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ESTABLISHING A PLATFORM FOR SPRAY DRYING INHALABLE VACCINES IN SOUTH AFRICA

André Germishuizen, Bernard Fourie

Vaccine Technology III, Nuevo Vallarta, Mexico

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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

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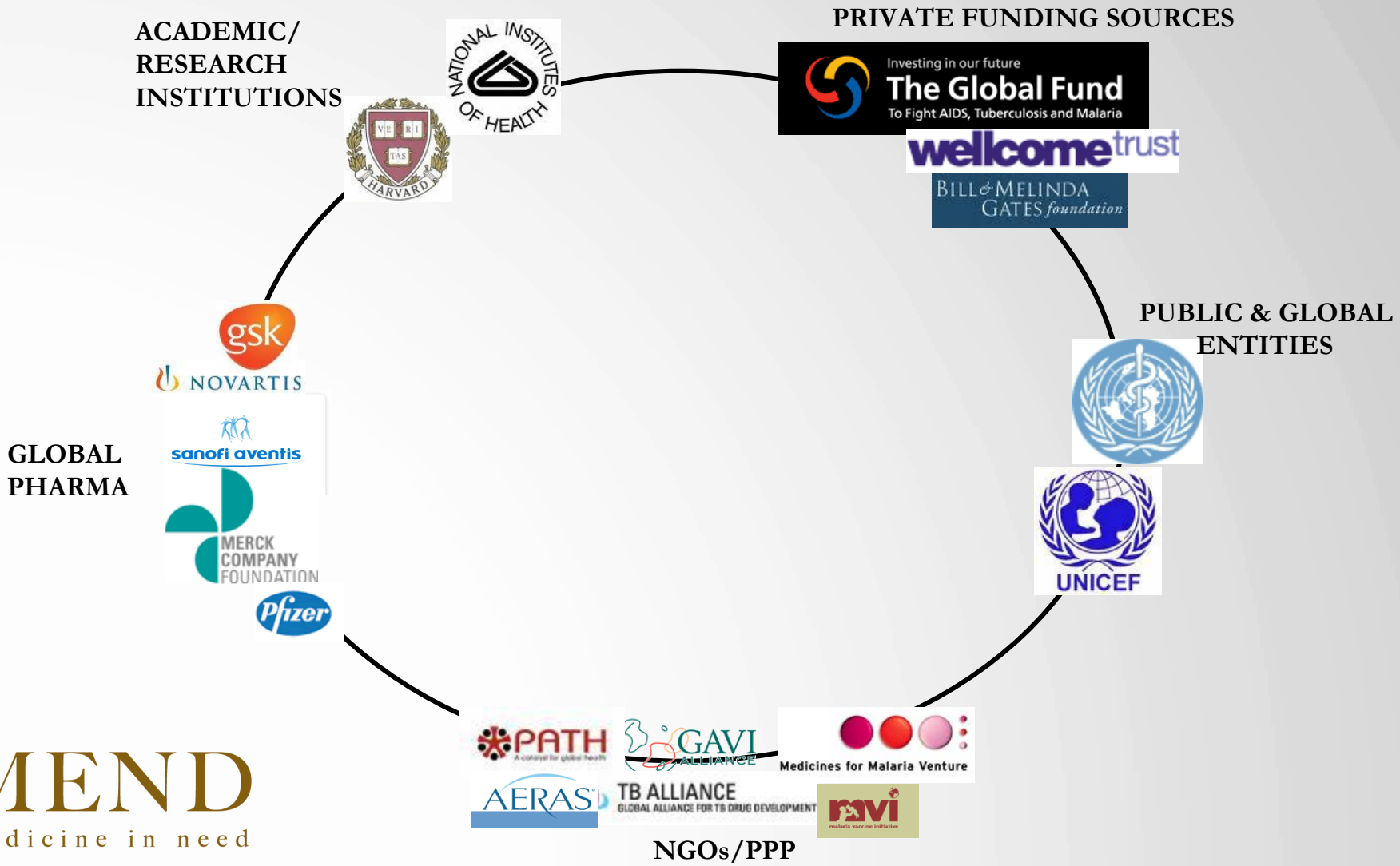
Background on MEND

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



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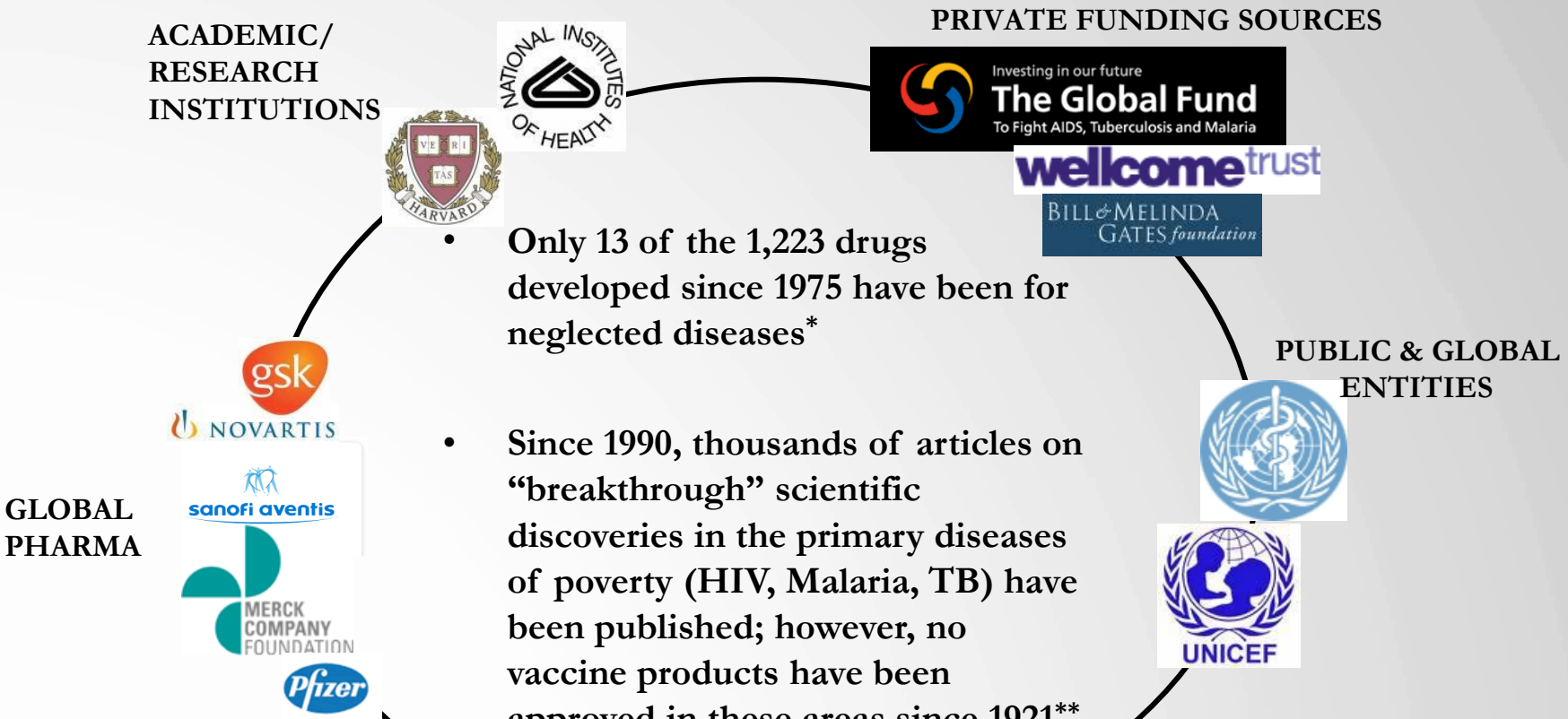
Background on MEND

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****

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* Butler, D *et al.* (2007) "Lost in Translation", Nature. **449**, 158

** 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

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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

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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%

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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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* Dietrich, G *et al.* (2002) Journal of Biotechnology. **96**, 259

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

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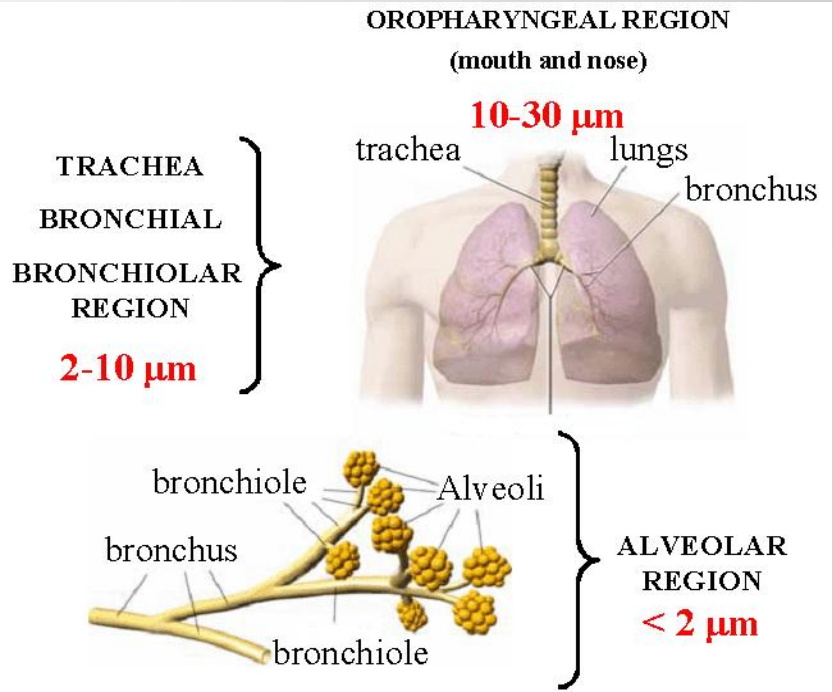
* Dietrich, G *et al.* (2002) Journal of Biotechnology. **96**, 259

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



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The Mend solution: Targeting BCG to the lung

Advantages of needle-free vaccination: *

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

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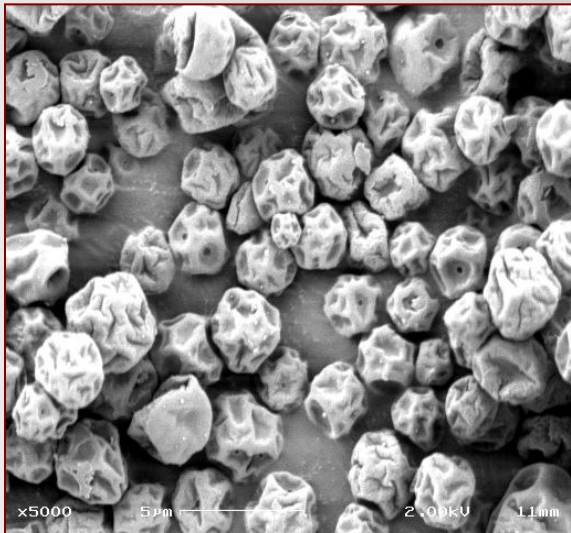
* Giudice, E *et al.* (2006) Advanced Drug Delivery Reviews. **58**, 68

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 -10 μm) but with a low mass density ($\rho < 0.4$ g/cm^3) for optimal delivery to the lungs (d_a = 1–5 μm) *
- Applied to TB drugs:
  - Para-aminosalicylic acid (Tsapis N, *et al.* (2003) Tuberculosis. **83**, 379)
  - Capreomycin (Garcia-Contreras L, *et al.* (2007) AAC. **51**, 2830)
  - PA-824 (Sung JC, *et al.* (2009) AAC. **53**, 1338)



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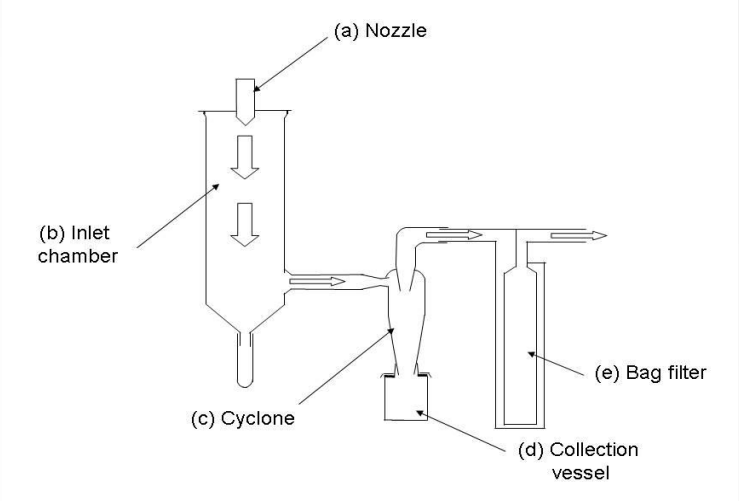
* Edwards DA, *et al.* (1997) Science. **276**, 1868

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**)

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Spray drying: a process to engineer particles for inhalation

Lyophilization	*Spray drying*
• Batch process • High capital/ops costs • Requires cold storage • Poor powder flowability limits delivery options	• Continuous process • Low capital/ops costs • Retain organism activity by controlled drying • Avoids cold storage • Flowable powders allows diverse delivery options

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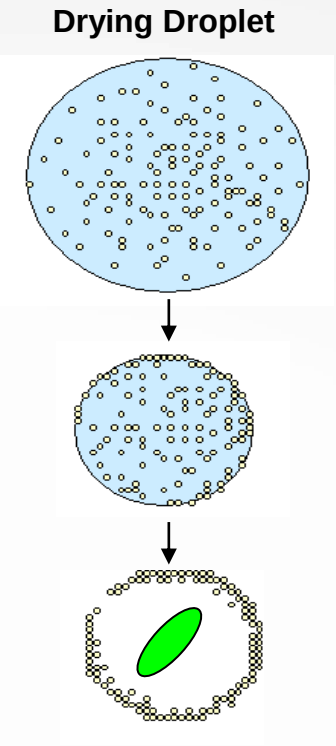
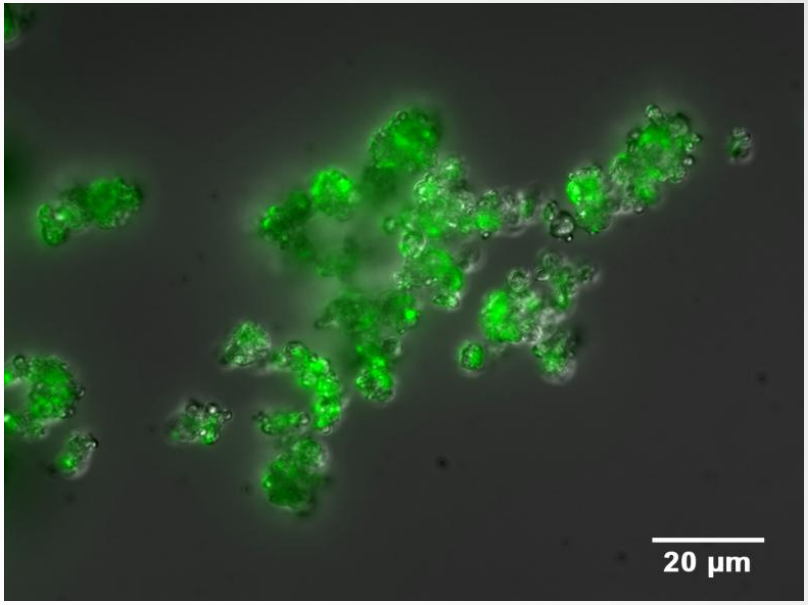
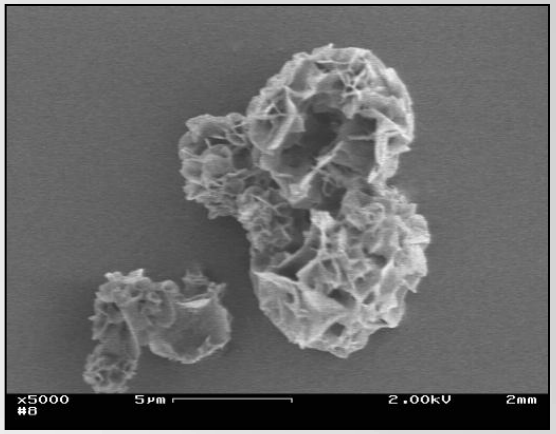
Spray drying: a process to engineer particles for inhalation

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

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* Wong Y-L, *et al.* (2007) (2007) PNAS. **104**, 2591

Preliminary results - Guinea pig study

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

		Diameter of Induration (*mm*) 6 weeks after Vaccination	
Treatment	Route of administration	100 TU	5 TU
BCG Powder	Pulmonary	18.60 2.61	11.80 1.92
BCG Solution	SC	17.83 1.83	11.33 3.14
Untreated	-	0	0

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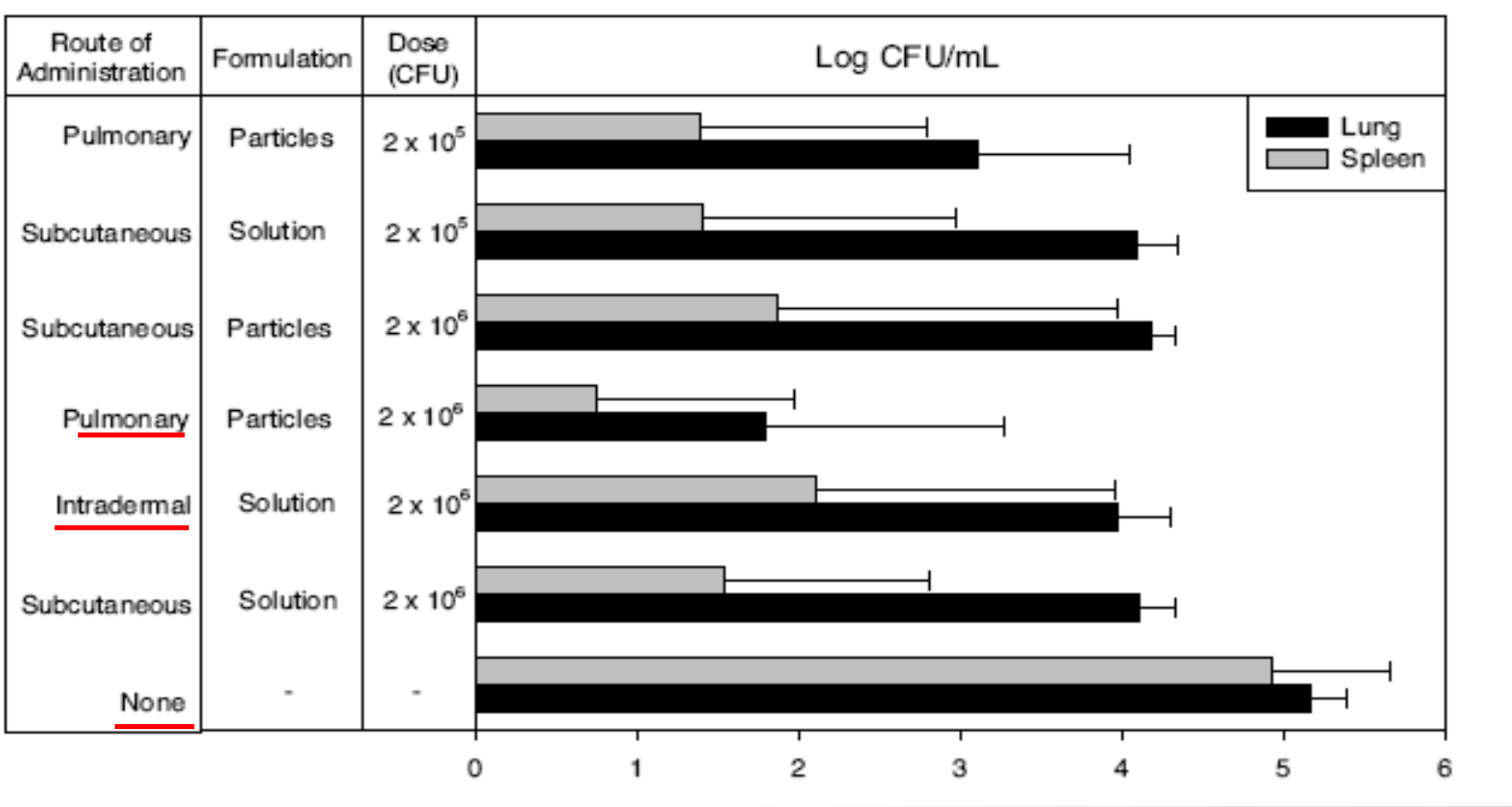
* Garcia-Contreras L, *et al.* (2008) PNAS. **105**, 4656

Preliminary results - Guinea pig study

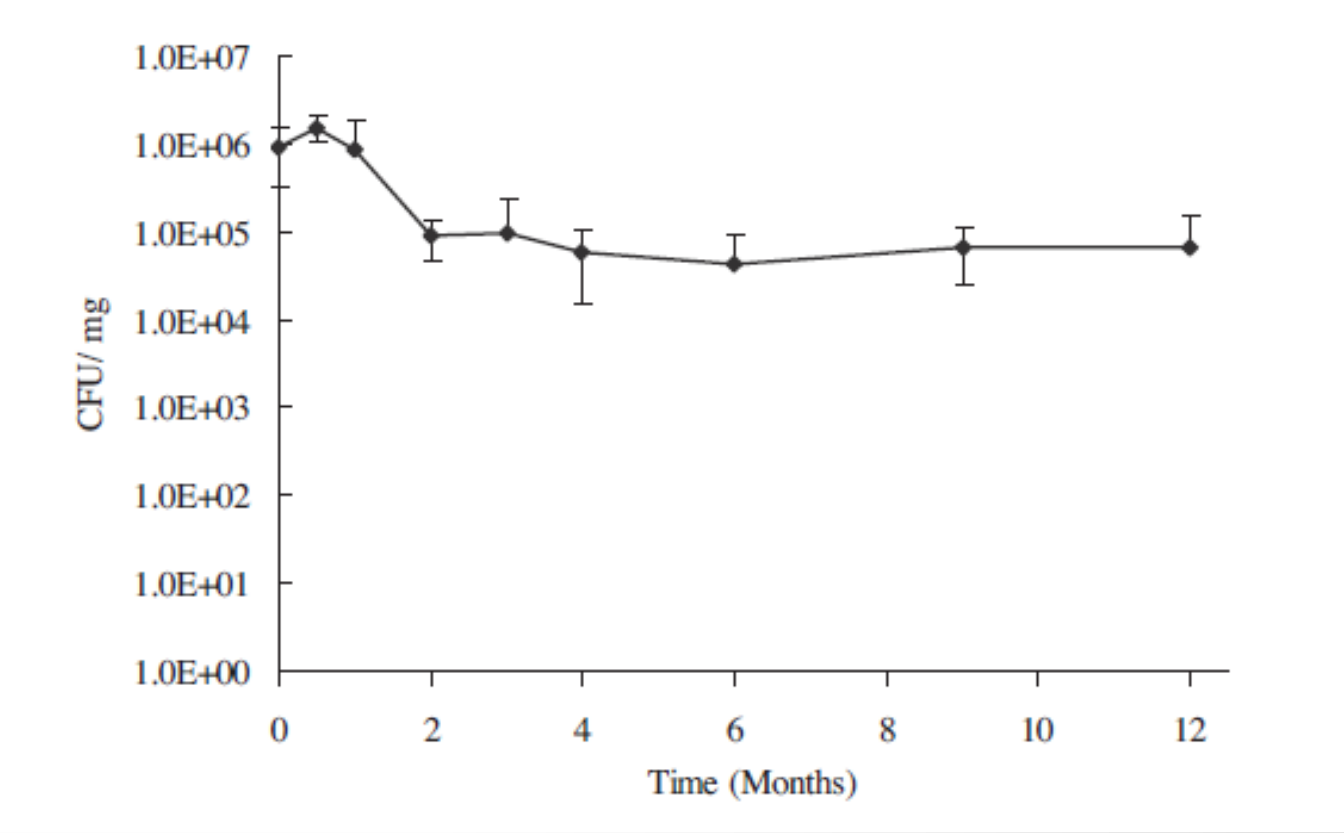
- Number of viable bacteria per ml of tissue homogenate at necropsy after bacterial challenge of animals immunized with BCG *



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

Stability studies

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



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* Wong Y-L, et al. (2007) (2007) PNAS. **104**, 2591

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

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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:

Physical property	Value
BCG content (wt%)	5
Viability (CFU/mg)	1-2x10^4
Geometric particle size distribution d_{50} (µm)	3-4
Aerodynamic particle size d_a (µm)	1.5-2.5
Fine particle fraction < 5.8 µm (%)	50
Density (g/cm^3)	0.08-0.1
Moisture content (%)	0.1-0.5

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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

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The MEND spray drying facility

- Laboratory conforming to OECD GLP and WHO BL3 requirements

sanas
GLP Compliant Facility
G0018

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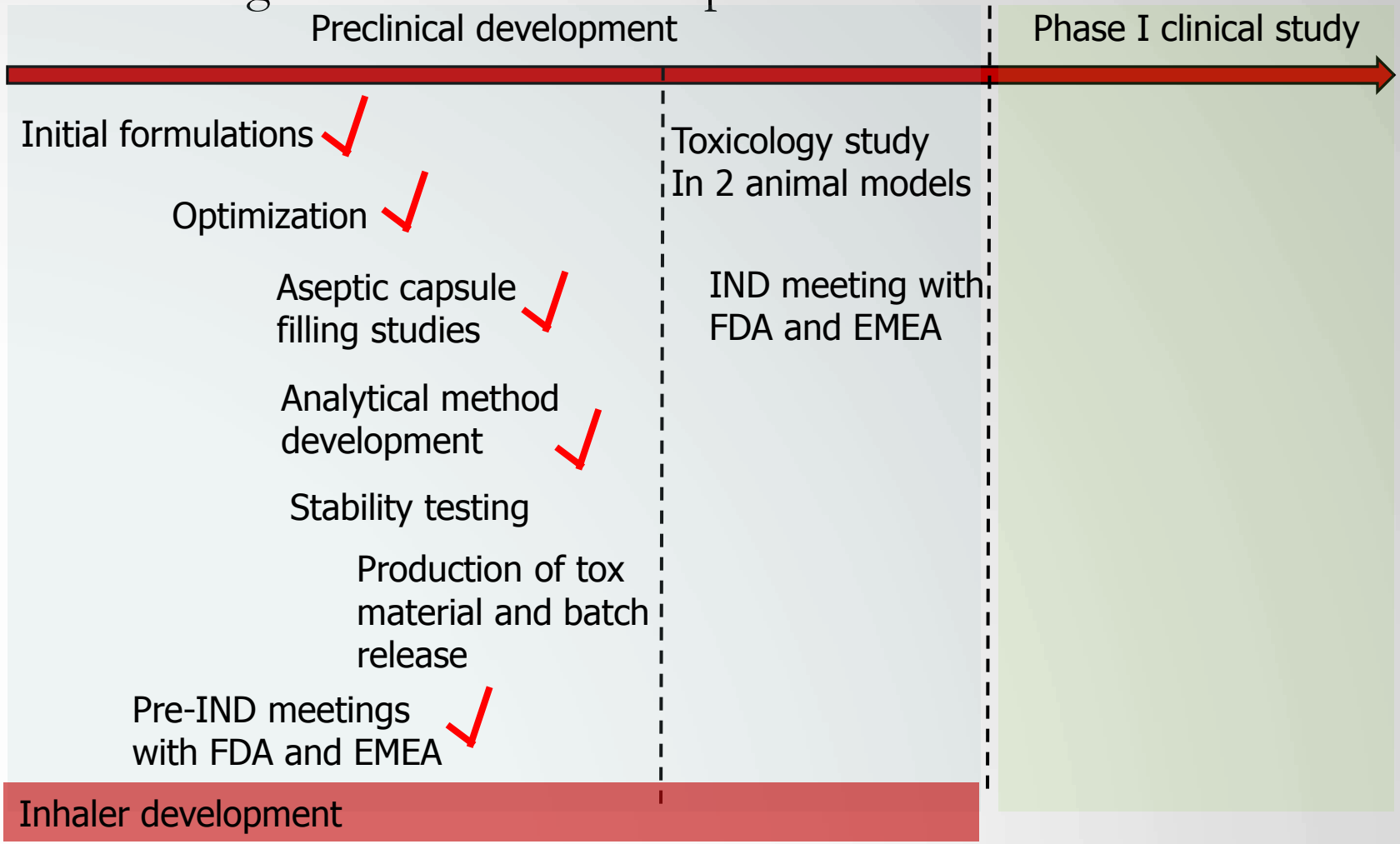
Regulatory pathway

Fast-tracking BCG vaccine development:



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Summary

- 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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Acknowledgments

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  - David Edwards, Ling Wong, Hunter Lauten
- **University of North Carolina, NC**
  - Tony Hickey, Lucilla Garcia-Contreras
- **Aeras Global TB Vaccine Foundation, Rockville, MD**
- **Statens Serum Institut, Copenhagen, Denmark**
- **Bill and Melinda Gates Foundation**