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SUMMARY of
FY2025 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, The University of Osaka

Research Title		Development of on-resin synthetic methodologies for the preparation of cell-permeable cyclic peptides containing dithiolanes
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Summary

Cyclic peptides are an important class of compounds in modern drug discovery, particularly for targeting protein–protein interactions that are often inaccessible to small molecules. Despite their high in vitro activity, many cyclic peptides suffer from poor cellular permeability, limiting their therapeutic potential. Traditional strategies to improve permeability, such as N-methylation or prodrug approaches, often compromise binding affinity. While cell-penetrating peptides (CPPs) offer an alternative, their highly cationic nature can lead to toxicity and nonspecific interactions.

To address these limitations, this work explores the incorporation of a 1,2-dithiolane moiety into peptides through the amino acid Adt (4-amino-1,2-dithiolane-4-carboxylic acid). This functional group enables thiol-mediated uptake via disulfide exchange with cell surface receptors, offering a non-endocytic pathway for cellular internalization. Additionally, Adt is designed to participate in on-resin cyclization through native chemical ligation (NCL), using the thioester method.

The synthesis of the Adt precursor, 2-amino-3-mercapto-2-(mercaptomethyl)propanoic acid, was achieved following optimization of literature procedures. The p-methoxybenzyl (PMB) group was selected as a suitable thiol-protecting group, allowing efficient handling and downstream transformations. Although the hydrolysis of the hydantoin intermediate proved slow and prone to side reactions, sufficient quantities of the desired product were obtained to proceed.

Incorporation of the Adt precursor into peptides was explored using solid-phase peptide synthesis (SPPS) on ChemMatrix resin. Initial coupling attempts using DIC/oxime were unsuccessful; however, the use of the activated N-carboxyanhydride derivative (9.b.) in combination with DIPEA and HBTU enabled rapid and complete coupling. Two strongly acidic deprotection protocols were evaluated and successfully removed PMB groups.

The model peptide sequence was assembled using Fmoc-SPPS, incorporating an N-methyl cysteine residue to enable NCL via an N-to-S acyl shift. After global deprotection, free thiols were generated under reducing conditions, and intramolecular on-resin cyclization was induced. MALDI-TOF analysis confirmed successful formation of cyclic peptides. However, partial desulfurization of the Adt moiety was observed, likely due to the reducing agent (TCEP), indicating that the 1,2-dithiolane ring is sensitive under the current conditions. This represents the main limitation of the methodology.

Overall, this work demonstrates the feasibility of synthesizing and cyclizing Adt-containing peptides on solid support. Future efforts will focus on optimizing reduction and cyclization conditions to preserve the integrity of the dithiolane ring, improving key synthetic steps such as hydantoin hydrolysis, and expanding the methodology to diverse peptide sequences. This strategy holds promise for the development of cyclic peptides with enhanced cellular permeability and improved therapeutic potential

***Deadline: May 11, 2026**
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