ESTABLISHING A PLATFORM FOR SPRAY DRYING INHALABLE VACCINES IN SOUTH AFRICA

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Achieving Global Health Solutions through advanced Technology, Innovation & Collaboration
Outline

1. Background
2. Brief Introduction to MEND
3. Design of Spray Dried Vaccine Aerosol Particles
4. Technology Transfer to South Africa
5. Conclusions
Background on MEND

Role players in the global effort to combat the three main “diseases of poverty” (malaria, TB, and HIV/AIDS)

PRIVATE FUNDING SOURCES

PUBLIC & GLOBAL ENTITIES

ACADEMIC/RESEARCH INSTITUTIONS

GLOBAL PHARMA

MEND medicine in need

NGOs/PPP
Background on MEND

MEND was founded to fill the gap in global effort to combat the three main “diseases of poverty”

- Only 13 of the 1,223 drugs developed since 1975 have been for neglected diseases* 
- Since 1990, thousands of articles on “breakthrough” scientific discoveries in the primary diseases of poverty (HIV, Malaria, TB) have been published; however, no vaccine products have been approved in these areas since 1921**

** FDA and EMEA registration data
Background on MEND

Bridging the gap:

• We are a 501(c)3 not-for-profit devoted to the successful development and manufacture of affordable and effective vaccines and therapies for diseases of poverty with characteristics that allow their widespread use and sustainability

• We do this by incubating (and subsequently applying) emerging and advanced delivery and manufacturing technologies to drug and vaccine candidates for diseases to make them well-suited for the daunting economic and logistical constraints of the developing world.

www.medicineinneed.org
Focus on TB

The global tuberculosis (TB) epidemic:

• 14.6 million chronic and active cases in 2008 *
• 1.8 million deaths
• 500 000 cases of MDR TB
• 31% of cases in Africa

• In terms of total numbers of cases in 2008:
  ➢ India (2.0 million)
  ➢ China (1.3 million)
  ➢ Indonesia (0.53 million)
  ➢ Nigeria (0.46 million)
  ➢ South Africa (0.46 million)

* WHO (2009) “Global tuberculosis control”
Focus on TB

Challenges to combating TB in high burden countries:

• Limited access to drugs and vaccines
• Increasing levels of drug resistance
• Toxicity of drugs for MDR TB
• Duration of treatment, patient default
• Largely ineffective vaccine against pulmonary TB in adults
• Limitations imposed by current diagnostics
• Lack of incentives for manufacturers
• Cost and risks associated with injections
Focus on TB

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BCG – The current TB vaccine

Mycobacterium bovis Bacille Calmette-Guerin (BCG):
• Developed by Calmette & Guérin (1906-1921)
• The most widely-used childhood vaccine (>100 million doses/year)
• Delivered intradermally
• No new TB vaccine in 88 years
• Requires cold-chain to ensure potency of vaccine
• Efficacy varies from 0 – 80%
BCG – The current TB vaccine

Variability is due to several reasons: *

• Genetic variability of vaccinated individuals;
• Unique characteristics of environmental mycobacteria
• Differences in immunization schedules and doses of BCG
• BCG strains differing in their genetic, biochemical and immunological characteristics;
• Variations in vaccine production – effect of lyophilization

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MEND aims to address most of these issues by utilizing an advanced and innovative approach to formulating BCG vaccine

The Mend solution: Targeting BCG to the lung

- Natural route of infection of TB
- Hypothesis: immunization via lungs may lead to greater immunity
- Large exposed surface area
- Elimination of risks associated with needle use
- Mucosal and/or systemic immunity
- Noninvasive – better patient adherence
The Mend solution: Targeting BCG to the lung

Advantages of needle-free vaccination: *

- Safety
- Compliance
- Cost
- Training of healthcare workers
- Cold chain

* Giudice, E et al. (2006) Advanced Drug Delivery Reviews. 58, 68
Spray drying: a process to engineer particles for inhalation

• David Edwards at Harvard University pioneered the application of spray drying in formulating drugs for inhalation

• Large Porous Particles: microparticles are geometrically large ($d_g = 5\text{ - }10\, \mu m$) but with a low mass density ($\rho < 0.4\, \text{g/cm}^3$) for optimal delivery to the lungs ($d_a = 1\text{–}5\, \mu m$) *

• Applied to TB drugs:
  - Capreomycin (Garcia-Contreras L, et al. (2007) AAC. 51, 2830)
  - PA-824 (Sung JC, et al. (2009) AAC. 53, 1338)

Spray drying: a process to engineer particles for inhalation

• Single-step dehydration technique used in the food, pharmaceutical and agricultural industries

• Solvent carrying solubilized substances atomized through a nozzle

• Rapid drying of droplets in contact with heated gas

• Separation of product using cyclone

• Control of particle size:
  ➢ inlet temperature
  ➢ flow rate
  ➢ excipient concentration

• Evaporation rates control particle density and thus aerodynamic diameter (Optimum particle size for lung delivery is 1-5 μm)
Spray drying: a process to engineer particles for inhalation

<table>
<thead>
<tr>
<th>Lyophilization</th>
<th>Spray drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Batch process</td>
<td>• Continuous process</td>
</tr>
<tr>
<td>• High capital/ops costs</td>
<td>• Low capital/ops costs</td>
</tr>
<tr>
<td>• Requires cold storage</td>
<td>• Retain organism activity by controlled drying</td>
</tr>
<tr>
<td>• Poor powder flowability limits delivery options</td>
<td>• Avoids cold storage</td>
</tr>
<tr>
<td></td>
<td>• Flowable powders allows diverse delivery options</td>
</tr>
</tbody>
</table>
Spray drying: a process to engineer particles for inhalation

Spray drying applied to live whole cells:

- Spray-drying BCG in salt-free suspensions minimizes osmotic stresses during drying, thus minimizing loss of bacterial viability *

- Microstructural properties adapted to optimize aerosol properties

Preliminary results - Guinea pig study

- Influence of BCG vaccination by different routes on Tuberculin reaction in guinea pigs *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Route of administration</th>
<th>100 TU Diameter of Induration (mm)</th>
<th>5 TU Diameter of Induration (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG Powder</td>
<td>Pulmonary</td>
<td>18.60 2.61</td>
<td>11.80 1.92</td>
</tr>
<tr>
<td>BCG Solution</td>
<td>SC</td>
<td>17.83 1.83</td>
<td>11.33 3.14</td>
</tr>
<tr>
<td>Untreated</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Garcia-Contreras L, et al. (2008) PNAS. 105, 4656
Preliminary results - Guinea pig study

- Number of viable bacteria per ml of tissue homogenate at necropsy after bacterial challenge of animals immunized with BCG

* Garcia-Contreras L, et al. (2008) PNAS. 105, 4656
Stability studies

• Stability of spray-dried BCG formulation after storage at 4°C *

Technology transfer to South Africa

• Spray dry facility established in South Africa with funding from Bill & Melinda Gates Foundation

• Focus: pharmaceutical development, production of material for toxicology studies and Phase I human trials

• South Africa has a high burden of TB sufferers

• Local knowledge and close proximity to where the products will be applied

• Availability of good infrastructure to support operation

• Establishing local expertise in pharmaceutical development of inhalable drugs
Technology transfer to South Africa

• Spray drying process and some analytical methods transferred
• Further process and product optimization, validation of process and analytical methods
• Product specifications: biological and physical properties for alveolar delivery:

<table>
<thead>
<tr>
<th>Physical property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG content (wt%)</td>
<td>5</td>
</tr>
<tr>
<td>Viability (CFU/mg)</td>
<td>1-2x10⁴</td>
</tr>
<tr>
<td>Geometric particle size distribution d₅₀ (μm)</td>
<td>3-4</td>
</tr>
<tr>
<td>Aerodynamic particle size dₐ (μm)</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Fine particle fraction &lt; 5.8 μm (%)</td>
<td>50</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>0.08-0.1</td>
</tr>
<tr>
<td>Moisture content (%)</td>
<td>0.1-0.5</td>
</tr>
</tbody>
</table>
The MEND spray drying facility

• Located at Medical Research Council in Pretoria

• Fully equipped for aseptic production, capsule filling and batch release of whole-cell vaccines according to cGMP requirements

• All the equipment and analytical methods fully validated:
  - Andersen Cascade Impactor: aerodynamic particle size distribution
  - Sympatec HELOS/RODOS: geometric particle size distribution
  - Karl Fischer titrator: moisture content analysis
  - Waters HPLC: chemical composition

• Bioanalytical testing:
  - Viability determination in terms of ATP and CFU
  - Sterility
  - Live/dead assay
The MEND spray drying facility

- Laboratory conforming to OECD GLP and WHO BL3 requirements
# Regulatory pathway

## Fast-tracking BCG vaccine development:

### Preclinical development

- Initial formulations
- Optimization
- Aseptic capsule filling studies
- Analytical method development
- Stability testing
- Production of tox material and batch release
- Pre-IND meetings with FDA and EMEA

### Phase I clinical study

- Toxicology study
  - In 2 animal models
- IND meeting with FDA and EMEA

### Inhaler development

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*[Image: Regulatory pathway diagram]*
• MEND has a unique approach to apply Harvard University technology to TB vaccine development in SA

• BCG vaccine can be spray dried into viable aerosol with good long term stability

• Guinea pig studies show the viable BCG aerosol to be as immunogenic as the intradermal control

• Mend has established a GLP laboratory for production of material for toxicology and Phase I human studies
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