INVESTIGATIONS IN THE DESIGN AND CHARACTERIZATION OF HIV-1 NEUTRALIZING MOLECULES

Thesis by

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This work is dedicated to the memory of my father,

RONALD ALLEN KLEIN

(1947 – 1988)

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ABSTRACT

Human Immunodeficiency Virus (HIV) is a T-lymphotrophic retrovirus that is the causative agent of Acquired Immunodeficiency Syndrome and is estimated to currently infect approximately 40 million people worldwide. Life-extending therapies are credited for the precipitous drop in HIV-related mortality in developed countries, but their high costs prevent widespread distribution in developing countries. To date, all attempts to produce a vaccine capable of preventing or controlling an HIV infection have failed, but a comprehensive explanation for these failures has yet to emerge from the available data. In this thesis the first chapter provides an overview of the pandemic, the antigenic properties of gp120 and gp41, which are the two glycoproteins that comprise the outer envelope spike of the virus, and the broadly neutralizing antibodies that have been isolated against them. The second and third chapters discuss biophysical characterizations of these monoclonal antibodies and newly designed molecules derived from them. Based on a comparison of these data with pre-existing research, a novel hypothesis called the “island effect” was developed and is presented as a possible explanation for the consistent failure of the human immune system to respond to infection or vaccination with an effective humoral response. The final chapter summarizes ongoing investigations in the capacities of broadly neutralizing monoclonal antibodies to recruit antibody-dependent cellular cytotoxicity, a mechanism by which antibodies can trigger the lysis of HIV-infected cells by the innate immune system.

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