Vaccine Research Technologies: Challenges and Opportunities for the Next Two Decades

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Historical Success

Traditional Vaccinology vs. Vaccinology of the Future

Scientific Advances

Challenges and Advances in Selected Areas
  – HIV
  – Influenza
  – Respiratory Syncytial Virus
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Global Smallpox Cases, 1920-2010

Source: World Health Organization
The Impact of Vaccines Around the World: Declining Cases 1980-2012

- Diphtheria: 95%
- Measles: 95%
- Pertussis: 90%
- Polio: 99+% (99 and a half percent)
- Tetanus: 91%

Benefits from Immunization During the Vaccines for Children Program Era — United States, 1994–2013

Among U.S. children born 1994–2013, routine childhood vaccinations will prevent (over their lifetimes) an estimated:
- 322 million illnesses
- 21 million hospitalizations
- 732,000 deaths

Net savings: $295 billion in direct costs and $1.38 trillion in total societal costs
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Conceptual Basis for Traditional Vaccine Development

Mimic Natural Infection  ➔  Recapitulate Natural Immunity
Future Directions in Vaccine Research

Challenges:
- Inadequate immune response to natural infection (e.g., HIV, Malaria)
- Strain Diversity (e.g., influenza)

New Paradigm:
- Go beyond recapitulation of natural immunity
- Induce “unnatural immunity”
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21st Century Vaccinology: Selected Scientific Tools

- Rapid, deep genomic sequencing of pathogens
- Reverse vaccinology
- Structure-based vaccine design
- New vaccine platforms
Rapid Genome Sequencing: SARS

- **March 24, 2003**: SARS CoV Discovered
- **April 14, 2003**: SARS CoV Sequenced
  - SARS CoV Sequenced:
    - orf1a polyprotein
    - orf1b polyprotein
    - S glycoprotein
    - E protein
    - M protein
    - N protein
- **December 13, 2004**: SARS Phase I Clinical Trial Initiated at NIAID VRC
Deep Genome Sequencing: HIV

Next Generation Sequencing reveals HIV strain diversity

Identification of HIV Superinfection in Seroconcordant Couples in Rakai, Uganda, by Use of Next-Generation Deep Sequencing

AD Redd, TC Quinn et al.
Reverse Vaccinology: Genetic Expression of All Possible Immunogens

EXPERT OPINION

on Biological Therapy

Reverse Vaccinology: A Genome-Based Approach for Vaccine Development

V Masignani, R Rappuoli and M Pizza
Reverse Vaccinology: Genetic Expression of All Possible Immunogens

1. Sequencing of genome
2. Expression of genes in E. coli generating all potential antigens
3. Gene coding for N. meningitidis protein
4. Plasmid
5. Immunize mice
6. Measure antibodies with highest titers and microbicidal activity
7. Select antigens eliciting such antibodies with minimal sequence variation to use as immunogens
8. Vaccine

Source: Adapted from C Donati and R Rappuoli. Ann NY Acad Sci 1285, 2013.
Structure-Based Vaccine Design: Crystallography and Cryo-EM

Crystal Structure of a Soluble Cleaved HIV-1 Envelope Trimer
J-P Julien, IA Wilson et al.

Cryo-EM Structure of a Fully Glycosylated Soluble Cleaved HIV-1 Envelope Trimer
D Lyumkis, AB Ward et al.

Crystallography of Env trimer in complex with PGT122

Cryo EM side view of Env trimer in complex with PGV04
Novel Vaccine Platforms: Viral Vectors

Enhanced Protection Against Ebola Virus Mediated by an Improved Adenovirus-Based Vaccine

JS Richardson, GP Kobinger et al.

Phase I human trial planned
Self-Assembling Influenza Nanoparticle Vaccines Elicit Broadly Neutralizing H1N1 Antibodies

M Kanekiyo, GJ Nabel et al.
Novel Vaccine Platforms: Virus-like Particles

Virion

Virion with genetic material

Virus-Like Particle: surface proteins with no genetic material

A Virus-Like Particle Vaccine for Epidemic Chikungunya Virus Protects Nonhuman Primates Against Infection

W Akahata, GJ Nabel, et al.

Image credit: Plant Biotechnology Journal
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Modest (31%) Efficacy in RV144 Trial Correlates with Non-Neutralizing Antibodies to Epitopes in the V1-V2 Region of HIV Envelope

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial
BF Haynes et al.

Increased HIV-1 Vaccine Efficacy Against Viruses with Genetic Signatures in Env V2
M Rolland, JH Kim et al.

Vaccine Induction of Antibodies Against a Structurally Heterogeneous Site of Immune Pressure Within HIV-1 Envelope Protein Variable Regions 1 and 2
HX Liao, BF Haynes et al.
Broadly Neutralizing Antibodies
HIV Epitopes Targeted by Broadly Neutralizing Human Antibodies

Adapted from Kwong and Mascola, *Immunity* 37(3), 2012.
Challenges to Developing an HIV Vaccine that Induces Broadly Neutralizing Antibodies (BNAbs)

- Conserved glycoprotein-rich regions on HIV envelope are often poorly immunogenic

- BNAbs are elicited in a minority of HIV-infected individuals and only 2 years (or longer) after infection

- Most BNAbs demonstrate a high degree of somatic mutation

- Certain BNAbs have other unusual traits such as autoreactivity
Co-Evolution of Virus and Antibody in an HIV-Infected Individual

Transmitted/Founder Virus

Infection

2+ Years

Unmutated ancestor antibody

Broadly neutralizing antibody

The “Paradox” of the Evolution of Broadly Neutralizing Antibodies

As HIV evades the evolving HIV-specific antibodies, it ultimately stimulates broadly neutralizing antibodies.
B-Cell Lineage Vaccine Design

Iterative immunogens used for sequential immunizations

Progressive B-Cell mutation and maturation

Germline

Mature cell producing broadly neutralizing antibodies

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Issues Related to Influenza Vaccines

- Lack of life-long immunity following infection and/or vaccination
- Invariable "drift" of seasonal influenza strains requiring "timetable" approach to vaccine development
- Imprecision in predicting seasonal strain
- Cost ($2-4 billion) to prepare seasonal influenza vaccines de novo each year
- Inability to stockpile vaccines for several years
- Potential for emergence of pandemic strain
Induction of Unnatural Immunity: Prospects for a Broadly Protective Universal Influenza Vaccine

GJ Nabel and AS Fauci
Universal Influenza Vaccine

- Induces immunity against all “drifting” strains of seasonal influenza resulting in protection from infections and/or significant disease

- Administered intermittently (intervals to be determined) starting from 6 months of age

- Effective against pandemic strains

- Capable of being stockpiled
Influenza A Hemagglutinin (HA)
Generating Broadly Neutralizing Antibodies: Targeting the Stem

Most antibodies bind to epitopes of highly variable head region.

Antibodies that neutralize multiple strains bind to a highly conserved area in the stem region.

Antibody Binding to Influenza Hemagglutinin

Antibody binding to hemagglutinin head – strain-specific
Antibody binding to hemagglutinin stem – broadly neutralizing

Influenza A Hemagglutinin (HA)
“DNA Prime – Boost” Vaccine Approach Generates Broadly Neutralizing Antibodies

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Global Respiratory Syncytial Virus (RSV) Mortality and Morbidity

Global Annual Burden of Disease

- 33.8 Million Acute Lower Respiratory Infections
- 3.4 Million Hospitalizations
- 66,000-200,000 Deaths

- Causes 6.7 percent of deaths in children aged 1 month-1 year
- Nearly 1/4 of children under age one hospitalized with RSV will develop asthma

Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization from Respiratory Syncytial Virus Infection in High-Risk Infants

The IMpact-RSV Study Group

- Palivizumab is a monoclonal antibody vs. Fusion protein
- Used for periodic prophylaxis of severe RSV for premature infants
- Shown to reduce RSV hospitalizations by 82%
Fusion Protein (F) is a Promising Antigen

- Part of the viral spike
- Required for RSV entry into cell
- Conserved across strains

EM of viral capsid

Envelope spike containing the F protein
F Protein Adopts Two Primary Conformations: Pre- and Post-Fusion

Pre-Fusion (Unstable)

Post-Fusion (Stable)
Broadly Neutralizing Antibodies Bind More Readily to the Pre-Fusion Form

Pre-Fusion F Protein Stabilized Using Structure-Based Vaccine Design

Pre-Fusion F Protein  

Vaccine immunogen  

Stabilization

Neutralization in Non-human Primates

Stabilized Pre-Fusion Proteins show superior neutralization

Structure-based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus

JS McLellan, BS Graham, PD Kwong et al.

Human trial planned
The Perpetual Challenge of emergence, persistence and re-emergence of vaccine-preventable diseases.

The Perpetual Challenge of scientific discovery and technological advances for the development of new and improved vaccines.