Oricula Therapeutics

Medicines to Preserve Hearing

Oricula Team

Vince Groppi, PhD, CEO & Co- Founder, Oricula Therapeutics. Translational Pharmacology.

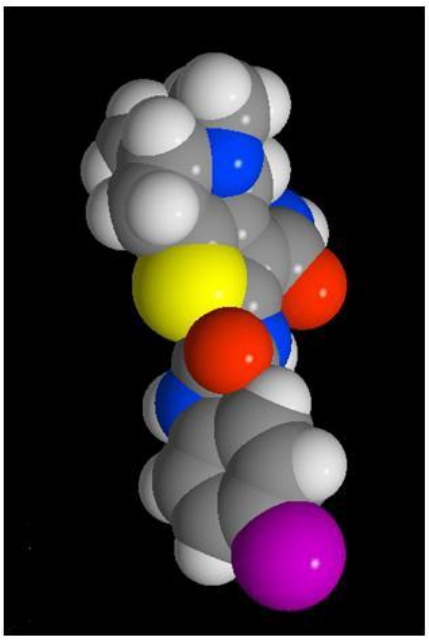
Edwin Rubel, PhD, CSO & Co-Founder, Oricula Therapeutics. Hearing Science.

Graham Johnson, PhD COO and Co- Founder, Oricula Therapeutics. Medicinal Chemistry

David Raible, PhD, Co-Founder Oricula Therapeutics. Cellular & Molecular Neuroscience.

Julian Simon, PhD Co-Founder Oricula Therapeutics. Medicinal Chemistry

Figure 1: Structure of ORC-13661



Our Mission

Oricula Therapeutics is an innovative biotechnology company committed to the development of the first in class drug that protects hearing and balance from the toxic effects of aminoglycosides, a highly effective class of antibiotics used to treat life-threatening, bacterial infections.

Unmet Medical Need

Aminoglycosides (AGs) are the second oldest class of antibiotic and are used to treat pseudomonas respiratory infections, endocarditis, neonatal septicemia, multiple drug resistant TB and other gram-negative infections. However, AG treatment causes permanent hearing loss in as many as 20 percent of the 2 to 4 million patients treated with parenteral AGs annually due to off-target toxicity. Physicians who use AG have to achieve a balance between using a dosing regimen that is effective in treating bacterial infections while causing as little damage as possible to the AG-sensitive cells of the inner ear. A clinically effective adjunctive therapy that protects against AG-induced ototoxicity would enable more effective use of these important antibiotics. We estimate the current market potential for adjunctive therapy would exceed $250 million per year and would grow as AG + adjunctive therapy was proven to be safe and cost-effective.

Innovation

AG-induced hearing loss is caused by the selective killing of the hair cells of the inner ear. Because the molecular target of AG-induced ototoxicity was not defined, we took the innovative approach of using a phenotypic zebrafish assay. The neuromasts in these fish are considered a translational model of mammalian auditory and vestibular hair cells in both pharmacology and physiology. Initial experiments demonstrated that AGs induced the expected toxicity in zebrafish. Using an unbiased high throughput screening strategy we identified drug-like molecules that protected AG-induced toxicity in zebrafish. An extensive medicinal chemical campaign using the zebrafish assay for primary pharmacology resulted the discovery of ORC-13661 (Figure 1), which has optimized both pharmacological and pharmaceutical properties. Further, ORC-13661 completely protected AG-induced hearing loss in a rat model at exposures similar to those that were effective in zebrafish.

Novel Mechanism of Action

It is now well established that AGs enter both inner ear hair cells and zebrafish lateral line hair cells through a specialized, nonselective cationic mechano-electrical transducer (MET) channel at the distal tip of the stereocilia. The pore of the MET channel is large enough to permit the entry of AG into the cytosolic compartment where cell toxicity occurs. ORC-13661 inhibits the entry of AGs through the MET channel, which in turn eliminates the toxicity of this class of antibiotic. The fact that the MET channel is evolutionarily preserved and functionally equivalent in zebrafish, rats and humans provides confidence that ORC-13661 will be effective in inhibiting AG-induced inner ear hair cell death in humans.

Rat Hearing Protection

Figure 2. ORC-13661 Protects Hearing. The black line shows amikacin-induced hearing loss in the rat. The red line shows that ORC-13661 at 5mg/kg/day provides nearly complete protection against amikacin-induced hearing loss.

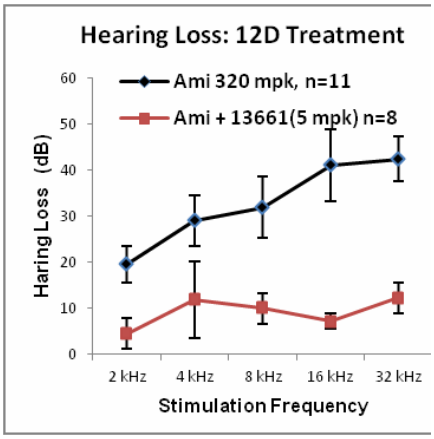


Figure 3. Amikacin treatment leads to loss of inner ear hair cells

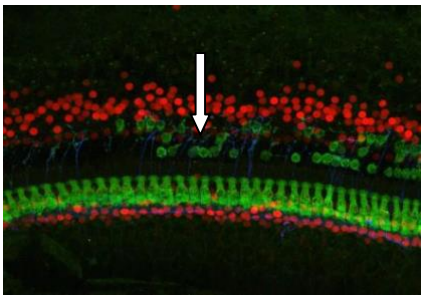
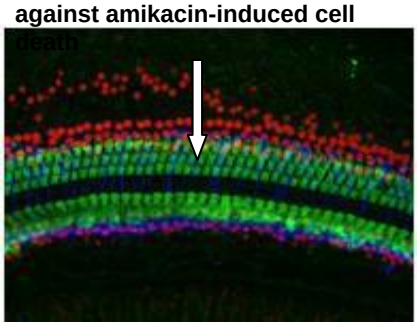


Figure 4. ORC-13661 protects against amikacin-induced cell death



Vincent Groppi, PhD
(email) groppi@oricularx.com
(mobile) +1 (269) 760-1159

Translational Pharmacology

The ability of ORC-13661 to protect hearing in laboratory rats was measured using the Auditory Brainstem Response (ABR), a common physiological test used in the laboratory and in the clinic to detect the threshold of hearing which is the lowest sound level at each frequency that produces a reliable response from the ear and brain. Subcutaneous treatment of mature Fisher 344 rats with 320 mg/kg/day of amikacin daily for 12 days results in permanent hearing loss of 20 – 60 decibels by two weeks following AG treatment. Figure 2 shows the results of ABR tests in rats tested with this protocol. The black line shows the hearing loss, the change from baseline sensitivity, in rats exposed to amikacin alone. The red line demonstrates that adding a once/day oral dose of 5 mg/kg ORC-13661 almost completely protects rat hearing.

Histological examination of the inner ear demonstrates that ORC-13661 protects the outer hair cells of the cochlea. In the photomicrographs shown in Figures 3 and 4, hair cells are stained green, supporting cells-stained red. In the amikacin only photomicrograph (Figure 3), the outer hair cells are missing and disrupted. In contrast, Figure 4 demonstrates complete protection with ORC-13661. The region of the cochlea that responds optimally to sound frequencies of about 16 kHz is shown.

Clinical Development

Additional testing has confirmed that ORC-13661 does not interfere with the *in vitro* bactericidal potency of aminoglycosides against E.coli, P. aeruginosa, or M. tuberculosis. ORC-13661's metabolic profile is similar in rats, dogs, monkeys and humans and there are no unique human metabolites. 28 and 90-Day GLP toxicology studies in rat and dog have been completed. No drug related abnormalities were identified at doses greater than threefold above the exposure that is predicted to be efficacious in human.

Phase 1 clinical trial in normal human volunteers for safety, tolerability and pharmacokinetics demonstrated linear dose exposure proportionality and a long half-life (> 72 hours) facilitating daily oral dosing. Overall, ORC-13661 was well tolerated and there were no serious drug related adverse events even at doses that are projected to be above the exposure required for efficacy.

Two Phase 2 proof-of-concept clinical trials are planned. The first is with patients that have Cystic Fibrosis and the second is patients that have non-TB mycobacterium (NTM). In both cases patients have severe lung infections that are treated with aminoglycoside antibiotics. We are working in close association with Cystic Fibrosis Foundation, NTM consortium, NIH/NIAID and NIH/NIDCD to ensure that the protocols and endpoints are designed to determine if ORC-13661 can improve the standard of care and quality of life of these patients.

Partnering

Oricula Therapeutics has an exclusive worldwide license for the controlling composition of matter patents (US 9416141, US 9493482 and 9,902,738) and other intellectual property. We are seeking a strategic partner to in-license the product, especially for Asia, to finance the upcoming clinical trials. We continue to acquire financial support through foundation and government grants and private equity financing. Our exit strategy is to out-license the product for worldwide clinical development and commercialization.

Interested industry or private equity investors should contact Vincent Groppi, PhD, CEO Oricula Therapeutics