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*

BAYONLE AMINU

On Monday, December 11, 2023 at 1:30 p.m. (online)

Thesis Title: **Targeted degradation of intracellular proteins using ubiquitin variant induced proximity**

Examination Committee:

Dr. Joseph Colasanti, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Jasmin Lalonde, Dept. of Molecular and Cellular Biology
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Cezar Khursigara, Dept. of Molecular and Cellular Biology
Dr. Mikko Taipale, Dept. of Molecular Genetics, University of Toronto (External Examiner)

Advisory Committee:
Dr. Wei Zhang (Advisor)
Dr. Jasmin Lalonde
Dr. Jim Uniacke

Abstract: Eukaryotic cells rely on proteasomal degradation mechanisms to maintain protein homeostasis, quantity, and quality, essential for regulating various biological processes. A recent trend in drug development involves harnessing the ubiquitin (Ub)-mediated proteolysis pathway for the targeted degradation of disease-causing proteins. One promising approach in this domain is the use of Proteolysis Targeting Chimeras (PROTACs), which are heterobifunctional molecules that contain a module to recruit E3 ligases, a target-binding module, and a linker, thereby directing the target protein to E3 ligases for ubiquitination and subsequent proteasomal degradation. Despite the progress in chemical PROTACs, limited information is available on peptide-based degraders. Previous research in our laboratory has focused on engineered Ub variants (UbVs) as inhibitors and activators of Ub related enzymes, targeting protein-protein interaction surfaces that are often elusive to chemical inhibitors. Building upon this foundation, we hypothesized that UbVs could serve as fusion protein components to facilitate targeted protein degradation—a concept we term UbV induced proximity (UbVIP). The UbVIP approach presents several advantages over small-molecule PROTACS, primarily due to its ability to bind protein-protein interaction sites on target proteins that small molecules cannot access and the utilization of novel E3 ligases. In this PhD thesis, I explore the application of UbVIP technology for intracellular proteins. Chapter 2 of this thesis demonstrates the successful degradation of the target protein, 53BP1, by employing UbVIP to recruit the E3 ligases RFWD3 and NEDD4L. Chapter 3 investigates the effectiveness of recruiting the E2 conjugating enzyme, UBE2B, in degrading target proteins. Collectively, the findings from this research shed light on a peptide-based targeted protein degradation strategy and provide compelling evidence for the exploitation of novel E2 conjugating enzymes and E3 ligases in the

Continued…

ubiquitination and degradation of intracellular proteins. The UbVIP approach holds great promise as a valuable tool in drug development and therapeutic interventions for a wide range of diseases.

Curriculum Vitae: Bayonle completed her Bachelor of Science in Zoology in 2012 and her Master of Science in Zoology (Cell Biology and Genetics option) in 2015 with the University of Ibadan, Nigeria. She then began her PhD in Molecular and Cellular Biology program at the University of Guelph in Dr. Wei Zhang's lab in January 2020.

Awards: QEII-GSST Scholarship (2022-2023, 2023-2024); CBS Winner, 3MT (2023).

Publications:

Aminu, B., Fux, J., Mallette, E., Petersen, N., and Zhang, W. (2022). Targeted Degradation of 53BP1 Using Ubiquitin Variant Induced Proximity Biomolecules 12, no. 4: 479. https://doi.org/10.3390/biom12040479

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: 791. https://doi.org/10.3390/ijms22020791

Bakare, A. A., Akinseye, K. M., **Aminu, B. A.**, Ofoegbu, F.C., ….and Alimba, C. G. (2020). Genetic and reproductive toxicity of lamivudine, tenofovir disoproxil fumarate, efavirenz and their combination in the bone marrow and testicular cells of male mice. Annals of Science and Technology 5(1): 1-10.