【Grant-in-Aid for Scientific Research (S)】

Broad Section E

Title of Project： **Elucidation of glycan function by synthetic glycans and glycan remodeling systems and their application to new immunotherapies**

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【**Purpose and Background of the Research**】

Glycans function as key substances for self and nonself recognition in both innate and acquired immunity. We have studied the structure and synthesis of glycans and glycoconjugates that activate or modulate immune systems, and clarified the mechanism of immune activation and inflammation by using synthetic compounds.

In this study, we will clarify new glycan recognition molecules and elucidate new functions of glycans in inflammation and immunity by using synthetic compounds and synthetic biology methods. Furthermore, treatments for cancer and immune diseases will be investigated by development of therapy candidates such as vaccine, cancer immunotherapy, and targeted α-particle therapy, and etc.

【**Research Methods**】

Structural complexity and heterogeneity are major features of glycans. Most classes of glycans exist as complex glycoconjugates such as glycoproteins, glycolipids, glycosaminoglycans, and etc. The biological functions of glycans have not yet been sufficiently elucidated due to their inherent complexity. Synthetic studies of glycans have greatly contributed to the functional studies of glycans by supplying homogeneous glycans to determine the active units or active principles.
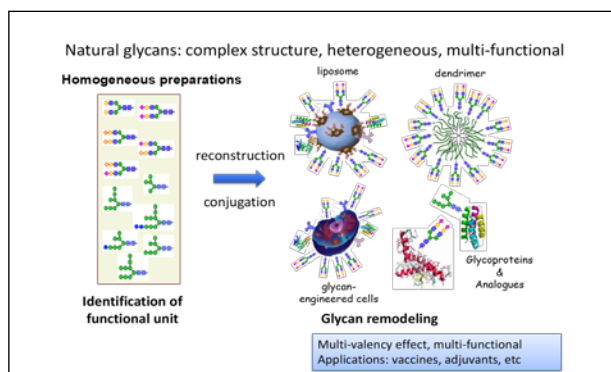

Figure 1   Functional analysis of glycans

In this study, we will investigate immunological functions of bacterial glycoconjugates as well as asparagine-linked glycans on glycoproteins (*N*-glycans) based on chemical synthesis. We will identify the glycan structure (functional unit) responsible for recognition, and elucidate the interaction between glycans with recognition proteins. A reconstruction model of glycans, e.g., glycodendrimers, glycan engineered cells, adjuvant-antigen conjugates will be used to investigate glycan functions in complex systems and to develop new candidates for treatments of cancer and immune diseases.

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

Glycan functions in inflammation and immune response will be clarified. We will also develop immunoadjuvants, self-adjuvanting cancer vaccines consisting of an immunoadjuvant and an antigen, glycosyl transferase inhibitors as regulatory molecules for inflammatory diseases, and new molecular targeting agents for cancer immunotherapy. Furthermore, we aim at developing the new treatment methods of intractable diseases, such as inflammatory bowel disease and pancreatic cancer.
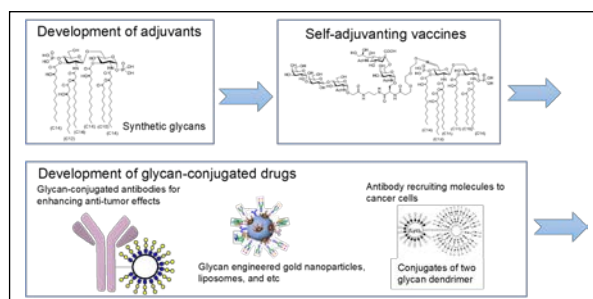

Figure 2   Development of immunotherapy candidates

【**Publications Relevant to the Project**】

· Manabe, Y.; Marchetti, R.; Kabayama, K.; Fukase, K.; Molinaro, A. *et al.*, The Core Fucose on an IgG Antibody is an Endogenous Ligand of Dectin-1. *Angew. Chem. Int. Ed.* **2019**, *58*, 18697-18702.
· Chang, T.-C.; Manabe, Y.; Kabayama, K.; Lin, C.-C.; Fukase, K. *et al.*, Syntheses and immunological evaluation of self-adjuvanting clustered *N*-acetyl and *N*-propionyl sialyl-Tn combined with a T-helper cell epitope as antitumor vaccine candidates. *Angew. Chem. Int. Ed.* **2018**, *57*, 8219-8224.

【**Term of Project**】FY2020- 2024

【**Budget Allocation**】154,300 Thousand Yen

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

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