COLLEGE OF PHARMACY
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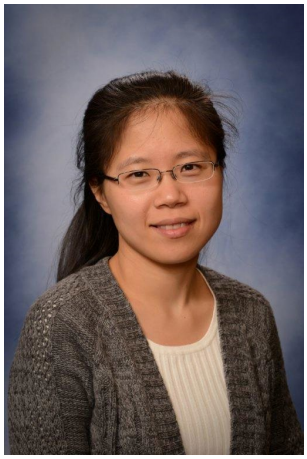
Pharmaceutical Sciences Seminar Series

Wednesday, November 8, 2023
4:00pm
2548 North University Building
Zoom Meeting

"Engineering locally delivered protein therapeutics"

Presented by:



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Abstract: The route of administration of a therapeutic agent has substantial impact on its success. Most biologics are administered systemically by intravenous, intramuscular, or subcutaneous routes. However, treatment of diseases affecting lung and GI-tract – tissues that are naturally refractory to the diffusion of macromolecules from the bloodstream – could be significantly improved by an alternative route of administration. In the past few years, the Chen lab has focused on the engineering of designed ankyrin repeat protein (DARPin) as locally delivered therapeutics. DARPin is a synthetic non-antibody protein scaffold that enjoys high storage stability and low immunogenicity, as well as a high expression yield in *E. coli* (15 g/L in soluble format in fermenters). Our lab has successfully engineered DARPins with pM-nM neutralization potency against *C. difficile* and Shiga toxins for treating enteric bacterial infections. To increase the residence time within the GI tract, and thus enhance the suitability for oral delivery, the DARPin scaffold was further engineered via directed evolution to increase its stability against trypsin and chymotrypsin digestion. During our study, we realized that conventional protein display technologies are ill-suited for protease stability engineering. To address this limitation, we developed a novel *in vitro* protein display technology – click display – that yields protein-cDNA complexes from double-stranded input DNA in a one-pot reaction within 2 hours and is ideal for the engineering of protease-stable biologics. Our lab has also engineered trimeric DARPins as intranasally delivered treatment candidates for SARS-CoV-2 infection. Interestingly, despite the use of a spike protein from a historical SARS-CoV-2 strain as the target for selections, our DARPins showed broad-spectrum neutralization of SARS-CoV-2 VOC strains. K18-hACE2 transgenic mice inoculated with B.1.617.2 and receiving intranasally administered DARPin showed significantly less weight loss and 10-100-fold lower viral burden in upper and lower respiratory tracts relative to the control mice. We believe that DARPins hold a unique potential to be formulated as locally administered biotherapeutics and click display technology should significantly accelerate the discovery of these types of agents.

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