



**Title of Project : Middle Molecular Strategy: Creation of Higher Bio-functional Molecules by Integrated Synthesis.**

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**【Purpose of the Research Project】**

Middle-size biomolecules (MW ca. 400-4000) such as natural products, glycans, peptides, nucleic acid drug, and etc have high chemical diversity and various biological activities. They are also termed as middle molecules, mid-size molecules, medium size molecules, and so on. Middle molecules have great potential as higher bio-functional molecules because of the following characteristics. Since middle molecules have relatively large surface area in comparison to small molecules, the strict and diverse molecular recognition is possible based on the multipoint interaction between middle molecules and target proteins, enabling both "lock and key" recognition in the binding pocket and the protein surface recognition. Some of middle molecules interact with several proteins simultaneously to dynamically control the signaling. In addition, some of middle molecules are membrane permeable and orally active.

However, the inherent structural complexity of middle molecules was an obstacle for the practical use of middle molecules, since the synthesis of them is often difficult and generally requires many reaction steps. Therefore, the present research project will achieve a highly efficient synthesis of bioactive middle molecules by an innovative synthetic strategy based on reaction integration. Further, novel bio-functional middle molecules will be developed by new strategies such as function integration.

**【Content of the Research Project】**

In this research project, bio-functional middle molecules will be developed based on the two strategies, i) efficient synthesis of bioactive natural products, ii) synthesis of hybrid middle molecules by function integration. The efficient synthesis of middle molecules by reaction integration will be also investigated.

In A01, efficient synthesis of bio-functional middle molecules such as glycans, nucleic acids, peptides, and lipids will be studied. Development of novel bio-functional middle molecules will be also investigated by function integration, i.e., conjugation of bioactive

compounds, creation of novel bio-functional molecules possessing the  $\pi$  electron system compounds.

A02 aims the highly efficient synthesis of bioactive middle molecules such as complex natural products. A02 will also study the reaction integration based on novel concepts and techniques such as synthesis using living cells and chemo-enzymatic synthesis.

A03 will develop continuous reaction processes using micro-flow and one-pot syntheses as well as practical reactions for multi-step synthesis. Synthetic transformations allowed by micro-flow methods, such as very fast reactions using unstable reactive species, will be also investigated.

**【Expected Research Achievements and Scientific Significance】**

This research project will realize highly efficient processes by reaction integration to achieve the efficient synthesis of complex middle molecules. Since middle molecules have high potential as bio-functional molecules such as pharmaceutical agents and agrochemicals, this research project will lead innovative pharmaceutical drugs, diagnostic agents, and pesticides, e.g., effective immunoadjuvants, synthetic vaccines, selective anti-cancer agents, environment-friendly pesticides, and etc.

**【Key Words】**

Middle molecule, natural product, glycan, peptide,  $\pi$  electron system compound, higher bio-functional molecule, reaction integration, micro-flow synthesis, continuous reaction process, multistep synthesis, catalyst, function integration

**【Term of Project】** FY2015-2019

**【Budget Allocation】** 1,108,100 Thousand Yen

**【Homepage Address and Other Contact Information】**

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