

# Licensing Opportunity



## Booster of immune response and antibody production

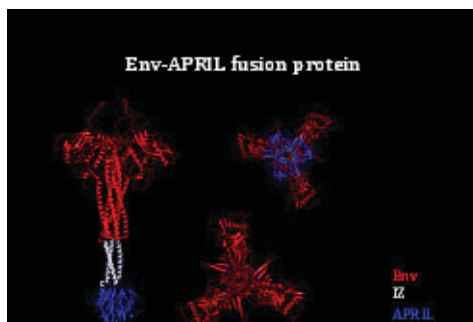
- Novel methodology to boost antibody production
- Many applications in vaccine development
- Direct targeting of the antigen to dendritic cells and/or B cell, simultaneously activating these same dendritic cells and B cells. This results in enhanced immunogenicity

Immunology, antibody production, infectious disease, cancer

2011

## Background

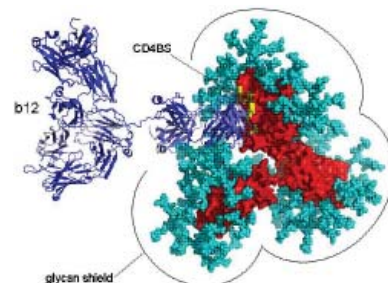
Protein vaccines are often poor immunogens compared to live-attenuated and whole-inactivated virus vaccines. One reason is the lack of co-stimulatory signals provided by various components of live-attenuated and whole-inactivated vaccines. In order to enhance the B cell response to poor protein immunogens, we explored the possibility of targeting proteins directly to B cells at the same time activating these cells. The HIV-1 envelope glycoprotein complex (Env) is one such notoriously poor antigen and all attempts to generate an effective HIV-1 vaccine have failed. Therefore the AMC set out to improve the immunogenicity of proteins in general, and of Env in particular.



## The Technology

AMC scientists have identified APRIL, a member of the TNF-superfamily that potently activates B cells, as a potent booster of the immune response when fused to the antigen of interest. APRIL fusion proteins were with three viral proteins, HIV envelope glycoprotein (Env), influenza hemagglutinin (HA) and Ebola glycoprotein (GP).

In all cases the fusion protein potently activated B cells to secrete IgM, IgG and IgA. The Env-APRIL fusion protein was further characterized in vivo and was shown to be superior at inducing neutralizing HIV-1 antibody responses compared to unconjugated Env. These studies provide proof-of-concept that fusion of APRIL to viral protein can enhance the antiviral antibody responses, but the invention should also work with non-viral proteins and be interesting for any vaccine or generic antibody producer. The invention is based on the premise that covalent linkage of an antigen to an adjuvant/co-stimulatory molecule ('cis-adjuvant') results in superior responses than simply mixing antigen and adjuvant, presumably because the activation by the adjuvant takes place directly on the immune cells that encounter the antigen. The additional invention that GM-CSF and IL-21 also enhance the immune response when inserted into a deletion variant of Env (in which there was sufficient space to insert IL-21 or GM-CSF without disruption of the 3D-structure of Env) is particularly interesting when optimizing specific (viral protein) vaccines.



Env's carbohydrate defenses (reproduced from: Eggink D, Melchers M, Sanders RW. 2007, Trends in Microbiology 15: 290-293 (9)). Part of the reasons that Env does not elicit neutralizing antibodies efficiently lie in the antigenic structure, which has evolved to minimize the elicitation and binding of neutralizing antibodies.

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## Applications

Vaccine improvement.  
Upscaling of immune response and antibody production.

## R&D Status

Proof of concept has been established in mice and rabbits. The invention improved both binding and neutralizing antibody titers.

## Intellectual Property

Priority application filed in March 2010, PCT application filed in March 2011

## Inventors

Dr. Rogier Sanders. The inventor is an Assistant Professor at the AMC and an Adjunct Assistant Professor at Weill Medical College of Cornell University in New York City. He is an expert on trimeric viral spike protein vaccines. One focus of his research is on improving the immunogenicity of protein vaccines by covalent attachment of costimulatory molecules. Another focus is on optimizing the antigenic structure of trimeric spike proteins by structure-based protein engineering.

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## Key publications

1. Van Montfort T, Melchers M, Isik G, Menis S, Huang P-S, Matthews K, Michael E, Berkhout B, Schief WR, Moore JP, Sanders RW. 2011. A chimeric HIV-1 envelope glycoprotein trimer with an embedded GM-CSF domain induces enhanced antibody and T cell responses. *THE JOURNAL OF BIOLOGICAL CHEMISTRY* VOL. 286, NO. 25, pp. 22250-22261, June 24, 2011
2. Melchers M, Matthews K, De Vries RP, Eggink D, Van Montfort T, Bontjer I, Van de Sandt C, David K, Berkhout B, Moore JP, Sanders RW. 2011. A stabilized HIV-1 envelope glycoprotein trimer fused to CD40 ligand targets and activates dendritic cells. *Melchers et al. Retrovirology* 2011, 8:48  
<http://www.retrovirology.com/content/8/1/48>
3. Melchers M, Bontjer I, Tong T, Chung NPY, Klasse PJ, Eggink D, Kang K, Montefiori D, Olson WC, Berkhout B, Binley JM, Moore JP, Sanders RW. HIV-1 envelope glycoprotein trimers fused to APRIL target and activate B cells, and induce enhanced antibody responses. Manuscript submitted.
4. Isik G, Van Montfort T, Chung NPY, Moore JP, Sanders RW. A chimeric HIV-1 envelope glycoprotein containing an IL-21 domain induces antibody secretion from human B cells. Manuscript in preparation.