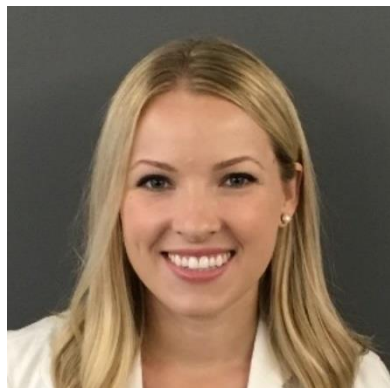# CHEMICAL ENGINEERING

DISTINGUISHED YOUNG SCHOLARS SERIES

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Monday, August 13, 2018

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Massachusetts Institute of Technology

Design of an Optimal Immunization Strategy for Evolving Broadly Neutralizing Antibodies Against HIV

ABSTRACT: In 2016 – the most recent year for which reliable data is available – an estimated 1.8 million people became infected with human immunodeficiency virus (HIV), with 36.7 million people living with HIV worldwide, highlighting a clear and urgent need for a solution [1]. The greatest challenge in developing a vaccine against HIV is undoubtedly accounting for and combating the highly mutable nature of HIV that allows it to continually escape the immune system's defenses. Every new virus produced by an HIV-infected cell will vary from the original infecting virus by one amino acid mutation, on average. Thus, an effective HIV vaccine will likely need to protect against many diverse "strains" or variants of the original infecting virus. Recently, antibodies (Abs) that can "broadly-neutralize" a wide range of HIV variants have been isolated from rare AIDS patients after many years of infection, so-called "bNAbs". Important studies have been performed to study the evolution of bNAbs during natural infection and to design immunization strategies for stimulating bNAb evolution through the process of affinity maturation (AM), which is a Darwinian evolutionary process that occurs upon infection or vaccination. However, a great deal remains unknown about the mechanisms underlying AM and how to effectively leverage this information to design a safe and effective vaccine against HIV. Evolving bNAbs will likely require vaccination with a number of variant antigens (i.e., foreign protein components that induce immune responses). Until recently, past studies have investigated AM in response to only a single antigen, which is unlikely to result in bNAbs. Computational approaches can offer unique insights into the process of AM – especially into the response of AM to multiple vaccine antigens – by providing detailed information about the individual evolutionary pathways that Abs can take during this process, and how these different pathways affect the global properties of the collective Ab response. Such studies can make testable predictions and guide the design of variant antigens and vaccination strategies. For example, past studies in our group showed that variant antigens can act as conflicting selection forces that can frustrate AM in some circumstances, a finding supported by

experiments. Through the study of a wide range of possible immunization schemes, this talk will discuss the use of multiple computational approaches with increasing molecular resolution for studying the development of bNAbs against highly mutable pathogens such as HIV.

The first part of the seminar will focus on the use of a coarse-grained model, based in statistical mechanics and biology, and incorporating available experimental data to determine fundamental principles that govern bNAb development during a vaccination response. In this part of the seminar, I will discuss our findings on the impact of different vaccination protocols (e.g., giving sequential injections with single antigens versus an injection with multiple antigens, and permutations therein) on both the quantity and quality of the produced Abs (i.e., mean neutralization breadth, where a high value implies bNAb development). I will further discuss the novel development of a tool that can be used to predict the quantity and quality of the produced Abs for a wide range of vaccination scenarios, based on
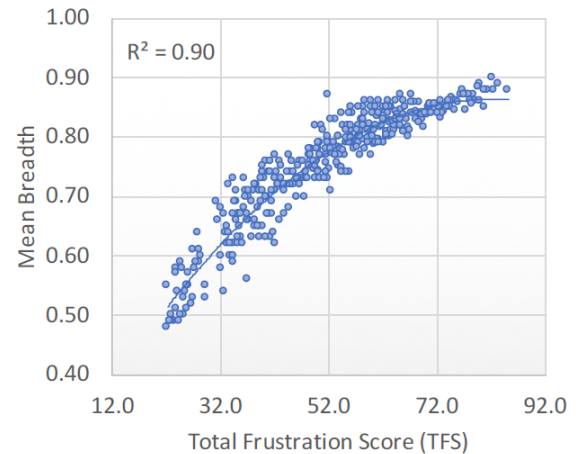

Figure 1. Results from a computational tool to predict the mean neutralization breadth of a population of Abs produced by various vaccination protocols, each defined by a "total frustration score".

varying the sequences of the vaccine antigens, the number of antigens to be administered, the concentration of the antigens, and the way in which these antigens are administered in time. Simulations of hundreds of diverse scenarios collapse onto a single "Master" curve, as shown in Figure 1.

In collaboration with the Karplus lab at Harvard, the second part of the seminar will describe recent efforts to develop and apply a model with atomic resolution to provide further insights into AM induced by variant antigens, and to design specific antigens. Using published crystal structure data and guided by our findings from using the coarse-grained model described above, we are working towards identifying the antigens, and the evolutionary mutational pathways taken by known bNAb precursors in the presence of these antigens, to develop into bNAbs. With the capacity to simulate AM under such realistic conditions and in response to actual sequences of potential vaccine-candidate antigens, this model is by far the most advanced of its kind. My talk will conclude with a discussion of some of our preliminary data and its implications for future vaccine design against HIV.

[1] "HIV/AIDS." Centers for Disease Control and Prevention, 18 Dec. 2017, www.cdc.gov/hiv/basics/statistics.html.

BIOGRAPHY: Kayla Sprenger earned her PhD from the UW Chemical Engineering department in August of last year (2017) under the mentorship of Associate Professor Jim Pfaendtner, earning her B.S. and M.S. degrees [here] as well. Her graduate work, which culminated in 10 first author papers with nearly 100 citations to date, focused on the development and use of molecular simulation tools to study the structure and function of biomolecules at interfaces. Kayla was recognized by several honors during her graduate studies, including the UW College of Engineering Student Research Award, AIChE's Computational Molecular Science and Engineering Forum Graduate Student Award, and a Research Excellence Award from the American Chemical Society. For the past year, Kayla has been engaged in postdoctoral research at MIT under the guidance of Professor Arup Chakraborty at the Institute for Medical Engineering and Science, working in close collaboration with Harvard Professor and Nobel Laureate Martin Karplus on designing an immunization strategy against HIV.

LECTURE 4:00 – 5:00   (PAA) A110
Happy Hour in Benson Hall Lobby Following

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