NIAID Influenza Vaccine Development:
Novel Strategies for Better Vaccines

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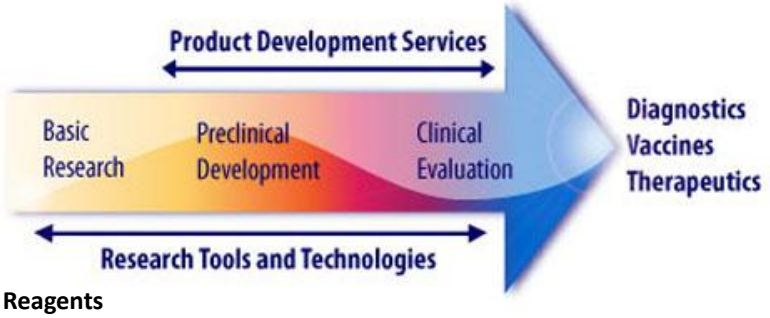
NIAID Research and Development

Product Development Services & Research Tools and Technologies

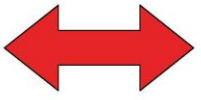
http://www.niaid.nih.gov/labsandresources/resources/dmid/Pages/default.aspx



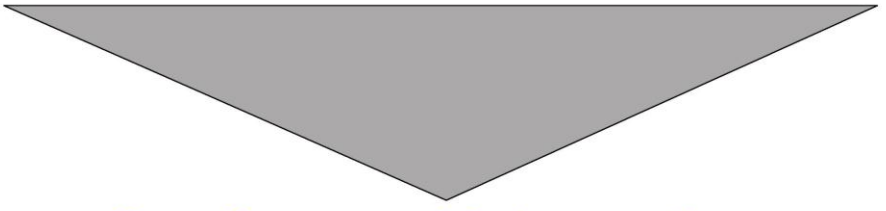
- **Reagents**
  - Biodefense and Emerging Infections Research Resources Repository (BEI)
  - Wild type and recombinant viruses, Purified proteins, Polyclonal & monoclonal antibodies, Cell lines
- **Preclinical Development Services**
  - Optimization, synthesis, formulation, medicinal chemistry, product development plans; cGMP manufacture
- **Assays**
  - In vitro antiviral screening of 2009 H1N1, Seasonal, & H5N1 (LPAI and HPAI) in MDCK cells
- **Animal models**
  - Animal models for H1N1, H3N2, & H5N1 subtypes testing of vaccines and candidate therapeutics.

NIAID Research: A Dual Mandate

Maintain and "grow" a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases

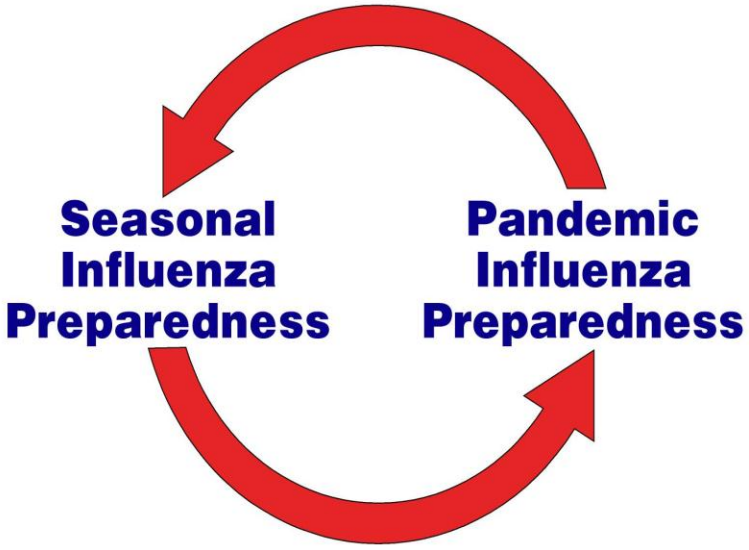


Respond rapidly to new and emerging disease threats

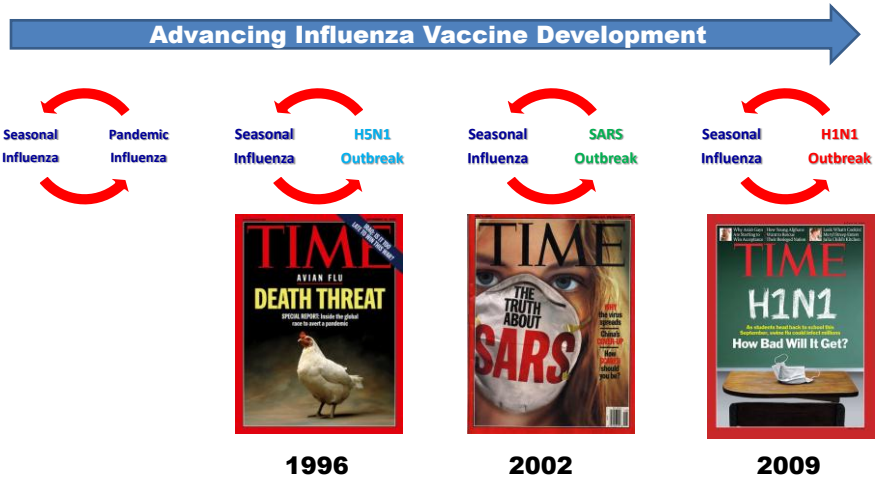


New/Improved Interventions

NIAID Dual Mandate Strategy for Influenza



NIAID Responds to Viral Respiratory Outbreaks



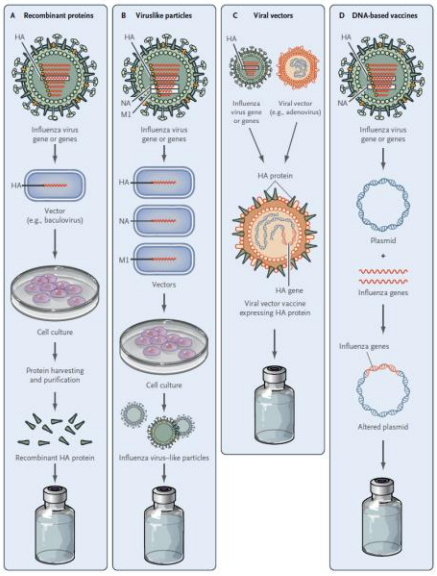
Current Goal:
Building a Better Influenza Vaccine

- Improved production and surge capacity
- Vaccine platforms that allow for more efficient manufacturing and potentially better efficacy
- Dose optimization strategies
- A "universal" vaccine

NIAID Influenza Vaccine Activities

- **Direct funding**
  - **40+ grants within DMID**
    - exploratory (R21s), R01s, SBIRs, U01s
  - **contract supported activities**
- **Collaborations, availability of resources**
- **Seasonal and Pandemic influenza vaccine trials**

Novel Approaches to Influenza-Vaccine Production



Lambert and Fauci
NEJM 2010

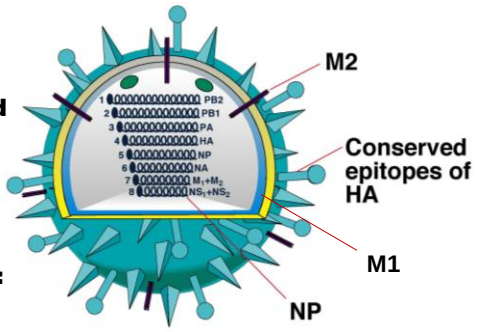
Current and New Approaches to Influenza-Vaccine Production

Vaccine	Stage of Development			
	Preclinical Development	Phase 1 and 2 Clinical Testing	Phase 3 Clinical Testing	Licensed or Approved
Inactivated vaccines				
Egg-based	Yes	Yes	Yes	Yes
Cell-based	Yes	Yes	Yes	In Europe but not in the United States
With adjuvant	Yes	Yes	Yes	In Europe but not in the United States
Live attenuated vaccines				
Egg-based	Yes	Yes	Yes	Yes
Cell-based	Yes	Yes	No	No
Next generation				
Recombinant proteins	Yes	Yes	Yes	No
Viruslike particles	Yes	Yes	No	No
Viral vectors	Yes	Yes	No	No
DNA-based vaccines	Yes	Yes	No	No
Universal vaccines	Yes	Yes	No	No

Lambert and Fauci
NEJM 2010

Universal Influenza-Vaccine

- Universal influenza vaccine needs to
  1. elicit humoral and cellular responses like natural infection
  2. provide long-lasting and cross-strain protection



- Major "universal" or "common-epitope" targets are conserved epitopes from:
  - HA
  - NP
  - matrix 1 (M1)
  - matrix 2 (M2)

NIAID Support for Universal Influenza-Vaccines

- **NIAID is supporting basic and preclinical research aimed towards generating a universal influenza vaccine.**
- **NIAID is promoting the advancement of universal flu vaccine products towards licensure and clinical trials.**
- **NIAID VRC has funded clinical trials of a universal influenza vaccine strategy and DMID can use VTEUs to support phase I/II trials for universal vaccine candidates**

Major Universal Influenza-Vaccine Targets and Strategies

Hemagglutinin	Matrix protein 2 Matrix protein 1	Nonstructural protein
▪ HA2 epitope-VLP ▪ Chimeric/consensus HA DNA ▪ Headless HA-VLP ▪ Ablated HA immunodominant epitopes - VLP	▪ M2e-VLP	▪ NP T cell epitopes-nanoparticle

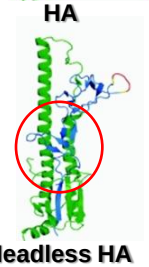
▪ M2e+HA2 fusion peptide recombinant protein

▪ M1+HA+NP peptide recombinant protein

Headless HA Universal Influenza-Vaccine Approach

HA

antibodies to variable immunogenic globular head → **NO** broadly neutralizing antibodies → **Does not** protect against challenge with different sub-types.

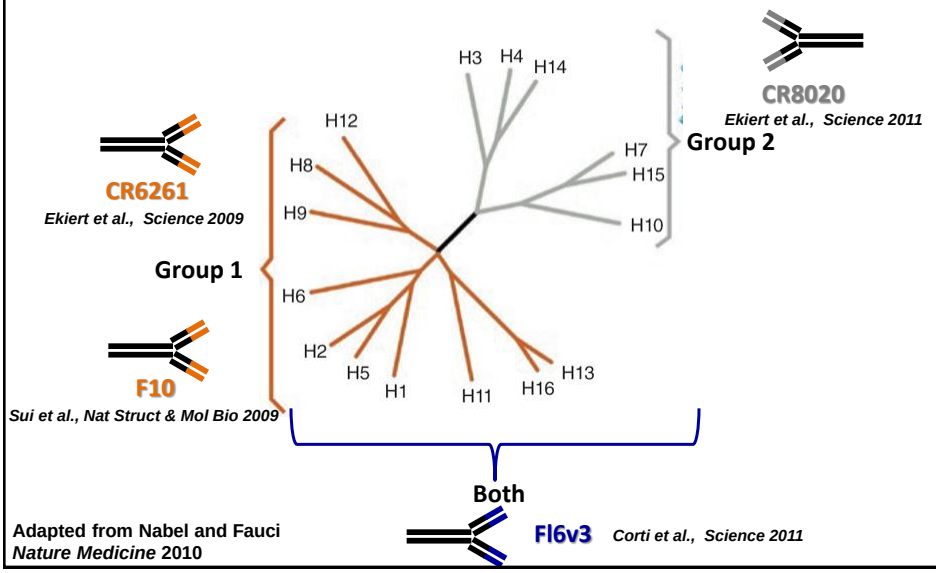


Headless HA

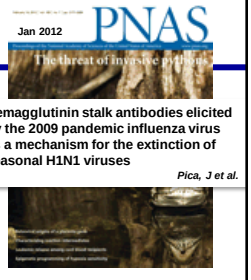
antibodies to conserved HA stalk domain → Broadly neutralizing antibodies → Protects against challenge with different sub-types.

Supported by RC1 AI086061-01 and U01 AI070469

HA Stem Universal Strategy: Induction of Broadly Neutralizing AB



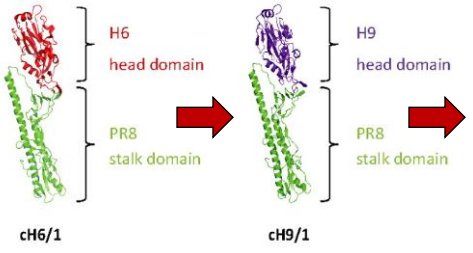
Chimeric HA Universal Influenza-Vaccine Approach



Hemagglutinin stalk antibodies elicited by the 2009 pandemic influenza virus as a mechanism for the extinction of seasonal H1N1 viruses

Pica, J et al.

Refocusing the immune response by sequential immunization



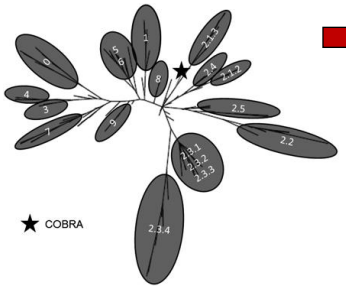
Anti-stalk broadly neutralizing antibodies

prime **boost**

Supported by UO1 AI070469, HHSN2662000700010C, U19AI089987, U54 AI057158-04, and U19-AI057266 with American Recovery and Reinvestment Act Supplement Funding Grants U19 AI057266-06S2, HHSN266200700006C, and HHSN272200800003C

Computationally Optimized HA Universal Influenza-Vaccine Approach

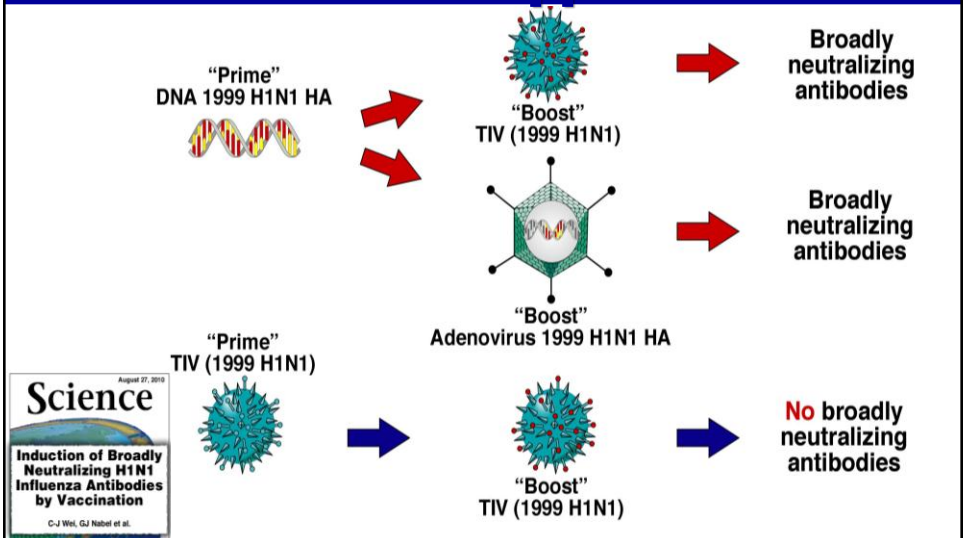
COBRA-
Computationally Optimized Broadly Cross-Reactive Antigen



Broadly neutralizing antibodies

Supported by U01AI077771

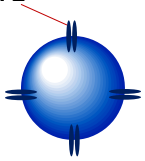
DNA-based Universal Influenza-Vaccines Approach



Supported by NIAID VRC

M2 Universal Influenza-Vaccine Approach

Matrix protein 2



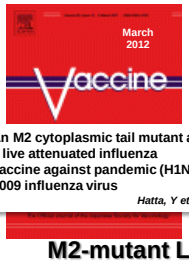
M2 VLP

Broadly neutralizing antibodies

Influenza Virus-Like Particles Containing M2 Induce Broadly Cross Protective Immunity

Jae-Min Song[1], Bao-Zhong Wang[1], Kyoung-Mi Park[1], Nico Van Rooijen[2], Fu-Shi Quan[1], Min-Chul Kim[1], Hyun-Tak Jin[1], Andrew Pekosz[3], Richard W. Compans[1]*, Sang-Moo Kang[1]*

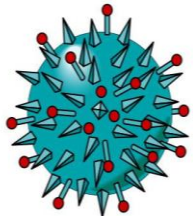
Supported by AI0680003



An M2 cytoplasmic tail mutant as a live attenuated influenza vaccine against pandemic (H1N1) 2009 influenza virus

Hatta, Y et al.

M2-mutant LAIV



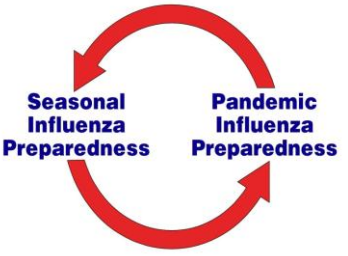
Broadly neutralizing antibodies

Supported by U01AI074515 and HHSN266200700010C

Challenges in the Production of Universal Influenza-Vaccines

- **No clear front-runners for universal influenza vaccine eliciting a broadly cross-reactive, durable response**
  - **Multiple targets, multiple technological platforms**
  - **Poor immunogenic response of universal targets**
- **Regulatory pathway to licensure is not clear**
  - **Unclear what strategy will be used to introduce a new vaccine into a market with very well tested, relatively efficacious vaccine**
- **Do not have certified assays to assess correlates of protection**

DMID Influenza Contacts



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