COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

The Department of Pharmaceutical Sciences is pleased to announce the
Ph.D. Dissertation Defense Seminar of

Hongxiang Hu
Pharmaceutical Sciences, Ph.D. Candidate
Mentor: Dr. Duxin Sun

Monday, January 17, 2022 at 10am
https://umich.zoom.us/j/94798985279
Meeting ID: 947 9898 5279 Passcode: 273706

"Different Strategies to Improve Drug Tissue Selectivity for Better Efficacy/Toxicity Profile"

Abstract: Even with tremendous effort devoted to improving drug discovery and development, clinical failure rate remains high (>90% since Phase I), especially attributed to efficacy and safety issues. Based on current strategies, drug candidates with optimized pre-clinical efficacy/toxicity and good plasma pk parameters are preferred to clinical studies. However, drug plasma exposure is not enough to represent in-vivo behavior and may mislead the selection of drug candidate to clinical trials. Instead, the importance of drug tissue exposure/selectivity which is more related with drug accumulation in disease or toxicity related tissues continues to be ignored. In our studies, we tried to improve drug discovery from the point of view of altering drug tissue exposure/selectivity.

In the first project, albumin-based nano-formulation (nano-1252) was prepared for BCL-2/BCL-XL inhibitor to improve tissue targeting, reduce platelet toxicity and enhance anticancer efficacy in myeloproliferative neoplasms (MPNs) and lymphoma. Due to the high formulation stability of nano-1252, large amount of nanoparticles was trapped in spleen and BM, resulting in high accumulation (up to 20-fold) in target tissues and low concentration in circulation system. Nanomedicine of BCL-2/BCL-XL inhibitor has been showed to significantly decrease the platelet toxicity (MTD increased at least 2 folds), and meanwhile prolonged survival rate, delayed paralysis occurrence, and reduced tumor infiltration in spleen and BM compared to clinical formulation.

In the second project, anti-SARS-Cov-2 small molecule, remdesivir, was optimized to improve lung targeting and enhance its efficacy against COVID-19. Our lead compound, MMT5-14, achieved 200-fold higher parent drug concentration in the target tissues (e.g. Lung) and about 5-fold higher active form (triphosphate form) compared to remdesivir. Besides, due to its high chemical stability, MMT5-14 showed 4 to 7-fold higher uptake into lung epithelial cells (Calu-3) compared to remdesivir, with 4 to 8-fold better in-vitro anti-SARS-Cov-2 activities.
In the third project (Chapter IV), structure-tissue exposure/selectivity relationship (STR) was studied with series of selective estrogen receptor modulators (SERMs). The results showed that drug exposure in plasma was not correlated with drug exposure in the target tissues (tumor, fatpad and bone) that was associated with clinical efficacy/safety. Slight structure modification altered drug exposure/selectivity in tissues despite similar drug exposure in the plasma. STR may correlate with clinical efficacy/safety which impacts success rate of drug development.

Overall, the work presented highlighted the importance of applying tissue selectivity in the early stage of drug discovery and development.