1 **Presidential Advisory Council on HIV/AIDS: New Vaccine Initiatives**

Carl W. Dieffenbach, Ph.D.
Director, Division of AIDS
October 22, 2008

2 Image of NIH News Article “Immunizations Are Discontinued in Two HIV Vaccine Trials,” 21 Sept 2007

3 Step Study Results

Vaccine did not protect against infection

Vaccine did not lower the viral “setpoint”

There were more infections in vaccinees than placebo recipients
-This trend was more pronounced in participants with higher baseline Ad5 titlers

4 Additional Step Analysis
Increased risk of HIV infection among vaccinees was most evident in uncircumcised men with pre-existing Ad5 immunity

No evidence of increased risk among vaccinnees in circumcised men without pre-existing Ad5 immunity

Further studies underway to provide clues as to possible biological mechanisms

5 **Immunogenicity Summary**

- Immune responses as measured by γ-interferon ELISPOT were similar in infected and uninfected subjects
- No clear explanation for increased number of infections observed in vaccinees in the Ad5 seropositive volunteers
  - More activated PBMC in volunteers with high Ad5 antibody titers at baseline
  - No difference between vaccinees and placebo recipients
    - Mucosal sites?
- Process in place to prioritize further studies

6 **STEP’s Unique Scientific Contributions**

- Demonstrated that a test-of-concept trial is useful to define vaccine efficacy
  - Quick pick-up of potential adverse or beneficial events
- Recalibrated the NHP Challenge Model
  - SHIV 89.6P is no longer favored for T cell vaccine evaluation
  - Need to screen out or randomize genetically resistant animals (MamuA01+; certain MHC types)
- Demonstrated that vector induced immunity needs to be evaluated in vaccine development, including tissue specific responses
- Raised questions about the “T cell vaccine” concept

7 March 25, 2008
Bethesda, Maryland
(Slide shows image of “Summit on HIV Vaccine Research and Development”)

8 Classical Vaccinology Versus HIV Vaccinology

9 Classical Vaccinology (image of down arrow) The response to natural infection provides the proof on concept

10 Characteristics of Viral Infections for Which We Have Vaccines: Nature’s Proof of Concept

*Variable courses and sequelae among different infections (e.g. polio, measles, smallpox); HOWEVER, the vast majority of people recover spontaneously.
*Virus is ultimately cleared and eradicated.
*Protective immunity against subsequent infection is usually complete and often lifelong.

11 Diagram presented on slide
Top Box: Vaccinology
First Down Arrow: Discovery
Items under Discovery: Often unpredictable, False leads, Serendipity, “Eureka moments”
Second Down Arrow: Development
Items under Development: Generally orderly process

12 Classical Vaccinology: Relationship Between Discovery and Development

(Slide shows image with text Discovery and Development; button points to development)

13 Common Elements in Classical Vaccinology

*Discovery, definition and propagation of etiologic agent

*Choice of live-attenuated, whole or subunit approach

*Maximize immunogenicity versus reactogenicity

*Preclinical and early clinical assessment

*Proof of protective efficacy and long-term immunity

*Development of surrogate markers

*Scale-up, licensure, manufacturing and distribution

Adapted from MR Hilleman, Nature Medicine, 5/98

14 HIV Is Different

*The natural immune response to HIV is inadequate

*HIV hides from the immune system

*HIV targets and destroys the immune system

*HIV mutates rapidly

(Slide shows image of HIV)

15 Slide shows image of cover of the New England Journal of Medicine article titled “An HIV Vaccine – Evolving Concepts”

16 HIV Vaccinology: “Turning the Knob” Toward Discovery Research (slide shows image with the words Discovery and Development; button is pointing to Discovery)

17 **New Approach—Back to Basics**

- Traditional approaches have yielded a tremendous amount of information but have not gotten us where we need to be after >27 years of research
- New strategies for HIV prevention and control rest squarely upon our unraveling the basic biologic conundrum of HIV and its interaction with its human host

18 **New Approach—Back to Basics**

- Formation of Vaccine Discovery Branch
- Major emphasis on antibodies already funded
  - B-cell Initiative
- Two major initiatives underway
  - HIT-IT
  - Basic Vaccine Discovery
- Additional initiatives are in development that reflect our increased discovery efforts

19 ## New Approach—Back to Basics

Discover and explore fundamental mechanisms of acquisition and progression of HIV disease

- Biology of HIV and its interactions with its human host
  - Systems biology
  - Visualizing the immune response
- Population-based research on the acquisition, incidence and efficacy of treatment of HIV infection
- Movement of basic discovery to development and testing of potential as targets for HIV intervention

20 ## New Approach—Back to Basics

- Emphasis on discovery research
  - Multiple opportunities with identified funding
  - Importance of hypothesis driven clinical research
  - Importance of research in non-human primates
    - Partnerships at NIH
- Preserve some development resources
  - Need to make clinical products

21 Will There Ever Be an HIV Vaccine?

*Best case scenario – high percentage protection against HIV acquisition

*Protection against HIV acquisition only in some individuals, related or not to genetic profile

*Slowing of disease progression in some patients, related or not to genetic profile

22 Slide shows diagram of “Comprehensive HIV Prevention”

23 **Questions?**