COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series

Wednesday, March 13, 2024
4:00pm
NCRC Building 10 South Atrium
Zoom

" Investigating Safety Liabilities of Delivering CD98hc Bispecific Antibodies to the Brain"

Presented by:

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Abstract: Neurodegenerative diseases including Alzheimer's, Parkinson's, and multiple sclerosis are the leading cause of cognitive and motor disability worldwide. Despite the worldwide prevalence and global burden of these diseases, progress of therapeutic development has been slow and arduous. This is primarily due to the highly restrictive nature of the blood-brain barrier (BBB) which is composed of specialized cellular architecture to protect the brain and regulate transport of essential nutrients. Surpassing this hurdle necessitates the development of BBB drug delivery technologies, a hitherto unmet need.

To address this need, our lab has designed a bispecific antibody comprised of a single-chain variable fragment (scFv) and an IgG connected by a short peptide linker. The scFv in the bispecific antibody binds to a target on the BBB, CD98hc, the heavy chain of the large neutral amino acid transporter (LAT1), and acts as a "shuttle," thereby carrying the attached IgG into the brain parenchyma. CD98hc-mediated shuttling is increasingly recognized as a viable pathway for biologic transport across the BBB. Unlike the more extensively studied transferrin receptor, little is known about the safety profile of anti-CD98hc bispecific antibodies crossing the BBB, especially with regards to repeat dosing. To address this gap in knowledge, we have explored various antibody characteristics and their impact on safety and pharmacokinetic profile, including valency and affinity.

We have found that repeat dosing of a bivalent anti-CD98hc in mice provokes strong immune responses including anaphylactic phenotype and even death. By reducing our shuttle to be monovalent and modulating its affinity, we are able to reduce the spike in anti-drug antibody titers and improve survival for up to 5 successive weekly doses. This research is ongoing and seeks to further understand the impact of epitope, antibody effector function, and various secondary targets in the brain parenchyma on the safety and efficacy of anti-CD98hc bispecific antibodies.