Development of Non-Traditional Therapies for Bacterial Infections

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Treatment of Intracellular Pathogens Represents Significant Unmet Need

Sequestered Within a Cell, Pathogens are Protected by the Cell Membrane Barrier

~2 million* people in the US become infected with antibiotic resistant bacteria annually¹

~23,000* people die each year as a direct result of these infections¹

Example Pathogens

Salmonella, Neisseria, Brucella, Mycobacterium, Listeria, Francisella, Legionella, Yersinia pestis

¹: https://www.cdc.gov/drugresistance/threat-report-2013/index.html
Matinas’ Lipid Nano-Crystal (LNC) Platform Technology Enables Safe, Targeted and Intracellular Delivery of Potent Medicines

- Highly stable lipid nano-crystal particles
- Sheets roll up and capture drug molecules between the sheets
- Validated in multiple clinical and preclinical studies

LNC Platform Benefits

- Multiple routes of administration
- Rigid, solid multilayered membrane
- Non-aqueous interior
- Resists environmental attack
- Non-toxic

* Phosphatidylserine

Calcium PS* Bilayer Drug

* Phosphatidylserine
Naturally Targeted Intracellular Drug Delivery

- Naturally targeted to activated cells including cells of the immune system (e.g. macrophage, dendritic cells, neutrophils) or virally infected cells
- Enter cells through non-destructive, natural membrane fusion process
- Naturally unwind (low calcium environment) releasing drug payload

**Fluorescent Labeled LNC Incubated with Mouse Spleenocytes**
## Preclinical and Clinical Development Experience of Matinas’ LNC Delivery Programs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Organism</th>
<th>In Vitro Studies</th>
<th>Animal Model Studies</th>
<th>Human Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAT2203</strong> (Amphotericin B-LNC)</td>
<td>Candida</td>
<td>X</td>
<td>X</td>
<td>Phase 2 Efficacy</td>
</tr>
<tr>
<td></td>
<td>Aspergillus</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryptococcus</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>MAT2501</strong> (Amikacin-LNC)</td>
<td>Mycobacteria</td>
<td>X</td>
<td>X</td>
<td>Phase 1 Toxicity</td>
</tr>
<tr>
<td></td>
<td>Francisella</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Atovaquone-LNC</strong></td>
<td>Pneumocystis</td>
<td></td>
<td>X</td>
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</tr>
</tbody>
</table>
MAT2203: Efficacy Results – NIH and VVC Phase 2 Studies

NIH Study – Dr. Alexandra Freeman, Principal Investigator

• 100% (4 out of 4) patients met the primary endpoint in achieving ≥ 50% clinical response
• Study met predetermined endpoint for success, which was 3/16 patients demonstrating clinical response
• All patients reported improved quality of life
• There have been no signs of nephrotoxicity, hypokalemia or hepatotoxicity after oral dosing:
  - Patient 1 – 545 days (800 mg/day)
  - Patient 2 – 554 days (400 mg/day)
  - Patient 3 – 205 days (800 mg/day)
  - Patient 4 – 169 days (800 mg/day)
• All patients have elected to enroll in the long-term extension study

VVC Study

• In the composite clinical cure score of signs and symptoms at Day 12, MAT2203 demonstrated an 81% improvement in clinical symptoms at 200 mg/day, 80% improvement at 400 mg/day, compared to 94% improvement in clinical symptoms for the patients on fluconazole
**MAT2203: Delivery Across the Blood Brain Barrier**

**Preclinical studies in a mouse model of cryptococcal meningoencephalitis**

_NIAID Clinical Center – Dr. Peter Williamson, Principal Investigator_

### Brain localization of fluorescent LNC after oral dosing

Three mice were infected by tail vein with $10^4 \text{Cn}$ and three remained uninfected. Five days later two from each group were treated daily for 3 days with fluorescent LNC preparations (Rh-AMB-LNC) by gavage and sacrificed. Brains were recovered and homogenized and subjected to microscopy using differential interference contrast (DIC), or red fluorescence (RFP) at the indicated magnifications. Black arrows indicate _C. neoformans_ encapsulated organisms, white arrows indicate LNC fluorescence. Bar = 10 mm

**Study design:**

<table>
<thead>
<tr>
<th>Rod-AmpB</th>
<th>C. Neoformans “Crypto(+)”</th>
<th>Uninfected “Crypto(-)”</th>
</tr>
</thead>
<tbody>
<tr>
<td>X X X</td>
<td>X X X</td>
<td>X X X</td>
</tr>
<tr>
<td>Rh-AMB-LNC treated N=2</td>
<td>Rh-AMB-LNC treated N=2</td>
<td>Rh-AMB-LNC treated N=2</td>
</tr>
<tr>
<td>Rh-AMB-LNC treated N=1</td>
<td>Rh-AMB-LNC untreated N=1</td>
<td>Rh-AMB-LNC untreated N=1</td>
</tr>
</tbody>
</table>

5 days 3 days
In the cystic fibrosis lung, infections by intracellular pathogens, such as intracellular mycobacteria, are problematic to treat due to a thick buildup of mucous in the lung, as well as the difficulty of many anti-microbial agents, such as amikacin, to penetrate across the plasma membranes of infected cells.

Oral administration of amikacin-LNCs safely and effectively treat mycobacteria infections in a mouse model on cystic fibrosis.
LNC Platform Technology Offers a New Paradigm for Drug Therapy with Broad Utility

- Proprietary LNC platform technology enables safe, targeted intracellular delivery of life-changing medicines
- Increase oral bioavailability of injectable drugs
- Cell targeting and intracellular delivery – sustained release activity
- Reduced toxicity of drugs – increased therapeutic index
- Inexpensive to manufacture and scale-up
- Stable as dry powders or in suspension
- Human clinical trials in progress
- Preclinical data supporting formulation and delivery of RNA and DNA polymers