COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

Monday, January 9, 2022
10:00AM Eastern Time
Hybrid
NCRC Building 10 –G064
Zoom Link

"Development of a Bispecific Shuttle for Efficient and Long-Lived Brain Delivery of Antibodies"

Presented by:

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Abstract: Antibodies are an emerging class of medicines with over 100 antibody-based therapeutics approved for treatment of a variety of diseases. While antibodies have been more successful in certain disease areas, antibodies for treatment of neurodegenerative diseases are limited. A major hurdle hindering the therapeutic success of antibodies is arguably the blood-brain barrier (BBB). While small and lipophilic molecules are readily allowed into the brain, larger molecules such as antibodies are extremely limited. The BBB has a natural mechanism known as receptor-mediated transcytosis (RMT) that allows specific proteins such as transferrin into the brain by utilizing the transferrin receptor (TfR-1). In addition to this receptor, a recent study has shown that CD98 heavy chain (CD98hc), a widely expressed extracellular protein on the BBB, can also transport antibodies into the brain. The advent of bispecific antibody technology in recent years have paved the way for new antibody formats with different structures and sizes. Here, we aim to develop a bispecific molecular shuttle for increasing brain delivery of validated 'off-the-shelf' antibodies. We show that these antibodies when reformatted into a bispecific shuttle retain similar affinities and avidity to the parental antibody, while being able to engage specific BBB targets (TfR-1 and CD98hc) and facilitate transport into the brain Notably, CD98hc shuttles lead to much longer-lived brain retention of IgGs than TfR-1 shuttles while enabling more specific brain targeting due to the apparent lack of CD98hc target engagement in the brain parenchyma. We demonstrate the broad utility of the CD98hc shuttles by delivering three existing IgGs to the mouse brain parenchyma that either agonize a neuronal receptor (TrkB) or target other endogenous antigens on specific types of brain cells (neurons and astrocytes). We anticipate this platform's potential in developing novel therapeutics for treatment of various neurodegenerative and challenging brain diseases.