DATE: Day 09 Month 05 Year 2025

SUMMARY of
FY2024 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Crystal structure of aminoimidazole ribonucleotide synthetase
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	Present Title	Scientist / Professor
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Summary

The enzyme aminoimidazole ribonucleotide synthetase (AIRS) catalyzes the first step in De-novo pathway which plays a vital role in cancer pathway by providing the enormous supply purine needed for cell proliferation. Hence targeting this enzyme may result in disruption of the pathway thus cancer can be blocked efficiently.

Purine biosynthesis is perceived as vital process because of their indispensable role involved in creating genetic material that is DNA and RNA. Aminoimidazole ribonucleotide synthetase (AIRS) catalyzes first step in de novo purine biosynthesis pathway facilitating that synthesizes of N(1)-(5-phospho-D-ribosyl)glycinamide from 5-phospho-alpha-D-ribose 1-diphosphate. Hence, inhibiting AIRS is crucial due to its involvement in the regulation of uncontrollable cancer cell proliferation.

This project aims to determine the crystal structures of aminoimidazole ribonucleotide synthetase (AIRS) at the highest resolution to elucidate the structural insights of the enzymatic mechanism. The high-resolution structure may ultimately help in developing inhibitory therapeutic agents against the enzymatic activity of this critical enzyme, which can contribute to expanding our understanding of the current purine biosynthetic pathway.

We have collected several data sets of the X-ray diffraction on the AIRS crystals. The phase determination of AIRS was carried out with the *ab initio* phasing method. Iterative refinement and model building was carried out for complete structure determination. High-resolution data was also collected for structural refinement and determination.

The final model of AIRS at 2.0 Å resolution is a dimer structure generated through a crystallographic twofold axis. Each subunit folds into 11 α-helices and 15 β-strands, and is divided into two domains: the N-terminal domain (NTD) and the C-terminal domain (CTD), connected by a linker. The NTD features a five-stranded β-barrel structure, which forms the interface between two subunits. This barrel is surrounded by four α-helices. The CTD comprises a seven-stranded mixed β-sheet, and is encircled by seven α-helices.

***Deadline: May 9, 2025**
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