

REGULATION OF THE HUMAN IMMUNE RESPONSE TO DENGUE  
VIRUS INFECTION BY AUTO ANTI-IDIOTYPIC

Investigator : Donald S. Burke, LTC, MC

OBJECTIVE : The overall objective of this project was to develop methods for regulation of the human immune response to dengue virus infection by selective use of human anti-idiotypic antibodies.

IMPORTANCE OF THE PROBLEM : Dengue is a historically proven infectious disease problem for U.S. troops in tropical theaters of combat; a major vaccine development program for dengue has been funded by the U.S. Army. The control mechanisms for regulation of the types and rates of antibody synthesis in dengue infections and other acute infections are unknown. Elucidation of these mechanisms could lead to physician-directed modulation of the immune response either to boost immunity during vaccination or to blunt the immune response during acute illness.

RELEVANCE TO THE CORE PROGRAM : A problem in the development of safe and effective live attenuated dengue vaccines is that vaccine immunogenicity is typically directly related to the reactogenicity (disease producing potential) of that strain. Thus the safest virus strains are not very immunogenic while those producing the disease confer solid immunity. A method which could selectively stimulate the immune response to vaccination, without increasing undesirable symptoms, would be a valuable practical step toward insuring troop combat effectiveness in tropical areas.

APPROACHES : (1) To screen human hybridomas for production of naturally occurring anti-idiotypic antibodies directed against idiotypic determinants on anti-dengue immunoglobulins. (2) To produce and purify these anti-idiotypic antibodies in quantity. (3) To purify from serum the corresponding set of anti-dengue antibodies bearing these idiotypic determinants. (4) To develop immunoassays for detection and quantitation of both the set of idio-type-bearing anti-dengue antibodies and the corresponding anti-idiotypic antibodies. (5) To determine the kinetics of both the idio-type bearing anti-dengue antibodies and the anti-idiotypic antibodies during natural dengue infections in humans. (6) To determine if exogenously added autologous monoclonal anti-idiotypic can regulate the production of idio-type bearing antibodies by *in vitro* cultures of peripheral blood monoclonal leukocytes from humans with acute dengue virus infection.

ACCOMPLISHMENTS : (1) A technique for rapid (18 hrs) detection and quantitation of *in vitro* synthesis of dengue specific IgM, IgG, and IgA by patient blood leukocytes was developed. The technique involves culturing leukocytes in vessels pre-coated with isotype specific anti-sera. (2) Continuous human B cell lines were obtained and their growth kinetics established. (3) Fusions of IgG anti-dengue producing peripheral blood mononuclear leukocytes with human lymphoblastoid cells were attempted but thus far without production of stable hybrids. (4) Evidence was obtained

by rate zonal centrifugation of sera from acute flavivirus infected patients for the regular occurrence of circulating complexes of IgM and rheumatoid factor IgA anti-IgM.

INTERPRETATION OF ACCOMPLISHMENTS : This project was knowingly submitted as an ambitious, speculative, "high risk for high yield" proposal, requiring large measures of effort and innovation for success. The accomplishments to date are modest when compared to the objectives, but are not at all modest when compared to resources expended.

INTENTIONS FOR THE FUTURE OF THE PROJECT : This project is important and feasible. It should continue on ILIR funding for at least one more year.