DATE: 12 May 2025

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

Research Title		**Establishment of the efficient synthetic route of macrocycle FAP-2286**
Applicant	**Name**	**Gloria Serra**
	Affiliation	**Department of Organic Chemistry, School of Chemistry, Universidad de la República, Uruguay.**
	Present Title	**Full Professor**
Research Collaborator (Host PI)		**Professor Hironobu Hojo**

Summary

FAP-2286 is a promising peptide-based compound for cancer diagnosis and therapy, targeting fibroblast activation protein (FAP), which is highly expressed in cancer-associated fibroblasts. Its synthesis involves multiple steps, including solid-phase peptide synthesis (SPPS), macrocyclization, and DOTA chelator coupling.

Two main synthetic strategies were developed in IPR for the key intermediate cyclopeptide:

1. SPPS followed by solution-phase macrocyclization (using Cys(Trt)): This approach yielded moderate results (20%) under optimized basic and reductive conditions. However, it required multiple purification steps and encountered issues such as peptide aggregation and side-product formation.

2. Fully solid-phase synthesis (using Cys(StBu) on 2-CTC resin): This method improved overall yield (30%) and simplified the process by avoiding intermediate purifications. Still, peptide aggregation during the final deprotection step remained a significant limitation.

The final coupling with the DOTA chelator was straightforward, but difficulties in removing DMSO before purification led to some loss in yield.

As conclusion, significant progress was made toward the synthesis of FAP-2286, with two viable synthetic routes developed. The major challenge ahead is reducing peptide aggregation during final deprotection to improve yield and reproducibility.

***Deadline: May 9, 2025**
***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.**