COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, April 12, 2022
4:00pm
2548 NUB or Zoom

"Multi-objective engineering of therapeutic antibodies"

Presented by:

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Abstract: Despite the success of antibody therapeutics, there are several outstanding challenges related to antibody drug development that impede progress. First, it is challenging to generate large and relevant datasets of antibody biophysical properties (e.g., affinity, self-association and non-specific binding). Second, even if this data is available, it is also difficult to develop predictive models needed for antibody co-optimization. To address both challenges, I have first developed multiple high-throughput and ultra-dilute experimental techniques for high-throughput evaluation of antibody colloidal interactions. Second, I applied machine learning methods to predict antibody affinity and colloidal properties to improve the development of therapeutic antibodies in both the early- and late-stage engineering processes.

To address limitations in late-stage engineering, where large high-quality datasets are lacking, I have evaluated and analyzed the colloidal properties of a large panel (80 IgGs) of clinical-stage antibodies. Through structural modeling and interpretable machine learning models, I have validated a computational approach for the de-risking of the late-stage development process via the accurate prediction of colloidal properties from antibody sequences alone. Additionally, I have validated a methodology for optimizing suboptimal therapeutic antibody candidates through the interpretation of these models and rational redesign of antibody molecules, resulting in improvements of biophysical properties for antibody variants that maintain antigen binding.

To address limitations in early-stage engineering, where large high-quality datasets are abundant yet remain challenging to utilize, I have validated a novel computational approach for analysis of deep sequencing data of antibody libraries. Interestingly, I have found that models generated using supervised dimensionality reduction enabled the prediction of continuous measures of affinity and non-specific binding from binary datasets. These models illustrate strong tradeoffs between antibody affinity and specificity, yet facilitate co-optimization of both properties via multi-objective, Pareto optimization. Exploration of the maximally optimized antibodies located at the Pareto frontier resulted in identification of many co-optimized sequences with both improved antigen binding and non-specific binding. Finally, I have developed methods for interpreting these predictions from the models using explainable artificial intelligence, elucidating structural motifs responsible for these properties and providing insight for future therapeutic antibody development.

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