Global Vaccine and Immunization Research Forum

Vaccine Research and Development: Challenges and Opportunities

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National Institutes of Health

March 4, 2014

NIH National Institute of Allergy and Infectious Diseases

- Decade of Vaccines
- Historical Success
- Future Directions
- Challenges and Advances in Selected Areas
  - HIV
  - Influenza
  - RSV
  - Malaria

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DECADE of VACCINES COLLABORATION

- **Purpose:** Discover, develop, and deliver vaccines globally in the next ten years through enhanced collaboration across the international community
- **Outcomes:**
  - Global Vaccine Action Plan (2011) – integration of research & development, delivery, global access, public & political support
  - Special supplement of Vaccine (2013) – case studies and future directions

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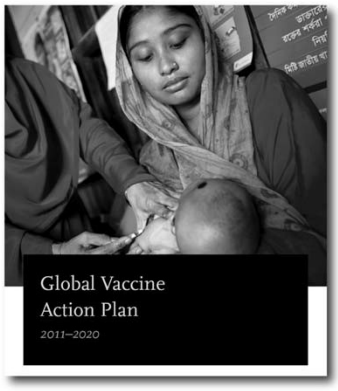

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Goals of the Decade of Vaccines (2011-2020)

- Achieve a world free of poliomyelitis
- Meet global and regional elimination targets
- Meet vaccination coverage targets in every region, country and community
- Develop and introduce new and improved vaccines and technologies
- Exceed the Millennium Development Goal 4 target for reducing child mortality

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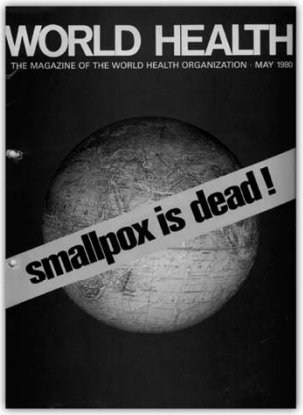

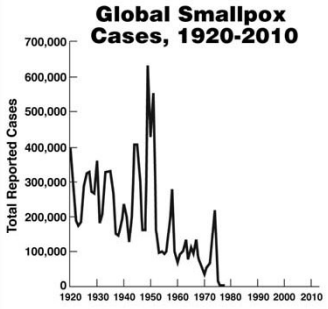

Source: World Health Organization

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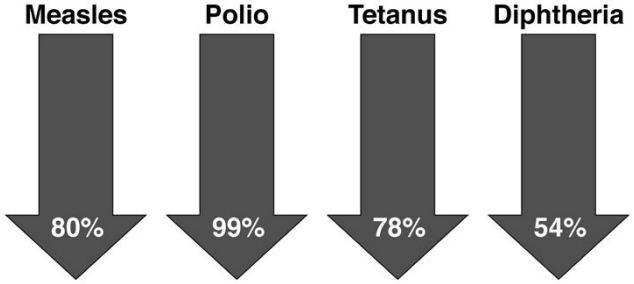
The Impact of Vaccines Around the World: Declining Mortality 1990-2010



Sources: WHO, Lozano R, Murray CJ, et al. *The Lancet.* 380: 2095-128 (2013).

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Vaccine Implementation: The GAVI Experience (2000-2013)

From GAVI's Founding in 2000 to 2013:

- US $8.4 billion committed to countries
- 440 million additional children immunized
- An estimated 6 million prevented deaths

GAVI ALLIANCE — Saving children's lives and protecting people's health by increasing access to immunisation in poor countries
unicef
World Health Organization
BILL & MELINDA GATES foundation
THE WORLD BANK

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Conceptual Basis for Traditional Vaccine Development

Mimic Natural Infection → Recapitulate Natural Immunity

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Future Directions in Vaccine Research

Challenges:

- Inadequate immune response to natural infection (ex: HIV, Malaria)
- Strain Diversity (ex: influenza)

New Paradigm:

- Go beyond recapitulation of natural immunity
- Induce "unnatural immunity"

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21st Century Vaccinology: Selected Scientific Tools

- Rapid genomic sequencing of relevant pathogens
- Reverse vaccinology – genetic expression of all possible immunogens
- Structure-based vaccine design – crystallography; Cryo-EM
- New vaccine platforms – ex: nanoparticles, vector expression
- B cell lineage vaccine design – single cell cloning of B cell repertoire; deep sequencing of B cell Ig genes
- Harnessing the innate immune system – effective adjuvants

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The Search for an HIV Vaccine - 27 Years and Counting

- First FDA-approved HIV vaccine clinical trial, 1987 - gp160 subunit candidate

HHS News

U.S. Department of Health and Human Services — www.hhs.gov/news

FOR RELEASE
Tuesday, August 18, 1987
12 noon, EDT

Dr. Robert E. Windom, assistant secretary for health, today announced that the National Institute of Allergy and Infectious Diseases is beginning tests in human volunteers of an experimental vaccine against acquired immunodeficiency syndrome (AIDS). This is the first clinical study of an AIDS vaccine to be approved by the Food and Drug Administration and to be conducted in the United States.

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First Signal of Efficacy in an HIV Vaccine Clinical Trial

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim, NL Michael et al. for the MOPH–TAVEG Investigators

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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.

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Broadly Neutralizing Antibodies

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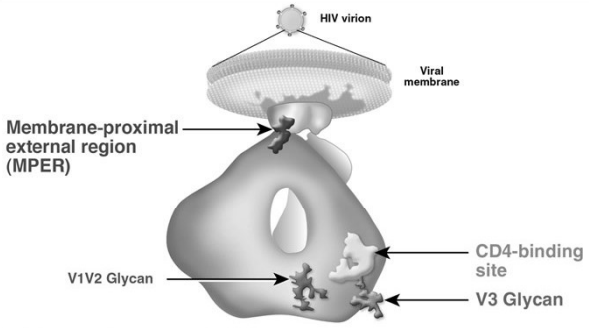
HIV Epitopes Targeted by Broadly Neutralizing Human Antibodies



Adapted from Kwong and Mascola, *Immunity* 37:412, 2012.

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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

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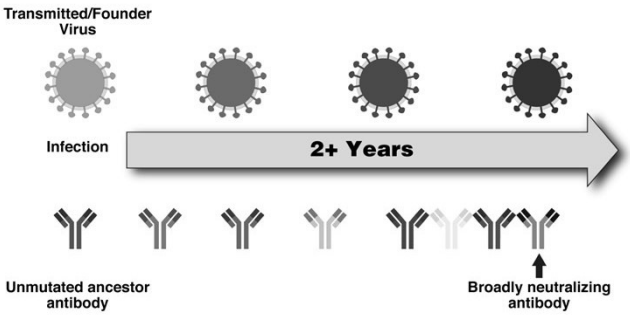
Co-Evolution of Virus and Antibody in an HIV-Infected Individual



Source: H-X Liao, BF Haynes et al. *Nature* 496:469-76 (2013)

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The "Paradox" of the Evolution of Broadly Neutralizing Antibodies

As HIV evades the evolving HIV-specific antibodies, it ultimately stimulates broadly neutralizing antibodies

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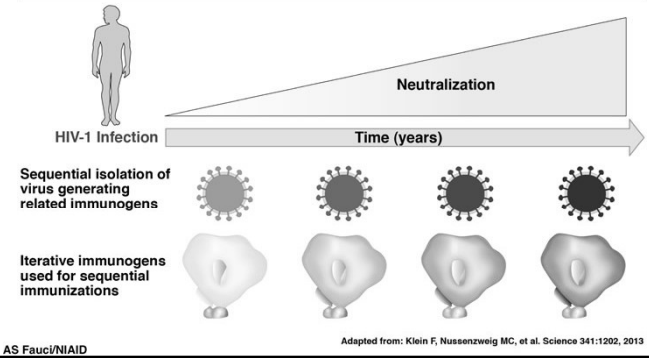
Immunogen Design Mimicking Natural HIV Infection



Adapted from: Klein F, Nussenzweig MC, et al. Science 341:1202, 2013

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The Threat of Influenza

- Seasonal Influenza – annual burden:
  - USA
    - up to 49,000 deaths
    - more than 200,000 hospitalizations
    - $27 billion in medical costs plus lost earnings
  - Global
    - 250,000 to 500,000 deaths
- Pandemic Influenza
  - 1918, 1957, 1968, and 2009
  - 1918 "Spanish Flu" pandemic caused 50 to 100 million deaths worldwide

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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

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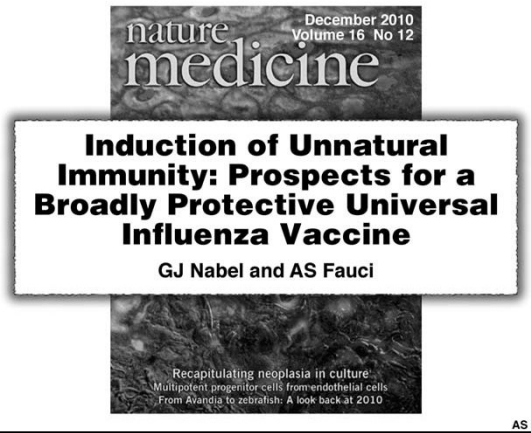

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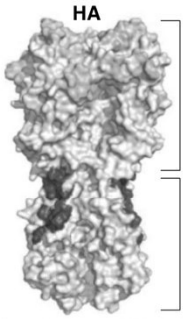
Generating Broadly Neutralizing Antibodies: Targeting the Stem



- Most antibodies bind to epitopes of highly variable head region
- Antibodies that neutralize multiple strains bind to a highly conserved region (red) in the stem region

Source: Doms, *Science* 329:1021, 2010

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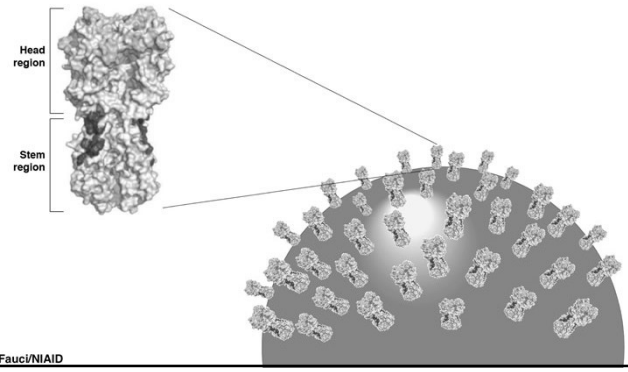
Influenza A Hemagglutinin (HA)



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THE LANCET Infectious Diseases

Volume 11 December 2011

DNA Priming and Influenza Vaccine Immunogenicity: Two Phase 1 Open Label Randomized Clinical Trials

J.E. Ledgerwood, G.J. Nabel, B.S. Graham, et al. and the VRC 306 Study Team

- Initial immunization with DNA vaccine boosts effectiveness of traditional influenza vaccine and could help prepare for future pandemics

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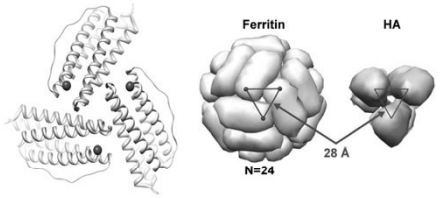
Generating a More Potent Immune Response Using Nanoparticles



- Ferritin self assembles into nanoparticles to which hemagglutinin can be affixed
- Offers the ability to show more antigen on stable platform

Source: Kanekiyo M, Wei CJ, et al. *Nature*. 499: 102-6 (2013).

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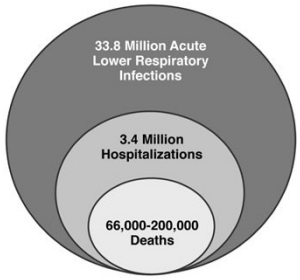
RSV Causes Significant Global Mortality and Morbidity

Global Annual Burden of Disease



- Causes 6.7 percent of deaths in children aged 1 month-1 year
- Nearly ¼ of children under age one hospitalized with RSV will develop asthma

Sources: Nair H, Nokes DJ, Gessner BD, et al. *Lancet*. 375: 1545 (2010). Régnier SA and Huels J. *The Pediatric Infectious Disease Journal*. 32: 823 (2013).

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Proof of Concept: Palivizumab

VOL. 102 NO. 3 September, 1998
PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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 monocolonal antibody vs. Fusion protein
- Used for periodic prophylaxis of severe RSV for premature infants
- Shown to reduce RSV hospitalizations by 82%

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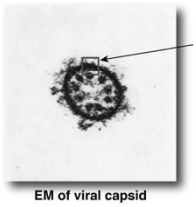
Fusion Protein (F) is a Promising Antigen

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



EM of viral capsid

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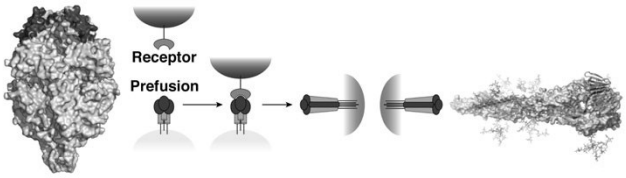
F Protein Adopts Two Primary Conformations: Pre- and Post-Fusion



Pre-Fusion (Unstable)

Post-Fusion (Stable)

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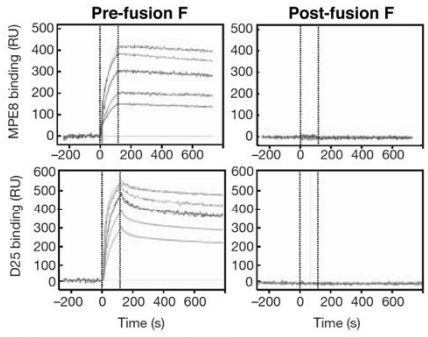
Broadly Neutralizing Antibodies Bind More Readily to the Pre-Fusion Form



Source: Corti D, Bianchi S, Minola A, et al. *Nature.* 501: 439-43 (2013).

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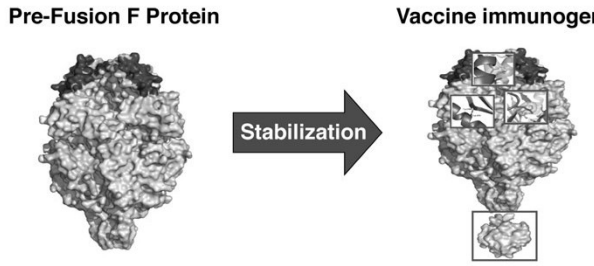
Pre-Fusion F Protein Stabilized Using Structure-Based Vaccine Design



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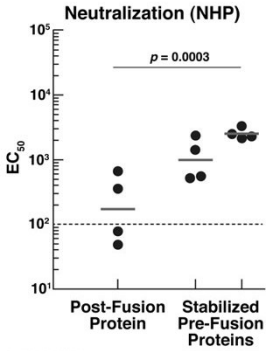
Source: McLellan JS, Chen M, Joyce MG, et al. *Science.* 342: 592-8 (2013).

Neutralization in Non-human Primates



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The Global Burden of Malaria, 2012

- 627,000 malaria deaths, 90% in Africa
- 207 million malaria cases
- Ongoing transmission in 97 countries
  - Almost half the world's population is at risk
- Every 60 seconds a child <5 years old dies from malaria

Credit: S. Hollyman

Source: WHO, World Malaria Report 2013

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Vaccine for Malaria (and Other Parasitic Diseases): Unique Challenges

- Large eukaryotic genomes
- Complex life cycles
- Antigenic variations
- Lack of lifelong protection resulting from natural infection
- Immune evasive techniques
- Special consideration for formulation and delivery in developing nations

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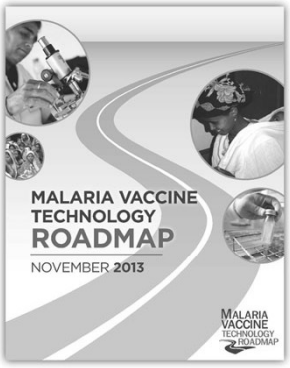

Vision:

"Safe, effective vaccines against *P. falciparum* and *P. vivax* that prevent disease, death and transmission to enable eradication"

Strategic Goals:

1. Vaccines with 75% efficacy against clinical malaria, readily deployed
2. Vaccines that reduce transmission of the parasite

World Health Organization

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Malaria Vaccine Products in Clinical Trials, 2013

Phase 1a	Phase 2a		Phase 1b	Phase 2b	Phase 3
ChAd63/MVA ME-TRAP + Matrix M™	Ad35.CS/ RTS,S-AS01	ChAd63/MVA MSP 1	Ad35.CS	ChAd63/MVA ME-TRAP	RTS,S-AS01
Polyepitope DNA EP 1300	Ad35.CS/Ad26.CS	ChAd63/MVA AMA 1	AMA1-C1-Alhydrogel+CPG 7909	MSP3 [181-276]	
PfCelTOS FMP012	ChAd63/MVA (CS; ME-TRAP)	FMP2.1-AS01B (AMA1 3D7)	BSAM-2-Alhydrogel + CPG 7909	GMZ2	
CSVAC	*Pf*SPZ	NMRC.M3V. Ad.*Pf*CA	CSP, AMA1 (PEV 301, 302)		
ChAd63.AMA/MVA. AMA1 + AI/CPG7909	*Pf*GAP p52- / p32-	NMRC.M3V.D/ Ad.*Pf*CA	EBA 175.R2		
SR11.1			SE36		
*Pfs*25-EPA					

NIAID supported concepts: 11/27 = 41%

P. falciparum vaccines:
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking

DMID Support
DIR and/or VRC Support

Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

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The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Published Online October 18, 2011

First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership

March 21, 2013 Volume 368 Number 12

Four-Year Efficacy of RTS,S/AS01E and Its Interaction with Malaria Exposure

A Olotu, P Bejon et al.

- Initial phase 3 trials in 5-17 month old infants showed safety, immunogenicity and 50% efficacy
- Protection waned over time. 4-year efficacy was 16.8%.

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Investigational Malaria Vaccine Found Safe and Protective in Early-Stage Clinical Trial

Irradiated sporozoites, NIAID VRC

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Beyond the Decade of Vaccines: Research and Development

The Perpetual Challenge of Discovery, Delivery, and Implementation

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