Nussenzweig: Isolation of Human Monoclonal Antibodies for HIV Prevention

OVERVIEW

An effective vaccine against HIV remains elusive and AIDS continues to be a major source of morbidity and mortality worldwide. The failure of many HIV vaccine products has elevated the importance of pursuing an alternative form of prevention, namely the concept of using anti-HIV monoclonal antibodies as a passive form of prevention. Recent studies in macaques have shown that antibodies can prevent HIV infection. Moreover, a significant fraction of HIV-infected individuals develop serum antibodies that neutralize a broad spectrum of viruses even at low concentration. Until two years ago, only a very small number of such antibodies had been characterized and the most potent of these, b12, was not a naturally occurring product.

The consortium assembled and led by Dr. Michel Nussenzweig seeks to push the passive prevention avenue forward by discovering and characterizing additional neutralizing antibodies. They plan on accomplishing this by building upon techniques developed by Dr. Nussenzweig for the cloning of anti-HIV human antibodies from single cells. An additional step for the development of broadly neutralizing antibodies for passive prevention will be the optimization of in vivo effector functions such as antibody dependent cytotoxicity or antibody dependent anti-viral activity. Dr. Jeffrey Ravetch at Rockefeller University discovered and characterized the Fc receptors responsible for antibody effector function and developed methods to optimize antibody effector function in vivo.

RESEARCH OBJECTIVES

1.) Isolate broadly neutralizing antibodies from the memory cells and plasma cells from a large group of patients with high titers of serum neutralizing activity,

2.) Engineer a scalable, highly cost-effective platform to rapidly identify natural human mAbs capable of neutralizing HIV-1,

3.) Determine the optimal Fc effector function in novel in vitro and in vivo systems and combine broadly neutralizing antibodies with optimal Fc function and validate their efficacy in relevant in vivo systems

Select clones for manufacturing antibodies for preclinical and clinical trials.

PROGRESS

Research objectives 1-4 above were accomplished and extended to carry out the following clinical trial. A phase IIa open-label clinical trial evaluating 3BNC117, a broad and potent neutralizing antibody (bNAb) against the CD4 binding site of HIV-ENV, was initiated in the setting of analytical treatment interruption (ATI) in 13 HIV-1-infected individuals. Participants with 3BNC117-sensitive virus outgrowth cultures were enrolled.

Infusions (30mg/kg) of 3BNC117 were generally well tolerated. The infusions were associated with a delay in viral rebound for 5-9 weeks after 2 infusions, and up to 19 weeks after 4 infusions, or an average of 6.7 and 9.9 weeks, respectively (compared with 2.6 weeks for historical controls). Rebound viruses arose predominantly from a single provirus. In most individuals, emerging viruses showed increased resistance indicating escape. However, 30% of participants remained suppressed until antibody concentrations waned below 20 □g/ml, and the viruses emerging in all but one of these individuals showed no apparent resistance to 3BNC117, suggesting failure to escape over a period of 9-19 weeks. These results demonstrate that administration of 3BNC117 exerts strong selective pressure on HIV-1 emerging from latent reservoirs during ATI in humans.

Grant at a Glance

Principal Investigator

Michel C. Nussenzweig, MD, PhD

Grantee Institution

The Rockefeller University, New York, USA

Project Title

Isolation of human monoclonal antibodies for HIV prevention

OPPID

1033115

Grant Award

Up to $6.4 Million, awarded September, 2011

Collaborating Institutions

- Massachusetts Institute of Technology, USA
- University fuer Bodenkultur, Austria
- University of Cologne, Germany
- University Medicine Berlin, Germany
- The General Hospital Corporation (MGH, Ragon Institute), USA