ANTIGEN SPECIFIC IMMUNOMODULATION (ASIM): THE RATIONAL DESIGN OF MOLECULES THÀT HAVE POSITIVE OR NEGATIVE EFFECTS ON ANTIBODY RESPONSES

Vidal F. de la Cruz

Director, Dept. Immunolgoy and Dept. Molecular Biology, Cortech, Inc. 6840 N. Broadway, Denver, CO 80221, USA.

The ASIM technology is based on the Immunon hypothesis, formulated by Drs. H. and R. Dintzis, which describes the parameters necessary for the activation of B cells. Their work demonstrates that this activation occurs via the ligation of surface immunoglobulin by multivalent arrays of antigen (e.g. fluorescein arrayed on polyacrylamide). However, activation does not occur until a threshold number of receptors are ligated with arrayed epitopes, and the activation is therefore considered to be quantized. This minimal unit of cross-linked receptor plus antigen complex required for activation of the B cell is termed the **Immunon**. Interestingly, clusters of receptor-ligand that are sub-thereshold appear to have the opposite effect, i.e. the cells are not activated and animals fail to respond to active immunization against the epitope of interest. Cortech, Inc is making use of both aspects of the **Immunon** hypothesis, via the ASIM technology, to make molecules that are immunostimulatory or immunosuppressive by nature.

The suppression aspect is being used with the aim of preventing, and possibly treating, antibody-mediated hypersensitivity reactions to the commonly used antibiotic, sulfamethoxazole (SMX). This antibiotic is routinely used in AIDS patients for treatment or prophylaxis of *Pneumocytis carinii* pneumonia. However, as many as two thirds of these patients experience hypersensitive reactions to the SMX, with a large proportion of these (25%) requiring alternative (albeit more costly and less effective) treatment. In animal models the SMX antigen-specific immunosuppressive construct is able to prevent the induction of an antibody response to SMX conjugated to a protein carrier. The construct is also able to eliminate or reduce the SMX-specific antibodies in actively immunized animals. Representative data from these experiments will be presented.

The stimulation aspect of the hypothesis is being used in the construction of vaccine candidates. These constructions are inherently stimulatory in that they do not require and adjuvant for the induction of an immune response. However, the use of adjuvant does further enhance the immune response induced by these molecules. Furthermore, nonimmunogenic haptens have been coarrayed on high molecular weight scaffolds, together with attached T cell helper epitopes, which then renders them immunogenic (i.e. anti-hapten IgG is induced). Representative data from experiments demonstrating the immunogenicity of such corrays will be presented.