UNIVERSITY of GUELPH

COLLEGE of BIOLOGICAL SCIENCE

DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY

Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of ***Doctor of Philosophy*** *of*

QI LIU

on Thursday, April 4th, 2024 at 9:30a.m. (SSC 1504)

Thesis Title: Development of Inhibitors for Human Deubiquitinases

Examination Committee:

Dr. Ian Tetlow, Molecular and Cellular Biology (Exam Chair)
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Nina Jones, Dept. of Molecular and Cellular Biology
Dr. Alicia Viloria-Petit, Dept. of Biomedical Sciences, OVC
Dr. Vivian Saridakis, Dept. Biology, York University (External Examiner)

Advisory Committee:
Dr. Wei Zhang (Adv)
Dr. Jim Uniacke
Dr. Alicia Viloria-Petit

Abstract: Ubiquitination is an important protein post-translational modification that is essential for almost all cellular processes in human cells. The reverse process, deubiquitination is catalyzed by deubiquitinases (DUBs), malfunction of which has been implicated in numerous diseases. Consequently, extensive efforts have been put into developing DUB inhibitors in the past two decades. However, most chemical compounds with DUB inhibitory activities only confer mild potency and low selectivity. This is presumably due to the diversity, complexity, and dynamic regulation of DUB catalysis. To tackle this problem, a protein engineering-based strategy of developing ubiquitin variant (UbV) inhibitors for systematic targeted inhibition of human DUBs was devised. This technology was further expanded to develop inhibitors of E2 conjugating enzymes and E3 ligases. In this thesis, the UbV technology is employed to develop inhibitors for STAMBP and OTUD1, in DUB families of JAMM and OTU, respectively. Unique UbV sequences are identified from phage display-based selection of the UbV library. Following biochemical and cellular characterizations indicate UbVs are potent and specific inhibitors. In addition, the crystal structure of STAMBPL1 in complex with a UbV reveals its inhibitory mechanism. Finally, UbVs for OTUD1 are explored for targeted stabilization, which mediates the deubiquitination and stabilization of EGFR in a UbV-induced proximity (UbVIP) approach as a proof-of-concept. The UbV inhibitors developed in this work are the first potent and specific inhibitors targeting the selected DUBs, thus providing new tools for the research community to probe the DUB biochemical mechanisms and facilitate the development of small-molecule inhibitors and the investigation of targeted protein stabilization.

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Curriculum Vitae: Qi obtained her Bachelor of Science in Bioengineering at the Beijing Institute of Technology in Beijing, China in 2018. In the fall of 2019, she entered the Masters Program at the University of Guelph. In the fall of 2020, she transferred into the Ph.D. program under the supervision of Dr. Wei Zhang.

Awards:

Donald R. Phillips MCB Award, 2022
Ontario Graduate Scholarship (OGS), 2020
International Doctoral Tuition Scholarships (IDTS), 2020-now

Publications: Liu Q*, Mallette E,* Zheng H, Zhang W. (2023) Development of an OTUD1 ubiquitin variant inhibitor. Biochemical Journal. 480(16):1317-1330

Liu Q, LaPlante G, Zhang W. (2022) Targeting the ubiquitination cascade in drug discovery. Protein Homeostasis in Drug Discovery: A chemical Biology Perspective. John Wiley and Sons. 179-225.

Guo Y*, Liu Q*, Mallette E*, Caba C, Hou F, Fux J, LaPlante G, Dong A, Zhang Q, Zheng H, Tong Y, Zhang W. (2021) Structural and functional characterization of ubiquitin variant inhibitors for the JAMM-family deubiquitinases STAMBP and STAMBPL1. J Biol Chem. 297(4):101107.

Liu Q*, Aminu B*, Roscow O, Zhang W. (2021) Targeting the Ubiquitin Signaling Cascade in Tumor Microenvironment for Cancer Therapy. Int J Mol Sci. 22(2):791.