Afrigen’s RSV mRNA vaccine project

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Introduction - RSV

- Causes respiratory cold-like symptoms (spectrum of disease)
- Most common cause of hospitalization in infants
- Significant burden of disease in elderly (>65 yrs)
- Majority of deaths occur in LMICs & outside of hospital setting
- Mab treatment palivizumab/nursevimab (high income countries)
- No Licenced vaccine but Ph3 Pfizer/GSK/Moderna

- 34 million acute lower respiratory tract infections in young children
- 3 million hospitalizations
- 66000-199000 fatalities
- 99% LMICs

WHO, 2017
RSV infection and immunity

- Natural infection doesn't result in durable immunity and reinfection occurs throughout life
- Antibodies target viral envelope F & G proteins but F is well-conserved
- Nabs preferentially target prefusion F (PreF)
- RSV IgA and Nabs correlate with reduced infection risk
- Th1 response, IFN-γ
- Th2 tracks with disease severity
Stabilization of F protein in prefusion state

Pre-fusion F is absent on the surface of formalin-inactivated respiratory syncytial virus

Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody

Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus

Prefusion F–specific antibodies determine the magnitude of RSV neutralizing activity in human sera
What does an mRNA RSV vaccine look like?

- PreF membrane-bound
- Delivered by mRNA LNP
- Nabs & Cellular immunity without Th2 skewing
- Maternal immunization followed by paediatric
- In line with WHO preferred product characteristics for RSV vaccine

Graham et al., 2015
### Clinical pipeline for RSV vaccines

#### Phase 1
- **Live-Attenuated/Chimeric**
  - Blue Lake
    - PIVS/RSV
  - Codagenix
    - LID/NAID/NIH
  - Intravacc
    - RSV-ΔG
  - Pontificia Universidad Catolica de Chile
    - BCG/RSV
  - SIPL, St Jude Hospital
    - SeV/RSV

#### Phase 2
- **Protein-Based**
  - Icosavax
    - RSV/hMPV VLP
  - Immunovaccine, VIB
    - RSV SH protein
  - NIH/NAID/VRC
    - RSV F protein
  - Virometix
    - VLP
  - Advaccine Biotechnology
    - RSV G Protein
  - Daiichi Sankyo
    - Protein?
  - GSK
    - F protein
  - Sanofi, LID/NAID/NIH
    - RSV

#### Phase 3
- **Nucleic Acid**
  - Moderna
    - RNA
  - Sanofi
    - RNA

- **Recombinant Vectors**
  - Janssen
    - Ad26
  - Bavarian Nordic
    - MVA
  - Janssen
    - Ad26

**Elderly** | **Maternal** | **Paediatric** | **Modified from PATH**
Afrigen’s value proposition for RSV

1. Partnerships for end-to-end vaccine development
2. mRNA technology transfer programme driving access for LMICs
3. 2nd Generation technology promising lower cost
4. Formulation partnerships geared at improved temperature stability
5. Local production of drug substance and drug product
6. Strengthen biomanufacturing know-how in Africa
7. Harness the capacity & ecosystem for end-to-end manufacturing
Preclinical development plan

Go/no go
1. Safety
2. Immunogenicity
   - Binding Abs
   - Nab induction
   - Multifunctional cellular response
   - No Th2 polarization

Go/no go
1. Purity >90%
2. Integrity

Go/no go
1. High expression in vitro
2. Pref formation

Go/no go
1. IM rats, GLP
2. Safety

Go/no go
- Low reactogenicity
- High potency
- Stability
Afrigen network for RSV

- Antigen design
- mRNA sequence optimization
- Lipids/formulation
- Structural Biology
- Immunogenicity testing

RSV vaccine manufacture
Summary

• High disease burden in Africa
• Likely lack of access to vaccine
• Well established concept for safe & effective vaccine
• Supported by clinical efficacy data (GSK, Pfizer, Moderna)
• Integration of novel UTRs & alternate lipids = freedom to operate
• Targeting refrigeration temperature stable formulations
• Establishing supporting network to commence experimental work
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