Infectious diseases caused by microorganisms are an increasingly serious problem throughout the world. Many of the most serious and difficult to treat pathogens have evolved strategies that enable these microorganisms to invade cells of the immune system and subvert or even utilize the immune cell physiology to multiply and cause disease. A major challenge to the effective treatment of intracellular microorganisms is the difficulty in achieving highly efficient delivery of antimicrobial agents across the plasma membrane of infected cells. Many existing, highly effective antimicrobials can currently only be delivered by injection, demonstrate potential toxic side effects, and inefficient intracellular delivery.

Solution: Cochleate Technology

The proposed solution is to reformulate existing anti-infective drugs using cochleate technology. Cochleate delivery vehicles have been shown to mediate oral bioavailability for injectable drugs, reduce toxicity, and significantly enhance intracellular drug delivery. Cochleates are stable, crystalline phospholipid-cation precipitates composed of simple, naturally occurring materials: phosphatidylserine and calcium. They have a unique multilayered structure consisting of a large, continuous, solid, lipid bilayer sheet rolled up in a spiral or as stacked sheets, with no internal aqueous space. This unique structure provides protection from degradation for "encapsulated" molecules. Components within the interior of the cochleate remain intact, even though the outer layers of the cochleate may be exposed to harsh environmental conditions or enzymes.

How Cochleates Encapsulate Drugs

Cochleate preparations, given I.P. or orally, were active, reducing the number of bacterial load in the spleen. The amikacin cochleate preparation with high salt showed good safety in rats and dogs in 7 and 28 day toxicity studies. A commercially viable and cost effective manufacturing process for AmB-cochleates has been developed, and scaled-up 100 liter GMP batches of AmB-cochleates have been produced. An IND for AmB-cochleates is open, and data from a phase Ia clinical trial were supportive of further studies.

Applications to Antimicrobials

Ampicillin B Cochleates

The lead product in development using cochleate technology is ampicillin B (AmB).

- Oral administration of AmB-cochleates has been shown to be as effective as injectable, injectable doses of the leading AmB formulation (Fungizone) in mouse models of systemic candidiasis and aspergillosis.
- AmB-cochleates also demonstrate substantially lower toxicity than existing commercial AmB products.
- AmB-cochleates showed safety in rats and dogs in 7 and 28 day toxicity studies.
- A commercially viable and cost effective manufacturing process for AmB-cochleates has been developed, and scaled-up 100 liter GMP batches of AmB-cochleates have been produced.
- An IND for AmB-cochleates is open, and data from a phase Ia human clinical trial were supportive of further studies.

Amikacin Cochleates

Amikacin cochleates have also been developed. The in vivo efficacy of amikacin cochleates against Mycobacterium avium complex (MAC) was evaluated using C57BL/6 mice. The macrophage engulfed amikacin and loaded it into the phagolysosome. The low level of calcium in the cytoplasm caused the cochleate to open, releasing the drug molecule. Specific macrophage delivery can change the PE profile of a drug. For example, in the penicillin model, high plasma levels are needed to get the drug into the cell, and the drug enters by diffusion across the membrane. In contrast, in the azithromycin model, the drug is taken up by phagocytosis, leading to more efficient delivery, lower doses, and less systemic toxicity.

Cochleate preparations, given I.P. or orally, were active, reducing the number of bacterial load in the spleen. The amikacin cochleate preparation with high salt concentration dosed orally was significantly more active than free amikacin.

Development Partners

- Amikacin cochleates have been developed for the treatment of leprosy caused by Mycobacterium lepraum, leishmaniasis caused by Leishmania braziliensis, and visceral leishmaniasis caused by Leishmania donovani. The cochleate formulation was shown to be as effective as equivalent, injectable doses of the leading AmB formulation (Fungizone) in mouse models of systemic candidiasis and aspergillosis. Amikacin cochleates also demonstrated substantially lower toxicity than existing commercial AmB products.
- An IND for AmB-cochleates is open, and data from a phase Ia human clinical trial were supportive of further studies.