COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

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4:00pm
2548 NUB or Zoom Info

"Different strategies to improve drug tissue selectivity for better efficacy/toxicity profile"

Presented by:

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Abstract: In the past few decades, despite of significant effort to optimize the drug discovery and development process, the success rate from clinical phase I trial to launch was less than 10%. Among all clinical failures, insufficient efficacy and unmanageable toxicity account for more than 70% according to the clinical trial data from 2010-2017. Drug profile in the plasma is normally optimized for lead compounds, but often fails to ensure adequate therapeutic exposure in target tissue (efficacy) or low toxic exposure in normal tissues (toxicity), likely to mislead the selection of drug candidates to clinical trials. Therefore, strategies to improve drug selectivity in target tissue or toxic related tissues are critical for better efficacy/toxicity profile.

We firstly observed nanomedicine of Bcl2/Bcl-xL inhibitor could lower blood exposure while increasing tissue exposure in bone marrow, spleen and lymph nodes. The special formulation changed tissue distribution majorly from mononuclear phagocyte system and lymphocytes, leading to reduced platelet toxicity and enhanced anticancer efficacy in lymphoma and myelofibrosis models. In the next example, we also found long lipid modification of anti-virus drug, remdesivir, could increase lung, spleen, fatpad and blood accumulation while maintaining similar drug level in liver and kidney. Finally we studied the structure-tissue selectivity relationship (STR) through a series of selective estrogen receptor modulators (SERMs). Even slight structure change in SERMs could alter drug tissue exposure in various tissues. Besides, iv or oral administration of studied SERMs also showed different tissue preference.

Overall, we found that long lipid modification, minor structure change, special formulation or even administration route could possibly influence drug tissue exposure/selectivity. Strategies utilizing this correlation could be beneficial to improve clinical success rate.

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