Oricula Therapeutics

Medicines to Preserve Hearing

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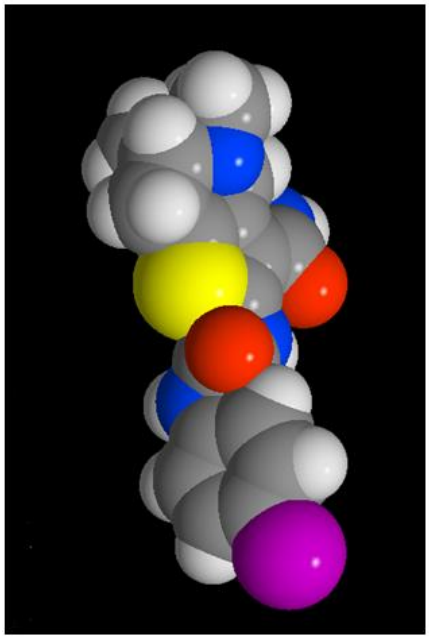
Figure 1. ORC-13661



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 2-4 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 prevent this sometimes debilitating side effect and enable more effective use of these important antibiotics. We estimate the current market potential for adjunctive therapy would exceed $400 million per year and would grow as AG + adjunctive therapy was proven to be safe and cost-effective.

Innovation

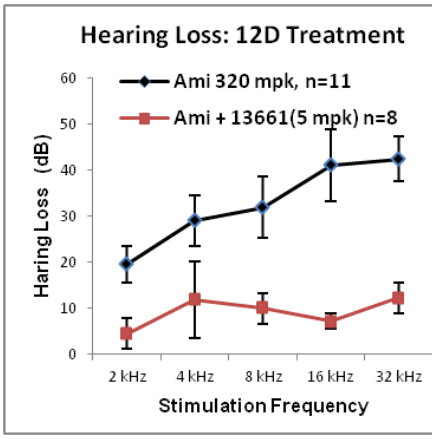
AG-induced hearing loss is caused by the selective killing of the hair cells of the inner ear. Because the molecular target of AG-induced ototoxicity is not defined, we took the innovative approach of using a phenotypic zebrafish assay because the fish neuromast are a translational model of mammalian auditory and vestibular hair cells 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 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 well established that AGs enter 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 protects against AG-induced hair cell death by inhibiting the entry of AGs through the MET channel, which in turns 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. **Hearing protection**. Hearing loss = post-treatment threshold minus pre-treatment threshold. Positive values indicate hearing loss. The red line shows that ORC-13661 at 5mg/kg/day provides nearly complete protection of hearing loss.



Inner ear hair cell protection

Figure 3. Amikacin only

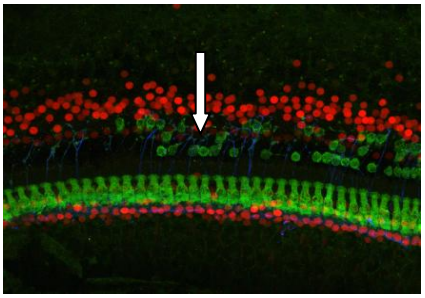
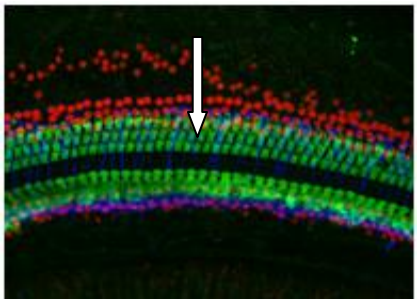


Figure 4. **A**mikacin + ORC-13661



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Translational Pharmacology

The ability of ORC-13661 to protect hearing in laboratory rats was tested using the Auditory Brainstem Response (ABR), a common physiological test used in the laboratory and in the clinic to detect the threshold of hearing, 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 moderate 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. Genotoxicity testing shows that it is not mutagenic. ORC-13661's metabolic profile is similar in rats, dogs, monkeys and humans and there are no unique human metabolites. No concerns were identified in standard GLP safety testing in rats and dogs. 28-Day toxicology testing identified high dose related liver and muscle damage that was completely reversible and will be easily monitorable in human testing.

A late 2016 Pre-IND meeting with the FDA allowed us to finalize our preclinical development plan. We are on track to submit the IND at the end of 2017. We expect to begin human testing with a Phase 1 normal human volunteer study of safety and blood level concentrations of ORC-13661 in early 2018. Following successful completion of the Phase 1 trials, we expect to run a Phase 2 proof of concept clinical trial in cystic fibrosis patients with severe lung infections. These patients receive repeated treatments with IV tobramycin over the years, and a significant number of these patients lose some additional hearing with each additional exposure. Our preliminary calculations, based upon hearing tests of CF patients before and after AG treatment at UCSD, suggests that we can power the demonstration of human efficacy of ORC-13661 with less than twenty patients per treatment group.

Partnering

Oricula Therapeutics acquired an exclusive worldwide license for the controlling composition of matter patents (US 9416141 and US 9493482) and intellectual property from the University of Washington. We are seeking a strategic partner to sublicense the product, to finance the upcoming clinical trials and take the product to market. Also we continue to seek financial support, as needed, through foundation and government grants and private equity financing. Interested industry or private equity investors should contact Malcolm Gleser.