DATE: July 26, 2016 Year 2016

SUMMARY of
2015 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**Design and synthesis of macrocyclic inhibitors targeting polo box domain of polo like kinase-1**
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Summary

Over the years, a great attention has been focused on the design and synthesis of potent inhibitor targeting the Polo-like kinase 1 (Plk1) because of their prominent roles in regulating mitotic progression and cell proliferation. An elevated Plk1 activity is thought to promote tumorigenesis, and it is considered an attractive anti-cancer drug target. Several research groups discovered peptide-based inhibitors targeting Plk1-PBD, with high binding affinity towards *in vitro* assay. However, cell permeability and proteolytic stability are the two important drawbacks, which hinder their transformation into novel therapeutics. Recently, we reported (*Scientific reports*,**2015**,*5*,14626) that one of our synthesized peptide AB103-8 targeting the polo-box domain of polo-like kinase Plk1PBD prevents the interaction between Plk1PBD and Emi2, subsequently, that affected the meiotic maturation and meiosis resumption. Hence, it is evident from the study that discovering suitable drug candidate which disrupts the specific interaction between Plk1 and Emi2 may be an attractive strategy for the development of new contraceptive agents. In this project, To overcome the demerits of the peptide-based inhibitors targeting Plk1-PBD and to compare the oocyte maturation arrest of our previously synthesized peptide AB103-8, we designed and synthesized a series of non-peptidic, *N*-alkylphenyl pyrrole based macrocyclic inhibitor. All the synthesized compounds were evaluated for their oocyte maturation studies. We found that some of our compounds are remarkable in displaying oocyte maturation arrest, in particular, C-3 found to be excellent in oocyte maturation arrest, compared to the previously reported peptidomimetics AB103-8. To understand the binding features with Plk1PBD, complex co-crystal structure studies are under progress. In addition, we synthesized the macrocyclic peptide targeting PBD of Plk1 using the N-alkyl cysteine-assisted thioesterification method. This cyclic peptide will be tested for PBD inhibition property in future studies.