COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

Tuesday, January 10, 2023
3:30PM Eastern Time
Hybrid
NCRC Building 10 – South Atrium
Zoom Link

"Multi-objective engineering of therapeutic antibodies"

Presented by:

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Abstract: Despite the success of antibody therapeutics, there are outstanding challenges related to antibody drug development that we have sought to address in this work. First, it is challenging to generate informative datasets of antibody biophysical properties with current experimental technologies. Second, even if data is available, it is also difficult to develop predictive models sufficient for antibody co-optimization. Therefore, we developed ultra-dilute (<0.02 mg/mL antibody) and highly reproducible experimental techniques for evaluating two important biophysical properties of therapeutic antibodies which significantly impact their likelihood of clinical approval. These experimental techniques measure two forms of off-target interactions (self-association and non-specific binding) which impede therapeutic antibody development. We then applied these experimental techniques (and others) to acquire high-quality datasets which are amenable for the application of machine learning. We first demonstrate that modest datasets describing diverse clinical-stage sequence space can be analyzed via simple interpretable machine learning models. These models accurately classify antibody properties and improve the development process by obviating the need for time- and resource-intensive experimentation. The interpretation of these models also facilitates re-engineering of suboptimal antibodies to improve their biophysical properties without disrupting antigen binding. We also demonstrate additional machine learning models applied to high throughput screening data which enables prediction of continuous property values from binary labels. These methods facilitate the selection of antibody candidates with co-optimal biophysical properties. In sum, the work improves therapeutic antibody development by increasing the accuracy, throughput, and reliability with which we can experimentally measure and computationally predict important properties of antibodies that impact their therapeutic potential.