DATE: Day 12 Month 05 Year 2023

SUMMARY of
2022 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**Drug screen strategy targeting RpoS against bacterial antibiotic resistance**
Applicant	**Name**	**SAQIB UZMA**
	Affiliation	**Indian Institute of Technology Indore**
	Present Title	**Woman Scientist**
Research Collaborator (Host PI)		**Kenji Mizuguchi**

Summary

The role of RpoS in protecting bacteria against antibiotics as well as their constitutive expression in bacterial cells minimize the antibiotic sensitivity in a multidrug-resistant strain of E. coli. Hence, newer therapeutic strategies should be employed to inhibit this bacterial defense protein. In the proposed work, we planned to screen novel compounds from multiple public databases in pursuit of potent inhibitory molecules against RpoS. This will be followed by testing the candidate compound(s) for their efficacy to weaken the UPEC resistance to gentamicin. Gentamicin belongs to a class of drugs known as aminoglycoside antibiotics. Gentamicin is used to treat several types of bacterial infections including bone infections, inflammatory diseases, meningitis, pneumonia, urinary tract infections (UTI's), and sepsis among others. We anticipate that our ongoing work will discover novel candidates effective in inhibiting RpoS and eventually antibiotic resistance. Also, this will be the first-of-its-kind study on RpoS based inhibitor discovery against UPEC.

Specific aims:

We proposed the following objectives;

Aim1: To identify novel RpoS inhibitors using in silico database search.

Aim2: To determine the potency of selected compounds in inhibiting RpoS in UPEC**.**

The goal of **Aim1** was to develop potent RpoS inhibitory compounds using structure-based computational screening. We utilized a high resolution crystal structure of Rpos (PDB 5IPL) to screen compounds from various databases, including; ZINC, Maybridge and microbial database. Our high-throughput virtual screen strategy involved docking based analysis. Hence, we used state-of-the-art docking software programs based on AutoDock to sequentially dock the datasets. This was preceded by identifying the binding site of the enzyme for potential inhibitors. Inclusion of compounds from multiple datasets would be beneficial in getting molecules of different scaffolds, which in turn increases diversity and potency. After a thorough investigation of "hits" from the molecular docking run using scoring methods and binding site analysis, we moved to our **Aim 2.** Currently, we are performing experiments to test the efficacy of the compounds using reactive oxygen species (ROS) assay.

We anticipate that targeting RpoS with screened compounds would increase the ROS formation inside the bacterial cell further disrupting the structural configuration of the gut microbiota. By selectively depleting intestinal UPEC reservoirs, the selected compounds could be anticipated to reduce the rate of Urinary Tract Infections (UTIs).

***Deadline: May 12, 2023**
***Please submit it to E-mail: tanpakuken-kyoten@office.osaka-u.ac.jp.**
***Please describe this summary within 1 sheet. Please DON'T add some sheets.**
***This summary will be published on the web.**