MERS-CoV R & D
A Case Study for the WHO Blueprint

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WHO Blueprint

• To develop a roadmap for MERS-CoV R&D
  ○ Diagnostics, Vaccines, Therapeutics

• State of the science and product development as a baseline for the roadmap
Background - I

- Middle East respiratory syndrome coronavirus (MERS-CoV)
  - A β coronavirus that causes severe acute respiratory infection
  - First identified in Sep 2012
    - >1200 cases/>500 deaths since
    - >75% of cases in KSA
    - 25 countries affected so far
State of the Outbreak: Aug 2012

Number of cases reported:
- 1 - 5
- 6 - 20
- 21 - 100
- 101 - 500
- 501 - 1037

Source: C. Fuhrer, WHO
State of the Outbreak: Dec 2012

Number of cases reported

- 1 - 5
- 6 - 20
- 21 - 100
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Source: C. Fuhrer, WHO
State of the Outbreak: Dec 2013
• Epidemiology is not well-defined
  • Zoonosis – dromedary camel reservoir
  • Human-to-human transmission limited ($R_0 \sim 0.7$)
    • Nosocomial outbreaks, familial clusters, super spreaders
  • Mode of transmission unclear (droplet?)
  • Incidence/severity greater with co-morbidities
• Infection of lower airways in humans and non human primates
• Infection restricted by presence of receptor / Dissemination rare
• Acute respiratory failure and acute renal failure most common
Mechanism of Infection

- Virus spikes responsible for binding to target cells in body organs
- Once binding occurs, virus genetic material enters cell, replicates
- New viruses are made, leave cell, infect more cells
- Basis of treatment or vaccines = prevent virus replication
Countermeasures

- No licensed therapeutics or vaccines are currently available
- Prevention through case detection, contact tracing, isolation, quarantine, infection control measures
- Uncontrolled use of experimental therapeutics (e.g. ribavirin, interferons, convalescent plasma)
- Active vaccines, monoclonal antibodies, antivirals all in preclinical development
Diagnostics

• Gold standard for diagnosis is rRT-PCR
  • Highest yield lower respiratory tract specimens
  • Can be detected from nasopharynx, urine, feces, serum

• Serology
  • ELISA, IFA, Microneutralization

• No antigen capture assays in use
• No standardization of current diagnostics
Therapeutics

• Drug and Antibody Preparations
  • Preserve life, reduce complications, reduce transmission
  • Prevent virus attachment to cells and replication
  • Allow the patient’s immune system to clear virus
## MERS-CoV Vaccine Snapshot

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccine</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Live Attenuated</strong></td>
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<td></td>
<td></td>
<td>Recombinant MERS-CoV</td>
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<td><strong>Nanoparticle</strong></td>
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<td></td>
<td>NOVAVAX</td>
<td>Full-length S trimers</td>
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<tr>
<td><strong>Subunit</strong></td>
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<tr>
<td>Spike glycoprotein</td>
<td>NIH</td>
<td>S1 subunit</td>
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<td>Erasmus</td>
<td>S1 fused human Fc</td>
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<td></td>
<td>MRC</td>
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<tr>
<td>Receptor Binding Domain</td>
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<td>Erasmus</td>
<td>RBD fused human Fc</td>
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<td></td>
<td>GDRC</td>
<td>Truncated RBD</td>
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<td><strong>DNA</strong></td>
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<td></td>
<td>NIH</td>
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<td><strong>Recombinant Vector</strong></td>
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<tr>
<td>Adenovirus</td>
<td>Greffex</td>
<td>Ad6 S</td>
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<td></td>
<td>Erasmus</td>
<td>Ad5/Ad41 S</td>
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<td></td>
<td>UPMC</td>
<td>Ad5 S or S1</td>
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<tr>
<td>Modified Vaccinia Ankara</td>
<td>MVA-S</td>
<td>MVA-S</td>
</tr>
</tbody>
</table>

*World Health Organization*
Monoclonal Antibodies (mAbs)

- Murine, non-human primate, human survivor mAbs against the Spike protein

- Prevent infection/disease, reduce severity
- Passive prophylaxis studies in animal models
Objective
○ Interrupt zoonotic transmission between camels and to humans

Mechanism
○ Reduce viral shedding in upper airways of camels

Precedent
○ Hendra virus vaccine licensed for horses to interrupt transmission to horses

Current activities
○ S1 protein subunit (NIH)
○ MVA vector (EMC)
Animal models

• Lack of a relevant animal model that recapitulates human disease
• Absence of cognate DPP4 receptor
• Current models:
  o Transient transfection mouse model
  o Transgenic mouse model
  o Rhesus macaque exhibit mild LRI
  o Lethal marmoset model
  o Camelids manifest a mild URI
WHO Consultative Process

• Gap analysis

• Prioritization of R&D activities
  o Assay development/standardization
  o Better epidemiologic data
  o Animal models
  o Downselection criteria for clinical development

• Suggested MERS-CoV R&D priorities from PD VAC committee?