UNIVERSITY OF RHODE ISLAND
Department of Chemistry
SEMINAR

3:00 P.M., Monday, January 27, 2025
Room 105 – Beaupre Center

Prof. Jun Yong Choi

Queens College – City University of New York

Structure-guided Design and Development of Potent and Selective Small Molecule Inhibitors for Biomedical Research

HOST

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Structure-guided Design and Development of Potent and Selective Small Molecule Inhibitors for Biomedical Research

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Abstract: Computer-aided molecular modeling is an efficient and cost-effective approach for the discovery and development of biomedically interesting chemical agents in academic institutes. This seminar highlights the structure-based development of small molecule agents inhibiting *Trypanosoma brucei* Replication Protein A1 (TbRPA1) and Casein Kinase 1 (CK1) for the treatment of parasite infections and cancers, respectively. Using molecular modeling, we identified a small molecule inhibitor (JC-229, EC_{50} = 6.5 μM), which is toxic to *T. brucei* parasite due to its inhibition against TbRPA1. JC-229 treatment mimics the effects of TbRPA1 depletion, including DNA replication inhibition and DNA damage accumulation. In vitro ssDNA-binding assays demonstrate that JC-229 inhibits the activity of TbRPA1, but not the human ortholog. We applied structure-guided design and developed highly potent TbRPA1 inhibitors (~100-fold improvement of EC_{50}). In the second part of this talk, highly selective and potent matrix metalloproteinase 10 (MMP-10) inhibitors will be presented. MMP-10 shows overactivity in non-small cell lung cancer, skin cancer, and pulmonary hypertension. Currently, there is no potent and selective MMP-10 inhibitors. Starting from a screening hit, we have developed highly potent and selective inhibitors targeting MMP-10 vs. MMP-3 by applying computer-aided molecular design techniques. The enhanced inhibition potency to MMP-10 and selectivity against MMP-3 are explained by induced fit docking and molecular dynamics simulations. These small molecule inhibitors will be further optimized to develop in vivo chemical probes and eventually therapeutic candidates for the treatment of parasite diseases and human cancers.