Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Antibody-guided vaccine design: identification of protective epitopes

Antonio Lanzavecchia[1,2], Alexander Frühwirth[1], Laurent Perez[1] and Davide Corti[3]

In the last decade, progress in the analysis of the human immune response and in the isolation of human monoclonal antibodies have provided an innovative approach to the identification of protective antigens which are the basis for the design of vaccines capable of eliciting effective B-cell immunity. In this review we illustrate, with relevant examples, the power of this approach that can rapidly lead to the identification of protective antigens in complex pathogens, such as human cytomegalovirus and *Plasmodium falciparum*, and of conserved sites in highly variable antigens, such as influenza hemagglutinin and HIV-1 Env. We will also discuss how the genealogical analysis of antigen-stimulated B cell clones provides the basis to delineate the best suitable prime-boost vaccination strategy for the induction of broadly neutralizing antibodies.

Addresses
[1] Institute for Research in Biomedicine, Via Vincenzo Vela 6, 6500 Bellinzona, Switzerland
[2] Institute of Microbiology, ETH Zürich, Vladimir-Prelog-Weg 1, 8093 Zürich, Switzerland
[3] Humabs BioMed, Via Mirasole 1, 6500 Bellinzona, Switzerland

Corresponding author: Lanzavecchia, Antonio (lanzavecchia@irb.usi.ch)

Current Opinion in Immunology 2016, **41**:62–67

This review comes from a themed issue on **Vaccines**

Edited by **Rino Rappuoli** and **Ennio De Gregorio**

http://dx.doi.org/10.1016/j.coi.2016.06.001

Introduction

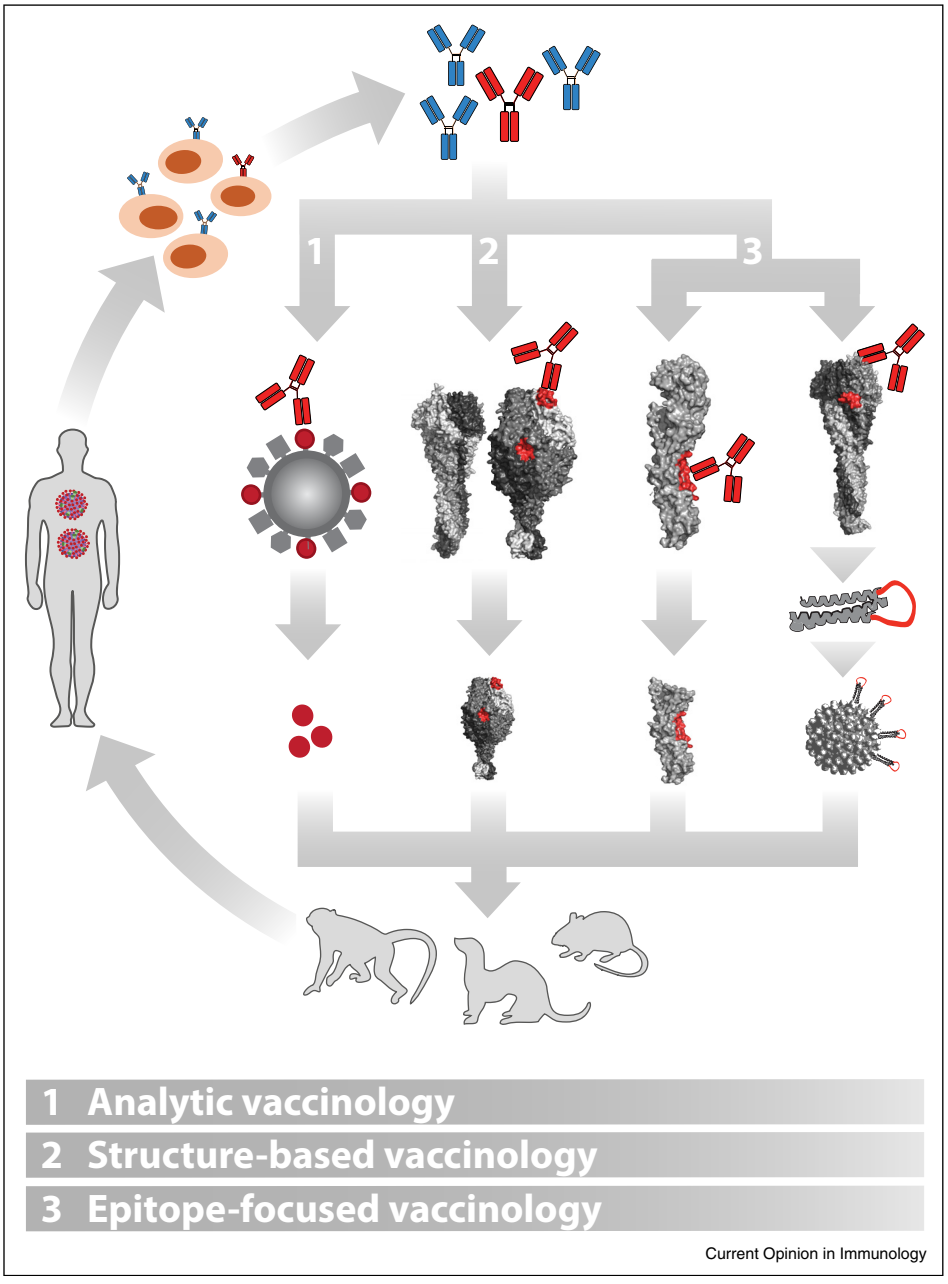
When our immune system is challenged by an infectious agent, a polyclonal antibody response is generated against multiple protein and non-protein antigens. The extent of the response reflects the immunogenicity of the individual components, which is determined by multiple factors such as their abundance, their complexity and their capacity to bind to cellular receptor and trigger innate immunity, not to mention the influence of pre-existing immunity. In general, only a fraction of the antibodies produced exerts protective activity by binding to molecules that are required for invasion or virulence or by eliciting effector mechanisms. For instance, the largest fraction of antibodies produced in response to a virus infection is directed against internal or surface proteins in a denatured or post-fusion conformation and is therefore devoid of neutralizing activity [1,2,3]. Thus, the immunogenicity of the most abundant proteins offers to the pathogen the opportunity to limit the most effective response by a mechanism of antigenic competition.

In this review we discuss how recent advances in the characterization of the neutralizing antibody response to human pathogens, combined with advanced protein engineering methods, have provided a new way to solve the problem of antigenic competition and have led to the production of vaccine candidates that elicit antibody responses of high magnitude and specific activity.

Analytic vaccinology: the cases of HCMV and malaria

Human cytomegalovirus (HCMV) is a herpes virus that establishes a lifelong infection in healthy individuals, but causes serious pathology in the fetus and in immunosuppressed patients and has been associated with immune senescence and atherosclerosis [4]. HCMV uses multiple glycoprotein complexes for binding and fusion to host cells and has a broad cell tropism, being able to infect fibroblasts as well as epithelial, endothelial and myeloid cells [5]. The fusion protein gB has been considered the most obvious vaccine candidate but clinical trials with recombinant gB (in the post-fusion conformation) has shown limited efficacy [6]. To identify the most potent HCMV vaccine, an analytic vaccinology approach was used to isolate, from memory B cells of naturally infected donors, a large panel of monoclonal antibodies selected for their capacity to neutralize HCMV infection of multiple cell types [7] (Figure 1). This approach led to the identification of a new class of antibodies that were 1000 fold more potent that antibodies to gB in neutralizing HCMV infection of epithelial, endothelial and myeloid cells. These antibodies were mapped to nine distinct sites on the gH/gL/UL128-131A complex, a pentameric complex that was previously found to be required for infection of those cell types [8]. The identification of the pentamer as the target of the most potent antibodies was subsequently confirmed by several studies [9,10••,11••]. As an example, a soluble pentamer produced by stably a transfected CHO cell line elicited in mice antibody titers that persisted to high levels over time

Figure 1



Antibody-guided vaccine design. Human monoclonal antibodies isolated from immune donors are used to identify protective antigens and epitopes. The antigens discovered from complex pathogens are produced as recombinant proteins (path 1; e.g. HCMV pentamer) and, when necessary, engineered for increased stability (path 2; e.g. stabilized pre-fusion HRSV F protein) or modified to express particular domains or epitopes (path 3; e.g. head-less HA or Palivizumab epitope displayed on VLPs).

and that were 300-1000 fold higher than those found in individuals that recovered from primary HCMV infection [10••]. Importantly, the antibodies elicited by the pentamer vaccine prevented cell-to-cell spread and viral dissemination from endothelial cells to leukocytes and neutralized infection of both epithelial cells and fibroblasts due to the production of antibodies to the gH glycoprotein, which is required for fibroblasts infection.

The target-agnostic approach can be particularly useful to identify targets in complex pathogens such as bacteria and parasites. An interesting example regards the identification of variant surface antigens (VSAs) which are present on the surface of *Plasmodium falciparum* (*Pf*)-infected erythrocytes and mediate adhesion to endothelia, leading to pathology. The VSAs are encoded by more that 200 genes that are polymorphic and clonally