Our lipid nano-cystal ("LNC") platform delivery technology has been shown to mediate oral availability for jacketable drugs, directly increasing systemic drug exposure and enhancing mucocutaneous drug delivery. Lipid nano-crystals are stable nano-particles composed of simple, naturally occurring materials: phospholipid and calcium. They have a unique multilayered structure consisting of a large, continuous, solid, lipid bilayer sheet rolled up in a spiral (nanocylindrical) manner. This structure provides protection from degradation or "encocleated" molecules. Cargo molecules within the interior of the cochlolate remain intact, even though the outer layers of the cochair may be exposed to harsh environmental elements or enzymes.

How Cochair Encapsulate Drugs

- The API is associated with the negatively charged lipid.
- The API forms a calcium-phospholipid complex.
- Nano-crystals are composed of layers of a lipid complex.
- The API is trapped in or between the layers protecting the API from harmful environmental elements.

Drug Delivery System

• A liquid nano-cystal delivery system that consists of the API, the API-cphospholipid complex, and the lipid complex.

Drug Loading

- The API is associated with the negatively charged lipid.
- The API forms a calcium-phospholipid complex.
- Nano-crystals are composed of layers of a lipid complex.
- The API is trapped in or between the layers protecting the API from harmful environmental elements.

Cell-Targeted Delivery

Macrophage readily engulf our lipid nano-crystals and their cargo.

Once inside the macrophage, the low level of calcium in the cytoplasm causes the nano-crystals to open, releasing the cargo molecule.

Divalent cation concentrations in macrophages and mucosal muscles are such that the cochair structure is maintained. Hence, the majority of the cochair associated molecules are present in the interior layers of a solid, impermeable structure. Once within the cell, however, the low calcium concentration results in the opening of the cochair crystal and release of the entrapped API.

Our LNC Platform Technology Can Change the Pharmacokinetics and biodistribution of Drugs

Traditional Model of Drug Delivery

• Drug delivery system

Model of Cochair-mediated Drug Delivery: The "Trojan Horse Hypothesis"

Free drug in the extracellular milieu must cross cell membrane in order to be effective against intracellular microbiota.

- High plasma and intracellular drug levels are needed.
- A relatively low percentage of circulating drug is effective.

- Drugs with these properties have difficulty treating intracellular targets.
- High circulating drug levels can result in nonspecific toxicities.

High calcium concentrations in gastrointestinal secretions, acid and intestinal fluid stabilizes the drug-cochair crystal.

Drug lipid nano-crystals enter the circulatory system, diffuse into tissues and/or are taken up by macrophages.

Intracellular levels of drug lipid nano-crystals increase and reach high levels.

The low intracellular calcium concentration causes the drug lipid nano-crystals to open, releasing their cargo molecules.

High drug concentrations in or on the cell open the cochair.

These lower plasma levels may result in less systemic toxicity.

Introduction: Amphotericin B (AMB), due to its fungicidal efficacy, broad spectrum and limited toxicity, is the preferred first-line treatment for fungal infections. It is often administered intravenously (IV) via a lipid carrier, such as MAT203, AMB cochleates, in order to enhance its efficacy and reduce side effects. AMB cochleates are a novel lipid formulation of AMB, which demonstrates antifungal activity with similar efficacy as intraperitoneal (IP) injections, but with a reduced risk of adverse effects. In addition, AMB cochleates are highly effective in preventing invasive candidiasis in neutropenic mice at a dose of 5 mg/kg.

However, AMB cochleates are associated with high toxicity due to the high calcium concentration of the drug carrier. This can result in serious side effects, including nephrotoxicity and neurotoxicity. Therefore, there is a need for a new formulation of AMB that can deliver the drug effectively while reducing its toxicity.

To address this challenge, we have developed a novel formulation of AMB, called MAT2203, which is a lipid nano-crystal (LNC) delivery system. This delivery system is based on MAT203, a liposome formulation of AMB, but with a significantly lower calcium concentration. This lower calcium concentration results in reduced toxicity and improved efficacy.

The LNC delivery system is composed of two main components: the drug (AMB) and the lipid carrier. The lipid carrier is a negatively charged lipid that is able to encapsulate the drug and protect it from degradation. The formation of the LNC is mediated by the addition of calcium, which causes the drug to be released from the lipid carrier.

In this study, we evaluated the efficacy of the new formulation of AMB, MAT2203, in preventing invasive candidiasis in neutropenic mice. We found that MAT2203 was highly effective in preventing invasive candidiasis in neutropenic mice at a dose of 5 mg/kg.

Methods: We intraperitoneally (i.p.) administered AMB at a dose of 5 mg/kg to neutropenic mice and evaluated the incidence of invasive candidiasis at 20% and 5% dosing levels. The results showed that MAT2203 was highly effective in preventing invasive candidiasis in neutropenic mice at a dose of 5 mg/kg.

Conclusion: MAT2203 is a promising formulation of AMB that can deliver the drug effectively while reducing its toxicity. This formulation has the potential to be used in the treatment of fungal infections, particularly in immunocompromised patients. Further studies are needed to evaluate the efficacy and safety of MAT2203 in humans.