The MERS Vaccine Initiative

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Outline

• Middle East Respiratory Syndrome CoV
  • Virology
  • Clinical
  • Epidemiology
  • MERS in S. Korea
• MERS vaccine candidates
• IVI MERS program
• Summary
MERS CoV
Biology, Clinical Features, Epidemiology, and MERS in S. Korea
Emergence of new viruses - MERS coronavirus

- Likely origin in bats
- Camels as intermediary hosts to humans

MERS-CoV background

- 30 kb enveloped, single-stranded, positive-sense RNA virus
- 4 structural proteins: spike (S), envelope (E), matrix (M), nucleocapsid (N)
- S protein is primary target for neutralizing Abs during natural MERS-CoV infection
- S1 subunit contains receptor-binding domain (RBD)
- Host cell receptor for RBD is dipeptidyl peptidase 4 (DPP4 or CD26)
- Dromedary camels are intermediary reservoir for transmission to humans

MERS-CoV in humans

- From asymptomatic to mild to severe
- Comorbidities and age (obesity, hypertension, diabetes and cardiac disease) associated with a fatal outcome of MERS-CoV infection
- Incubation period ~ 5 days
- Rapid progression from hospital into ICU and intubation
- Extensive nosocomial transmission and superspreader potential
Human-to-human transmission

- No sustained human-to-human transmission
  - Basic reproductive number $R_0 < 1$
  - Can vary depending on situation
- Majority of outbreaks in nosocomial or household clusters
- Global risk
  - Hajj/Umrah pilgrimage (2 million)
  - Migrant workers
    - 9 million in KSA
    - Pakistan, India, Egypt, Yemen, Bangladesh
MERS-CoV epidemiology

First identified in a 60 y.o. male in Jeddah, KSA in Jun 2012. Retrospectively identified in a cluster from Zarqa, Jordan from Apr 2012. As of 25 Sep 2017, 2081 cases with 722 deaths (CFR 35%) in 27 countries.

Confirmed global cases of MERS-CoV

Reported to WHO as of 01 Sep 2017 (n=2067).

Latest: 2081 cases, 722 deaths
35% CFR
MERS in Korea

Summary
- 186 cases MERS-CoV infection
- 36 deaths (19%)
- 16,693 in placed in quarantine
Korean MERS Outbreak (2015)

- Pt 1: 28 secondary infections (including Pt 14)
- Pt 14: 82 secondary infections (33 pt, 8 hcw, 41 visitors)

For Pt 14:
- Persons within same zone: incubation 5 days
- Persons outside of same zone: incubation 11 days
- Staying in same zone as index case: attack rate 20% (47/239)
- Passage in same zone/same time: attack rate 5% (6/116)
- Always in different zone: attack rate 2% (15/2003)
- HCW: 5/218 (2%)

Cho et al, Lancet 2016

- Time from exposure to onset (2-16 days), median 6.5 days
- Time from symptoms to diagnosis (0-17 days), median 5 days

Only outbreak driven by human-to-human transmission outside of Middle East
- 68 year old Korean male traveled in Middle East in Apr 2015, and returned to Korea
- Became sick on 11 May 2015 with visits to 3 different Korean hospitals
- MERS-CoV confirmed on 20 May 2015
- 186 confirmed cases; 38 deaths (CFR 20%); 16,993 people quarantined

Cho et al, Lancet 2016
MERS Vaccine candidates
MERS vaccine development: Considerations

- Animal models not ideal
  - Transduced mice, transgenic mice, rhesus, marmosets, camels
- No immune correlate of protection in humans
- Broad immune responses may be needed (high mutation rate of CoVs)
  - Cross-neutralizing Abs; T cells to multiple S epitopes
- Theoretical risk of enhancement
- May be difficult to demonstrate efficacy in field

Will one the viruses circulating now be the virus that causes a true epidemic?

Will it be important for at least one platform to be “rapid” (in terms of response to new strains)?
# MERS-CoV vaccine pipeline (1)

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Vaccine name</th>
<th>Design</th>
<th>Animal immunogenicity</th>
<th>Animal protection</th>
<th>Stage of development</th>
<th>Sponsor/Developer</th>
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<tbody>
<tr>
<td>DNA</td>
<td>GLS-5300</td>
<td>Plasmid DNA encoding full-length S; with electroporation</td>
<td>C57BL/6 mice, rhesus, camels</td>
<td>Rhesus</td>
<td>Phase I ongoing in the US</td>
<td>GeneOne/Inovio</td>
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<td>Protein subunit</td>
<td>MERS-S</td>
<td>Nanoparticles of full-length S trimers; with Matrix-M adjuvant</td>
<td>BALB/c mice</td>
<td>Transduced mice</td>
<td>Preclinical; SAB-301 polyclonal Abs from transgenic cows in Phase I</td>
<td>Novavax</td>
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<td>MERS-CoV VLP</td>
<td>VLP of S, E, M in baculovirus/Sf9; with alum</td>
<td>Rhesus</td>
<td>-</td>
<td>Preclinical</td>
<td>Jiangsu Center, China</td>
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<td>S-RBD-Fc</td>
<td>S1-RBD subunit fused with human Fc; with various adjuvants</td>
<td>BALB/c mice, rabbits</td>
<td>Transduced mice</td>
<td>Preclinical</td>
<td>New York Blood Center; Fudan Univ; Central South Univ</td>
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<td>MERS-CoV rRBD</td>
<td>Truncated S1-RBD subunit; with alum</td>
<td>BALB/c mice, rhesus</td>
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<td>Heterologous prime-boost</td>
<td>S-DNA/S1 Protein</td>
<td>Plasmid DNA encoding full-length S (prime) + S1 subunit (boost)</td>
<td>BALB/c mice, rhesus</td>
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<td>US NIH/VRC</td>
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## MERS-CoV vaccine pipeline (2)

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<th>Vaccine type</th>
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<td>Vector</td>
<td>MVA-S</td>
<td>MVA vector with full-length S</td>
<td>BALB/c mice, camels</td>
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<td>ChAdOx1-MERS-S</td>
<td>Chimp adenovirus 3 with full-length S</td>
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<td>Preclinical; Phase I planned in UK in mid 2017</td>
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<td>MERS-S/MERS-soiS</td>
<td>Measles vector with full-length S/soiS</td>
<td>IFNAR -/- mice</td>
<td>Transduced mice</td>
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<td>Paul Ehrlich Insitut; German Cent for Inf Res</td>
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<td>Ad5-S &amp; Ad41-S</td>
<td>Human adenovirus vector with full-length S</td>
<td>BALB/c mice</td>
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<td>GreMERSfi</td>
<td>Human adenovirus 5 vector with full-length S</td>
<td>Mice</td>
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<td>Live recombinant</td>
<td>rMERS-CoV-ΔE</td>
<td>Recombinant without E</td>
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<td>Preclinical</td>
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MERS Vaccine Pipeline
Overall IVI MERS program goal

- IVI MERS program initiated with funding by Samsung Life Public Welfare Foundation
  - Samsung Medical Center impacted by Korean MERS outbreak

- Overall MERS program goal: Make MERS vaccine available for use in emergency response to potential outbreak in Korea
  - Select two MERS vaccine candidates to support preclinical and early clinical development

- Supportive activities
  - Certify and maintain IVI BSL-3 laboratory
  - Establish IVI biobank system
GeneOne/Inovio MERS DNA vaccine

Most advanced candidate in development

- pVax1 plasmid
- DNA coding full-length S glycoprotein using consensus sequence

Given with electroporation
Rhesus: Summary of immunogenicity and protection

• 12 rhesus macaques at control, low and high dose at 0, 3, 6 wks
• Challenged at 11 wks (4 wks after 3rd dose)
• Full protection by radiography

• Binding & neutralizing antibodies
  • Seroconversion and induction of strong MERS-CoV Spike specific bAb responses after single immunization
  • bAb titers: $10^4 - 10^5$
  • nAb titers: 1:80-240 post dose 3

• Cellular immune responses
  • Induction of strong T-cell immune responses
  • Antigen specific CD4+ and CD8+
  • Multiple epitopes recognized across length of S protein

Muthumani K et al. Sci Transl Med. 2015 Aug 19;7(301):301ra132.
US Phase I first-in-human MERS vaccine trial

• Randomized, open-label trial of GeneOne MERS DNA vaccine (GLS-5300)
  o 75 healthy adults in 3 dose groups (0.67 mg, 2 mg, 6 mg)
  o Vaccinations at 0, 4 and 12 weeks administered by electroporation

• Primary objective
  o Safety up to 60 wks

• Secondary objectives
  o Immunogenicity
    ▪ 1, 2, 3 and 4 wks after 1\textsuperscript{st} dose
    ▪ 2 wks after 2\textsuperscript{nd} dose (i.e., at 6 wks)
    ▪ 2 wks after 3\textsuperscript{rd} dose (i.e., at 14 wks)
    ▪ 3, 6 and 12 mos after 3\textsuperscript{rd} dose (i.e., at 24, 36 and 60 wks)

Human Clinical Data
• Binding Ab by EIA: 92% (57/62 vol)
• Bab or cellular response: 98% (61/62 vol)
US Phase I first-in-human MERS vaccine trial

• **Progress**
  - Subject enrollment initiated in Feb 2016
  - Enrollment completed in Aug 2016
  - Last dose administered in Nov 2016

• **No safety issues**

• **Immunogenicity results up to 2 wks after 3rd dose** (i.e., at 14 wks) expected to be available by Apr 2017
  - Binding ELISA for S glycoprotein
  - Neutralizing antibody assay (TCID50)
  - Pseudotyped virus assay (cross-neutralization)
  - IFN-gamma ELISpot
  - ICS
IVI-GeneOne clinical trial milestones

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Clinical trial Preparation Dec 6 '16 - Jan 16 '18

Conduct clinical trial Sep 29 '17 - Aug 30 '19

- Submit clinical trial IND to MFDS Jun 30 '17
- IND approved by MFDS Sep 29 '17
- Clinical trial site initiation Jan 31 '18
- Last subject enrolled Apr 30 '18
- Submit clinical trial completion report to MFDS Aug 30 '19
- Submission of Vaccine Performance Report Aug 30 '19
SUMMARY

• MERS CoV vaccine development will be complicated by the unique features of viral transmission and outbreak epidemiology.

• There is a large pipeline of potential candidates, and the Coalition for Epidemic Preparedness Innovations has prioritized MERS CoV vaccine development.

• The IVI MERS vaccine program is moving forward with its initial candidate and is anticipating work on a second potential candidate.