Presidential Advisory Council on HIV/AIDS: New Vaccine Initiatives
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Image of NIH News Article “Immunizations Are Discontinued in Two HIV Vaccine Trials,” 21 Sept 2007

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

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

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

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
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

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

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
• 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?