Update on MERS-CoV

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BARDA Industry Day
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Middle East respiratory syndrome coronavirus (MERS-CoV)

• MERS-CoV belongs to the family Coronaviridae
• Other coronaviruses include:
  — SARS-CoV
  — Human coronavirus 229E & OC43
  — Feline coronavirus
• Enveloped viruses containing nonsegmented, positive-strand RNA genome
• Two outbreaks of novel coronaviruses (SARS and MERS) causing acute respiratory distress syndrome and high death rates this century
• There are currently no licensed/approved vaccines or treatments for Coronaviruses

MERS-CoV outbreaks in Saudi Arabia and South Korea

Saudi Arabia since 2012

- Deaths: 542
- Recovered: 675
- Active: 38

Confirmed global cases of MERS-CoV
Reported to WHO as of 04 Sep 2015 (n=1517)

- Republic of Korea
- Other Countries
- South Arabia

1569 confirmed cases
554 (35%) patients have died

South Korea, 2015

- Total Confirmed: 186
- Republic of Korea: 185
- China: 1
- Deaths: 36

Index case
Imported case
Family member of IC
Health care worker
Secondary cases
Tertiary cases
Family member of Secondary Cases
Deaths

Index Case
Travelled to Bahrain, KSA, UAE
Home in Korea
Hospital A
Hospital B
Hospital C
Isolation Facility

Hospital D
Hospital E
Hospital F
Hospital G
Hospital H
Travelled to Guangdong, China

http://www.who.int/emergencies/mers-cov/en/
Clinical Observations

• Symptom Onset median 5 (2-19) days after exposure. Range from asymptomatic to severely ill.

• Initial Illness
  — Fever, cough, bloody sputum, chest pain, hypoxia
  — Upper respiratory illness progresses quickly to:
    • Lower respiratory illness including pneumonia, Acute Respiratory Syndrome (ARDS), and Respiratory Failure
    • Septic Shock
    • Multi-organ failure, (high rate of renal failure)
    • Death
  — Older patients and those with pre-existing co-morbidities are most at risk

• High rate of advanced medical utilization: series of 70 consecutively identified MERS CoV infections:
  — 91% Hosp, 70% ICU, 66% Mechanical Ventilation, 60% Death
Findings and Updates from the ASPR MERS-CoV Stakeholder Workshop

April 3, 2015
• Multiple RT-PCR tests have been described
  — Two have FDA EUAs
  — Others are used in global referral centers
• Several serology tests for prior infection are described with reagents available
• Lower respiratory tract samples are optimal
  • Upper respiratory samples are not reliable for identifying infected patients
• Mice are not naturally susceptible due to lack of receptor for MERS-CoV (DPP4 receptor)
• Mice transduced with adenovirus expressing DPP4 are susceptible
• Transgenic mice expressing DPP4 are susceptible and have more severe disease/death

• Non-Human primates
  — Some NHPs are naturally susceptible to MERS-CoV
• Rhesus macaques have mild and transient disease
• Marmosets have more severe and protracted disease with some lethality

All models require further development and standardization
# MERS-CoV Immunotherapeutic Landscape

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<tr>
<th>in vitro studies</th>
<th>Pre-Clinical</th>
<th>Clinical</th>
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<tr>
<td>Juntendo University</td>
<td>Dana-Farber Cancer Institute</td>
<td>Regeneron</td>
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<tr>
<td>The University of Hong Kong</td>
<td>National Cancer Institute</td>
<td>Ministry of Health</td>
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<tr>
<td>University of Minnesota</td>
<td>SAB Biotherapeutics</td>
<td>Cerus</td>
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**Regeneron**
- Fully human antibodies from transgenic mice, Tested in Transgenic Mouse & NHP
- Clinical trial ongoing

**Cerus**
- Convalescent serum

**University of Minnesota**
- mAb from human, Tested in Ad-5 mouse
### MERS-CoV Small Molecules Landscape

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<tr>
<td>Alferon N (Host-directed)</td>
<td>Helicase Inhibitor</td>
<td>FDA-Approved Drug Screen (2 hits)</td>
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<tr>
<td>Soluble DPP4 Decoy (binding inhibitor)</td>
<td>Nitazoxanide In vitro-MERS (Host-directed)</td>
<td>Ribavirin (polymerase)</td>
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<tr>
<td>Protease Inhibitor</td>
<td>DPP4-peptide Micelle</td>
<td>Lopinavir SARS Drug Screen (protease inhibitor)</td>
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<tr>
<td>Peptide Inhibitor (fusion inhibitor)</td>
<td>BCX4430 (polymerase)</td>
<td>PEG Interferon Alpha (Host-directed)</td>
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<tr>
<td>T-705 (polymerase)</td>
<td>Interferon B1b (Host-directed)</td>
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Clinically approved drugs for a different indication. Not in clinical trials for MERS-CoV, but have been used for therapy.
MERS-CoV Vaccine Landscape

in vitro studies

- S Subunit (NY Blood)
- Live attenuated (University of Iowa)
- Ad5 S and S1 (University of Pittsburgh)

Pre-Clinical

- Purified S Protein Trimer (Novavax)
- Fully-deleted Adenovirus vector expression S Protein (Greffex)

Clinical Trials

- DNA Prime+Boost or DNA Prime+ S protein boost (National Institute of Allergy and Infectious Diseases)
- Adeno vector, Recombinant Spike, live attenuated (University of Iowa)
- DNA expressing S protein+ Electroporation (Inovio)

Priorities

- Therapeutic Development
- Vaccine Development
- Animal Model Development
- Diagnostic Development

MERS-CoV Clinical Trials
Priorities: Animal Model Development

- Mouse studies at University of Maryland School of Medicine
- NHP studies at NIAID Rocky Mountain Laboratories
- Utilize the BARDA Nonclinical Development Network to standardize models
- NIH MERS Animal Model Standardization Workshop
Priorities:
Therapeutic Development

- Work with university and government partners, industry, and affected countries to obtain necessary data to begin human clinical trials
- From preclinical efficacy data to planning clinical trials
Priorities: MERS-CoV Clinical Trials

- Meeting in KSA Sept 9 – 10, 2015
- Objectives:
  - Establish a collaborative approach with national and international authorities and agencies
  - Present and discuss research options/priorities
  - Discuss logistics and requirements for early phase clinical trials
- Outcomes:
  - International collaboration
  - Prioritization of therapeutic candidates
  - Pathway towards a common adaptive clinical trial protocol
Summary

- Coronaviruses are a continuing and emerging threat
  - Two novel coronavirus have caused large outbreaks since 2002
  - Potential for MERS-CoV spread globally and cause significant morbidity and mortality
  - Research on potential MERS-CoV MCMs remains preliminary
  - International collaboration is needed to better understand the virus, disease and to develop/evaluate MCMs
- BARDA’s experience in national and international preparedness and response can accelerate global preparedness for this emerging infectious disease