side effects, improved depletion of endogenous neurons
 - Both routes of administration appeared effective



ANP1 cells (labeled red) observed 7 days after administration

ANP1 Preclinical Study- Indication of Cell Engraftment

- Conclusions
 - ANP1 cells were observed 7 days post-administration.
 - ANP1 cells were able to spread beyond the injection site.
 - ANP1 cells were able to engraft and populate the cochlea.



ANP1 cells were identified by red label or IF using human nucleoli-specific antibody (green)

ANP1 (“ReSonance”) Summary and Future Path

- ANP1 is a novel cell-based product candidate composed of auditory neuron progenitors derived from clinical grade pluripotent stem cells
- ANP1 cells were successfully manufactured at scale, met pre-set release criteria, and demonstrated relevant in-vitro functional activity
- ANP1 cells were cryopreserved in a clinical dose, ready-to-administer format, and were successfully thawed and transplanted into a guinea pig hearing loss model
- ANP1 survived and engrafted in a 7-day in-vivo study
- ANP1 cells are currently being evaluated in long term efficacy study
- ANP1 holds promise as new therapeutic modality for hearing loss

Thank You.

CCN, Lineage Cell Therapeutics, Inc.
Teams

University of Michigan Team
Prof. Yehoash Raphael
Lisa A. Beyer
Diane M. Prieskorn

