Applying New Technologies in the Battle Against Ebola and Other Emerging Infections

Vaccine Development in the 21st Century
6th Annual Global Health Conference
Mobilizing Research for Global Health
Consortium of Universities for Global Health
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Outline

- Introduction
- A perspective on emerging infectious diseases
- Ebola - unprecedented crisis
- Chikungunya – emerging crisis
- MERS – regional outbreak with pandemic potential
- Conclusions
Can technology solve the problem of emerging and changing infections?

Emerging infections
- Increasing human mobility, poverty, refugees, and immunological vulnerability
- Rapidly changing ecology
- Threat of bioterrorism

Technology
- Structural biology
- Protein design
- High throughput sequencing
- Rapid isolation of human mAbs
- Rapid diagnostic tools
- New understanding of immunology and assay capabilities
- Advanced imaging
- Systems biology
New Human Viral Pathogens in the 20th Century

New species

New families

# Vaccine Track Record for Controlling Infectious Disease Epidemics

<table>
<thead>
<tr>
<th>Viral Disease</th>
<th>Year of Peak U.S. Prevalence</th>
<th>Peak # of Cases per Year in U.S.</th>
<th># of Annual U.S. Cases in Modern Vaccine Era*</th>
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<td>1971</td>
<td>59,606</td>
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<tr>
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<td>1900-1904</td>
<td>48,164</td>
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</table>

*Source: CDC 2009
New Vaccine Development is Usually Opportunistic

Viral Vaccines

- HPV
- Rotavirus
- Varicella
- Japanese encephalitis
- Hepatitis A
- Hepatitis B
- Rubella
- Mumps
- Adenovirus
- Measles
- Poliovirus
- Influenza
- Yellow fever
- Rabies
- Smallpox

Major Conceptual and Technological Advances

- Discovery of immunity
- Cell culture
- Molecular biology

Stabilization of antigenic site on conformationally active protein results in potent vaccine antigen

Postfusion F in 6-helix bundle conformation

Functional form of RSV F in pre-triggered conformation

Candidate RSV vaccine is stabilized native F trimer

RSV Postfusion F Structure (JVI 2011)

RSV Prefusion F Structure (Science April 2013)

RSV Vaccine Design (Science November 2013)
Convergence of Technologies Has Produced a New Vaccine Development Paradigm

1. Isolation of human monoclonal antibodies by cloning IgH and IgL genes from single B cells

2. High-throughput sequencing of plasmablasts or probe-selected memory B cells

3. Serological analysis and identification of broadly neutralizing antibodies that bind quaternary epitopes

4. Stabilize native structure of key antigenic sites and optimize immunogenicity

5. Structural analysis of antigenic sites on viral surface glycoproteins

New probes

Vaccine antigens

Class I Fusion Glycoproteins

- RSV F
- PIV F
- Influenza HA
- HIV-1 gp160
- Ebola GP
- CoV S

Viral membrane

<table>
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<tr>
<th>SP</th>
<th>± RBD</th>
<th>FP</th>
<th>HR1</th>
<th>± cysteine rich</th>
<th>HR2</th>
<th>TM</th>
<th>CT</th>
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New Technologies Have Made an RSV Vaccine Possible

Viral Vaccines

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<tr>
<th>Year</th>
<th>RSV?</th>
<th>HPV</th>
<th>Rotavirus</th>
<th>Varicella</th>
<th>Japanese encephalitis</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
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<th>Mumps</th>
<th>Adenovirus</th>
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<th>Poliovirus</th>
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</tbody>
</table>

Major Conceptual and Technological Advances

- Cell culture
- Molecular biology

Potential areas for new technical advances

- Structural Biology
  - Human mAb isolation
  - High throughput sequencing
  - New delivery platforms
- Animal Models
- Cell Biology
- Genetics
- Glycobiology
- Immunology
- Manufacturing
- Proteomics
Vaccines for the 21st Century

- Will be needed as a public health tool for emerging infectious diseases
- Establish global infrastructure for surveillance and virus discovery
- Establish platform technologies and define vaccine strategies for each family of viral pathogens
- Establish the capacity within government for advanced development and support of public-private partnerships
- Define more efficient regulatory pathways
How long does it take to develop a vaccine?

<table>
<thead>
<tr>
<th>Viral Pathogen</th>
<th>Virus Discovered</th>
<th>Vaccine Developed for Human Use</th>
<th>Years to Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow Fever Virus</td>
<td>1900</td>
<td>1935</td>
<td>35</td>
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<tr>
<td>Polio</td>
<td>1909</td>
<td>1954</td>
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<td>Measles</td>
<td>1911</td>
<td>1957</td>
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<td>HSV</td>
<td>1919</td>
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<td>Influenza</td>
<td>1933</td>
<td>1945</td>
<td>12</td>
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<tr>
<td>RSV</td>
<td>1956</td>
<td>Not available</td>
<td>&gt;59</td>
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<tr>
<td>Dengue virus</td>
<td>1960</td>
<td>Not available</td>
<td>&gt;55</td>
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<tr>
<td>Hepatitis B</td>
<td>1967</td>
<td>1984</td>
<td>17</td>
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<td>Rotavirus</td>
<td>1973</td>
<td>1998</td>
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<td>Hepatitis A</td>
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<td>1995</td>
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<td>HPV</td>
<td>1974</td>
<td>2007</td>
<td>33</td>
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<tr>
<td>HIV</td>
<td>1983</td>
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<td>&gt;32</td>
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<tr>
<td>HCV</td>
<td>1989</td>
<td>Not available</td>
<td>&gt;26</td>
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# VRC Filovirus Vaccine Clinical Trials

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<tr>
<th>Study</th>
<th>Study Design</th>
<th>Insert</th>
<th>Dosage, route, x N administrations</th>
<th>Accrual* Product/Placebo</th>
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</thead>
<tbody>
<tr>
<td>VRC 204 DNA ΔTM GP</td>
<td>Phase I, randomized, placebo-controlled, dose escalation</td>
<td>Ebola Z+S</td>
<td>2 mg IM x 3 doses 4 mg IM x 3 doses 8 mg IM x 3 doses</td>
<td>5/2 8/2 8/2</td>
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<tr>
<td>VRC 205 Ad5 PM GP</td>
<td>Phase I, randomized, placebo-controlled, dose escalation</td>
<td>Ebola Z+S</td>
<td>2x10⁹ vp IM (1 dose) 2x10¹⁰ vp IM (1 dose)</td>
<td>12/4 12/4</td>
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<tr>
<td>VRC 206 DNA WT GP</td>
<td>Phase I, open label</td>
<td>Ebola Z+S Marburg Angola</td>
<td>4 mg IM (3 - 4 doses) EBO or MBG</td>
<td>20</td>
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<td>RV 247 DNA WT GP</td>
<td>Phase Ib, randomized, placebo-controlled</td>
<td>Ebola Z+S Marburg Angola</td>
<td>4 mg IM x 3 doses of each 4 mg IM x 3 doses of both</td>
<td>90/6</td>
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<tr>
<td>VRC 207 cAd3 WT GP</td>
<td>Phase I, open label, dose-escalation</td>
<td>Ebola Z+S</td>
<td>2x10¹⁰ IM (1 dose) 2x10¹¹ IM (1 dose)</td>
<td>20</td>
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</table>

*numbers of subjects that received Ebola vaccine are shown in bold

- Full-length Ebola GP antigens delivered by DNA plasmid vaccination was well tolerated in 80 subjects in studies conducted in the U.S. and Uganda
- cAd3 vectors expressing other antigens have been well tolerated in >200 humans
Ebola GP Sequence Comparison
Mayinga 1976 (Vaccine) vs. Guinea 2014 (Outbreak)

Structure adapted from JE Lee et al. Nature 454, 177-182 (2008)
## Clinical Trials Underway or Pending

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<thead>
<tr>
<th>Trial</th>
<th>Site</th>
<th>PI</th>
<th>Product (dose)</th>
<th>Phase</th>
<th>N</th>
<th>Start Date</th>
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<tbody>
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<td>VRC 207</td>
<td>NIH CC</td>
<td>Ledgerwood</td>
<td>Bivalent 2e10 &amp; 2e11</td>
<td>I</td>
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<tr>
<td>VRC 207 Part 2</td>
<td>UMD</td>
<td>Lyke</td>
<td>Monovalent 1e10 &amp; 1e11</td>
<td>I</td>
<td>20</td>
<td>10 Nov 2014</td>
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<td>VRC 207 Part 2</td>
<td>Emory</td>
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<td>Ib</td>
<td>40-100</td>
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<td>cAd3-EBOZ Lau</td>
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<td>Genton</td>
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<td>MUWRP - Uganda</td>
<td>Kibuuka/Robb</td>
<td>Bivalent 2e10 &amp; 2e11 Monovalent 1e10 &amp; 1e11</td>
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<td>CVD-Mali Ebola Vaccine #2000</td>
<td>UMD - Mali</td>
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<td>I</td>
<td>91</td>
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Clinical Evaluation of cAd3-EBO(Z)

VRC 207 – NIH Clinical Center - Bethesda
Clinical Evaluation of cAd3-EBO(Z) – Phase 1

Extended Phase I/Ib – Oxford (UK)
CVD-Mali (Bamako)
CHUV (Lausanne)
Makere (Kampala)
CVD Mali Ebola Vaccine Team
Clinical Evaluation of cAd3-EBO(Z) – Phase 2

Phase II – Cameroon
Ghana
Mali
Nigeria

Adult
Pediatric
Clinical Evaluation of cAd3-EBO(Z) – Phase 3
Factors that made rapid response possible

• Prior preparation
  – Understanding of pathogenesis and immunity
  – Availability of animal model
  – Established scientific rationale for vaccine
  – cGMP product availability
  – Availability of preclinical data
• Involvement of a commercial partner
• Unprecedented public health crisis, global concern, extensive media coverage, political visibility
• WHO involvement and broad support from Governments
• Cooperation and coordination of:
  – Manufacturing
  – Funding agencies
  – Clinical trial sites
  – Laboratories analyzing clinical samples
  – Regulatory authorities
  – Rapid publishing by biomedical journals
Why can’t we respond to every public health crisis in this way?

- Unique issues for each pathogen and vaccine development process, but some factors are predictable
- Examples from ChikV and MERS CoV
Chikungunya Virus (ChikV)

• Alphavirus:
  • Discovered in 1952 in sample from Tanzania at the East African Virus Research Institute in Entebbe

• Mosquito-Borne Transmission:
  • Historically: Aedes aegypti
  • Recent adaptation to Aedes albopictus vector
    • Single amino acid mutation identified in 2006 resulting in expanded transmission

• Clinical:
  • Symptoms: Fever, arthritis, headache, nausea, rash
  • No vaccine or anti-viral therapy available

ChikV in the Americas

First report December 18, 2013. 1Q2015 >1 million cases.
ChikV Virus Like Particles

ChikV Genome:

VLP construct:

- **Advantages of the VLP vaccine platform**
  - Express fraction of genome as a particle
    - Highly symmetric and exterior natural appearance resembles wild type virus
  - Efficiently recognized by immune system
    - Elicits high titer neutralizing antibody
  - Safety
    - Other VLPs licensed and safe in humans
    - VLP does not replicate

- Typical alphavirus icosahedral symmetry
- 240 copies of viral spike on surface

Akahata and Nabel et al, Nature Med, March 2010
Phase I ChikV VLP Immunogenicity

OPY1 outbreak strain

Neutralization titer (IC$_{50}$)

CHIKV VLP Dose

Chang and Ledgerwood et al, Lancet 14 Aug 2014
Factors Delaying Advanced Development

- Lack of commercial partner
- Resources and focus needed for process development and scale-up
- Difficulty in establishing clinical trial infrastructure for defining efficacy and immune correlates of protection
Another Beta Coronavirus Emerges

2003 - SARS

2012 - MERS

World Health Organization
MERS is a regional disease with unknown pandemic potential

from Google maps: https://maps.google.com/maps/
Factors Delaying Development

- No commercial interest
- Still needs optimization
- Cost:benefit analysis for proceeding with vaccine development for a regional disease with minimal human-to-human spread
There is a need for better public options for vaccine development

How to improve response time to new emerging infectious diseases

- Scientists need to improve communication to government and other funding agencies about scientific capabilities and data required for rapid action.
- Public health authorities need to improve surveillance and discovery capacity and be more decisive about recommendations for product use.
- Need a new business model for developing and distributing interventions for public health especially for low prevalence pathogens and emergencies:
  - Public-private partnerships
  - Government-to-Government partnerships
  - Public-NGO partnerships
Acknowledgments

Clinical Trials Program
Mary Enama
Ingelise Gordon
Lasonji Holman
Sarah Plummer
Cynthia Starr Hendel
Laura Novik
Pamela Costner
Kathy Zephir
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Jamie Saunders
Sandra Sitar
Brenda Larkin
Galina Yamshchikov
Olga Vasilenko
Iris Pittman
Nina Berkowitz
Brandon Wilson
Pernell Williams
Carmencita Artis

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USMHRP-Makere

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