Prototype Pathogen Approach for Vaccine Development
Filoviruses

Nancy J. Sullivan, ScD
Director, National Emerging Infectious Diseases Laboratories
Edward Avedisian Professor and Professor of Microbiology
Chobanian & Avedisian School of Medicine
Professor of Biology, College of Arts and Sciences
Boston University

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WHO Consultation
Prototype pathogen approach for vaccine preparedness

- Basic research to identify prototype categories
- Define transmission, pathogenicity, immunity
- Develop prototype vaccines through Phase 1
How do we categorize pathogens to define “prototypes”?

<table>
<thead>
<tr>
<th>Pandemic Potential</th>
<th>High</th>
<th>Moderate</th>
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<tbody>
<tr>
<td>High</td>
<td>Orthomyxoviridae</td>
<td>Retroviridae</td>
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<tr>
<td></td>
<td>Coronavirus</td>
<td>Poxviridae*</td>
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<tr>
<td></td>
<td>Bunyavirales order</td>
<td>Papillomaviridae*</td>
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<td></td>
<td>Arenaviridae</td>
<td>Hepadnaviridae*</td>
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<td>Phenuviridae</td>
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<td>Peribunyaviridae</td>
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<td>Nairoviridae</td>
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<tr>
<td>Moderate</td>
<td>Filoviridae</td>
<td>Arteriviridae</td>
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<td></td>
<td>Flaviviridae</td>
<td>Pneumoviridae</td>
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<tr>
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<td>Paramyxoviridae</td>
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<td>Togaviridae</td>
<td>Bornaviridae</td>
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<td>Picornaviridae</td>
<td>Rabdoviridae</td>
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<td>Caliciviridae</td>
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<td>Hepeviridae</td>
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<tr>
<td></td>
<td></td>
<td>Parvoviridae</td>
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<td>Picobirnaviridae</td>
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<tr>
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<td>Reoviridae</td>
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<tr>
<td></td>
<td></td>
<td>Polyomaviridae</td>
</tr>
</tbody>
</table>
Virus features that can inform prototype design
Virus entry mechanisms as basis for prototype design

Class I
- Paramyxoviridae
- Pneumoviridae
- Coronaviridae
- Arenaviridae
- Retroviridae
- Orthomyxoviridae
- Filoviridae

Core Functions
- Sequencing/synthesis
- Protein production
- Structure/Antigen design
- Antigen display/delivery
- Animal modeling
- Pathogenesis and organ-specific immunity
- B cell biology/serology
- T cell biology/flow cytometry
- Single cell analysis
- Computational biology
- Bioinformatics
- Process development
- Pilot manufacturing
- Phase I clinical trials

Class II
- Togaviridae
- Matonaviridae
- Flaviviridae
- Hantaviridae
- Nairoviridae
- Phenuiviridae

Class III and others
- Herpesviridae
- Poxviridae
- Rhabdoviridae
- Hepadnaviridae (Arteriviridae)

Non-enveloped
- Picornaviridae
- Polyomaviridae
- Papillomaviridae
- Caliciviridae
- Astroviridae
- Adenoviridae
- Paroviridae
- Reoviridae
- Hepeviridae

B. Graham

Graham and Sullivan, Nat Imm 2018
Design target antigen prototype

RSV F
post-fusion

RSV F
Stabilized prefusion
(complex with D25 mAb)

MERS-CoV S-2P
Stabilized prefusion
(complex with G4 mAb)

SARS-CoV-2 S-2P
Stabilized prefusion

Pallesen et al, PNAS, 2017  
Wrapp et al, Science, 2020
Prototypes may span virus families

Stabilized spike preF and mRNA
- RSV, Nipah
- MERS, SARS-CoV-2
Filoviruses: “Prototypes” may not protect across virus family

<table>
<thead>
<tr>
<th></th>
<th>Marburg</th>
<th>Ebola</th>
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<tbody>
<tr>
<td>DNA-GP</td>
<td>Protected</td>
<td>Succumbed</td>
</tr>
<tr>
<td>rAd-GP</td>
<td>Protected</td>
<td>Protected</td>
</tr>
</tbody>
</table>

Nat Med 2003; J. Virology 2010; unpublished
Vaccine vector-specific immune skewing
Antibodies are not sufficient for protection by rAd5-GP against Ebola infection

Sullivan et al., Nature Med. 2011
CD8+ T-cells are required for rAd-GP Ebola vaccine protection

Nature Medicine 2011
Vaccine vector choice to “tune” immune responses

Front. Immunol. 2021
DNA Primes Tune the Dominance of Post Boost Responses from CD8+ to CD4+ T-Cells
Choice of vaccine platform to “tune” immune response

DNA
mRNA
Inactivated virus
Protein/Subunit
Viral Vector
VLP

Ab
T-cell

(AB4)
(AB8)
Vaccine platform technologies help define prototypes

Genetic Immunization
- DNA and RNA
  - Licensed vaccine: SARS-CoV-2
    - Ebola, Nipah, WNV, Zika, MERS, SARS-CoV-2
  - Influenza

Viral Vectors
- Ex. VSV, Adenovirus (replicating or not)
  - Licensed vaccine: Ebolavirus
    - Ebola, Marburg, Sudan

Protein/Subunit
- Protein with adjuvants (Ex. MF59, AS01)
  - Licensed vaccine: Influenza
    - SARS-CoV-2, HIV, Measles, Mumps

Killed/Inactivated virus
- Virus inactivated by heat/chemicals
  - Licensed vaccine: Polio, Rabies

Virus-like particles
- No genome; non infectious
  - Licensed vaccine: HepB
    - Chikungunya, WEE, VEE, EEE

Nanoparticles
- Influenza
Prototype Vaccines – Scientific Approach

- ~120 viruses known to infect humans with potential for epidemic outbreaks
- Strong basic and clinical research builds encyclopedia of prototypes
Summary

1. Vaccine prototype antigen designs can cross virus families

2. Choice of “family” prototype should account for differences in immune clearance mechanisms

3. Vaccine vector combinations can be used to “tune” immune responses

4. A comprehensive prototype program requires definition of immune mechanism, replication, pathogenesis and transmission