DATE: Day 30 Month April Year 2024

SUMMARY of
FY2023 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Artificial Intelligence-guided discovery of novel quorum sensing inhibitors as next-generation therapeutics against Pseudomonas aeruginosa infection
Applicant	**Name**	Rajnish Kumar
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	Present Title	**Assistant Professor**
Research Collaborator (Host PI)		Kenji Mizuguchi

Summary

Pseudomonas aeruginosa (PA) is a major nosocomial threat, causing severe infections in vulnerable patient groups. Its growing resistance to multiple drugs prompted its classification as a critical pathogen by the World Health Organization, necessitating new treatment approaches. PA's pathogenesis relies on motility, virulence factor production, and biofilm formation, which impede antibiotic effectiveness. These factors are controlled by quorum sensing (QS) systems, such as LasR/I, RhlR/I, and PQS. Targeting these pathways shows promise in reducing virulence and enhancing antibiotic susceptibility. However, despite efforts to inhibit LasR/RhlR, no compounds have advanced to clinical use. I have been collaborating with Prof. Mizuguchi since June 2019 and have been exploring opportunities for joint research work. In this IPR-International Collaborative Research Program 2023, we discussed the use of DruMap, an ML-based pharmacokinetic prediction server developed by his lab for predicting pharmacokinetic parameters for candidate compounds, and his lab's expertise in building machine learning models for the ultra-large virtual screening of LasR inhibitors.

We have used Deep Docking, an AI-based tool to virtually screen ultra-large libraries library of 1.3 billion compounds from the ZINC20 database to identify hit compounds against the LasR. 0.1% molecules were samples from the whole dataset and then subjected to docking into the binding site of LasR and the docking score was obtained which was used to train CNN-based models using TensorFlow. The final model effectively screened 116 million molecules, demonstrating good generalization capabilities with a recall of 0.9029 and precision of 0.068 with a model cutoff of -10.10 kcal/mol. The last phase of model building and screening is still ongoing to reduce the number of finally selected hits which will be procured and validated in vitro using a battery of assays to assess QS inhibition and anti-virulence activity, alongside cytotoxicity testing to ensure compound safety. Physicochemical and pharmacokinetic profiling helped select optimal hit compounds, considering parameters such as solubility, chemical stability, and ADMET properties. The project's anticipated outcomes include novel QSIs with potential as anti-virulence therapeutics against multi-resistant PA infections. Once, we identify and validate the hit compounds, we expect to collaborate with Prof. Mizuguchi to optimize those hit compounds using molecular dynamics simulation and ML-based lead optimization. The expected results of this project are novel QS inhibitors and their development into potential anti-virulence therapeutics for the treatment of multi-resistant PA infections.

***Deadline: May 10, 2024**
***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.**