Moving Experimental Vaccines and Medicines for Ebola Virus into Clinical Practice

Leem Press Workshop
March 10, 2015

Gary J. Nabel M.D. PhD.
Chief Scientific Officer
Sanofi
Gene-based vaccination for Ebola Virus

Immunization for Ebola virus infection
Ling Xu, Anthony Sanchez, Zhi-Yong Yang, Sherif R. Zaki, Elizabeth G. Nabel, Stuart T. Nichol & Gary J. Nabel

Development of a preventive vaccine for Ebola virus infection in primates
Nature, 408, 605-609, 2000
NP, VP35 and VP24 are Necessary and Sufficient for Nucleocapsid Formation

NIH NEWS RELEASE
Tuesday, November 18, 2003

National Institutes of Health
National Institute of Allergy and Infectious Diseases

NIAID Ebola Vaccine Enters Human Trial

The first human trial of a vaccine designed to prevent Ebola infection opened today. Scientists from the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), designed the vaccine, which was administered to a volunteer at the NIH Clinical Center in Bethesda. The vaccine does not contain any infectious material from the Ebola virus.
CD8 Cells Mediate Ad Vaccine Protection Against Ebola

CD8+ Cellular Immunity Mediates rAd5 Vaccine Protection Against Ebola virus Infection of Nonhuman Primates.


Pre-existing Ad5 Immunity Abrogates Ebola Vaccine Protection in NHP

- Ad5-immune and –naïve macaques
- Vaccinate with rAd5-GP
- Immune response and challenge at 4 wks
Definition of an Ebola Vaccine with Rapid Onset and Durable Protection in Monkeys

ChAd3 Prime MVA Boost

Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge

Daphne A Stanley¹, Anna N Honko²,³, Clement Asiedu¹,³, John C Trefry², Annie W Lau-Kilby¹, Joshua C Johnson²,³, Lisa Hensley²,³, Virginia Ammendola³, Adele Abbate³, Fabiana Grazio³, Kathryn E Foulds¹, Cheng Cheng¹, Lingshu Wang¹, Mitzi M Donaldson¹, Stefano Colloca³, Antonella Folgori¹, Mario Roederer¹, Gary J Nabel¹, John Masciola¹, Alfredo Nicosia³,⁴,⁵, Riccardo Cortese⁶, Richard A Koup¹ & Nancy J Sullivan¹

Received 18 August; accepted 2 September; published online 7 September 2014; doi:10.1038/nm.3702
Pharmaceutical Drug and Vaccine Development - A Slow Process

Target ID and Validation

Lead Identification

Lead Optimization

Preclinical

Development

Historical cycle times

Target cycle times small molecule

Target cycle times biologics

Average cycle times (months)

Research & Early Development | 9
Sanofi names chief scientific officer Gary Nabel as Sanofi Ebola response coordinator

Monday, November 24, 2014 02:30 PM

As part of its contribution to the global response to the Ebola epidemic, Sanofi has appointed chief scientific officer Dr. Gary J. Nabel, M.D., Ph.D., as its Ebola response coordinator.

In his mission, Dr. Nabel will identify how Sanofi can help advance countermeasures to contain the current outbreak and prioritize and foster opportunities to develop novel treatments for the future.

"Given his past experience in public health epidemics as director of the NIH Vaccine Research Center and his leadership in developing an Ebola vaccine at NIH, Nabel is uniquely qualified for this position," said Dr. Elias Zerhouni, M.D., president of Sanofi Global R&D. "Nabel is working with other organizations, including providing guidance to researchers based on the company's extensive experience in vaccine and drug development, to determine how Sanofi can assist in making progress with this global challenge."

"Working with our colleagues across the industry, Sanofi is helping to find ways to advance medicines to prevent or treat Ebola virus infection. We also are sharing our scientific, medical, regulatory and manufacturing expertise with the World Health Organization, government and non-governmental organizations—public and private—in an effort to contain this epidemic," Nabel said.
A Spectrum of Ebola Countermeasures
From Vaccines to Anti-virals

Prevention → Treatment

Vaccines
- Gene-based
- Live Vector

Biologics
- Antibodies
- siRNA

Small Molecules
- Viral Genes
- Cell Targets
Sanofi Priorities for Ebola Virus Countermeasures

**Tier 1**
Vaccines/Antivirals Already in Clinical Trials

**Tier 2**
Proof of Concept in NHP Not in Clinical Development

**Tier 3**
Antiviral activity but no NHP proof of concept
### Diverse Target Product Profiles

<table>
<thead>
<tr>
<th>Modality</th>
<th>Vaccines</th>
<th>Biologics</th>
<th>Small Molecules</th>
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<tbody>
<tr>
<td><strong>Prophylaxis</strong> (Pre or Post Exposure)</td>
<td><img src="image1" alt="Vaccines" /></td>
<td><img src="image2" alt="Biologics" /></td>
<td><img src="image3" alt="Small Molecules" /></td>
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<tr>
<td><strong>Treatment, EBOV+</strong> (early symptoms)</td>
<td><img src="image1" alt="Vaccines" /></td>
<td><img src="image2" alt="Biologics" /></td>
<td><img src="image3" alt="Small Molecules" /></td>
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<tr>
<td><strong>Ebola VHF</strong> (late stage)</td>
<td><img src="image1" alt="Vaccines" /></td>
<td><img src="image2" alt="Biologics" /></td>
<td><img src="image3" alt="Small Molecules" /></td>
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PHRMA Response to Ebola Outbreak: Ebola Response Coordination Team (ERCT)

- Organized by BMAC Co-Chairs Elias Zerhouni and Tachi Yamada
- Chaired by Gary J Nabel, Sanofi CSO,
- Other Members:
  - Mark Feinberg, MD, PhD, Chief Public Health and Science Officer, Merck Vaccines, Merck & Co., Inc.
  - John Houston, PhD, Senior Vice President, Disease Sciences and Biologics, Bristol-Myers Squibb
  - Dale Kempf, PhD, Director of Antiviral Research, AbbVie
  - Machelle Sanders, MHA, Vice President, Manufacturing & General Biogen Idec Inc.
  - Jonathan “JZ” Zalevsky, PhD, Head, Immunology Research, Takeda Pharmaceuticals U.S.A., Inc.
- Ex officio (PHRMA): Bill Chin-Executive VP: Scientific and Regulatory Affairs
Sanofi and PHRMA Ebola Activities

- Participated in Hever Group Ebola Medicines Day
  - November 24, 2014
  - Pharma, biotech and government representatives developed a Global Call for clinical compounds to be tested in the NIH and USAMRIID Ebola Screening Cascades

- Reviewed External Requests for Support of Discovery Programs

Sanofi Contributions

- 136 compounds identified for screening at USAMRIID

- 5 Biotech/Academic groups referred to USAMRIID for further testing.
Policy and Regulatory Concerns

**Indemnification**
- Vaccines/Prevention
- Anti-Viral Therapy

**Clinical Trials**
- Specific for TPP’s
- POC in humans
- Efficacy Studies (Placebo Controlled, Adaptive)
- Licensure Requirements

**Ethics**
- Ethical Review Committees
- Informal Consent
Licensure is only one step in combating disease
Manufacturing

- Production Capacity
- Reagents for Testing and Lot Release
- Formulation
- Delivery Strategies
Managing the Flow of Ebola Drugs or Vaccines to Patients

1. Vaccine or Drug Manufacturer
2. Territory (Guinea, Liberia, Sierra Leone)
3. Embassy or Designated Reciever
4. Local Delivery Distribution Partner
5. Clinical Trials, Data Collection, Pharmacovigilance
6. Ebola Treatment Centers
7. Physicians
8. Patients

http://i100.independent.co.uk/image/2706000-600x386.jpg

505655474662061_1051058733.png
Galaxies Colliding: Countering Emerging Infectious Diseases

Public Health Impact

Sustainable Funding/Commitment

The challenge facing countermeasures for emerging pathogens
Summary

1. Ebola virus is a prototypic filovirus with high lethality that is readily spread by human contact during active infection.

2. Ebola mortality is multifactorial, driven by viral cytopathicity for hepatocyte, reticuloendothelial, and endothelial cells whose damage ultimately causes septic shock.

3. It is possible to generate protective immunity to Ebola by vaccination. The cellular immune response plays a critical role in mediating protection. The antibody response correlates but is not responsible for immunity.

4. Two vaccine candidates are progressing in clinical trials. Antiviral therapies, including antibody (ZMapp) and anti-sense oligonucleotides, are in evaluation but are yet unproven in humans.

5. In the interim, barrier precautions and containment represent the key public health tools to control Ebola virus spread.