【Grant-in-Aid for Transformative Research Areas（A）】

Generative design to unlock the potential of protein function

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Project Information	Project Number : 24A207　Project Period (FY) : 2024-2028 Keywords : Protein design, Computational Science, Spatiotemporal measurements, biological tools, enzymes

Purpose and Background of the Research

●Outline of the Research

We will establish a theory of the generative design that enables conversion and creation of protein molecular functions. Protein molecules, which are responsible for biological functions, have been continuously changing in the evolution to adapt to the environment, resulting in diverse and highly capable molecular functions.

However, the protein molecules that have emerged in this evolution are only a small fraction of the theoretically possible set of protein molecules, and design studies of artificial proteins that do not exist in nature suggest that there are an enormous number of protein molecules that have not yet appeared in the evolution. Protein molecules therefore have immense potential for modification of their molecular functions and generation of new ones.

We therefore aim at establishing guiding principles to design protein molecules with new functions in a "generative" manner. We will develop a methodology for designing functional protein molecules based on the requirement definitions for the novel function, rather than a heuristic search. For that purpose, we will integrate theoretical methods based on computational chemistry and data science, spatiotemporal measurements, and protein molecule development technologies (Figure 1).

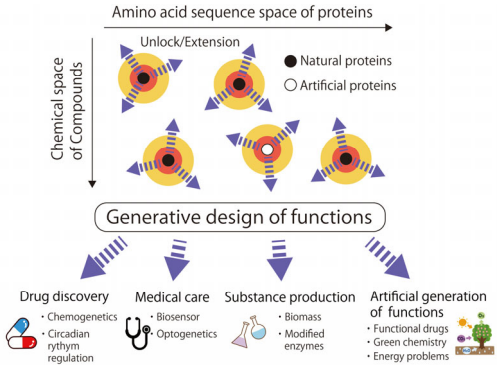

Figure 1 Generative design of protein functions

●Direct observation and design of “functional state”

When a protein performs a remarkable molecular function, it often generates a “functional state” that appears instantaneously and activates the function. Recently, it has become possible to accurately predict and analyze the functional states using advanced computational methods. In addition, time-resolved x-ray crystallography has made it possible to directly observe experimentally the movement of molecules in three-dimensional space in functional states. By making full use of the state-of-art computational and experimental techniques, we identify functional features that determine protein molecular functions, and theoretically design protein mutants of modified functions by directly analyzing the functional features. Then, by forming a feedback loop with experimental studies on the development of novel functional proteins that contribute to medicine, drug discovery, and creation of new substances, we will establish the theory of the generative design of protein functions (Fig. 2).

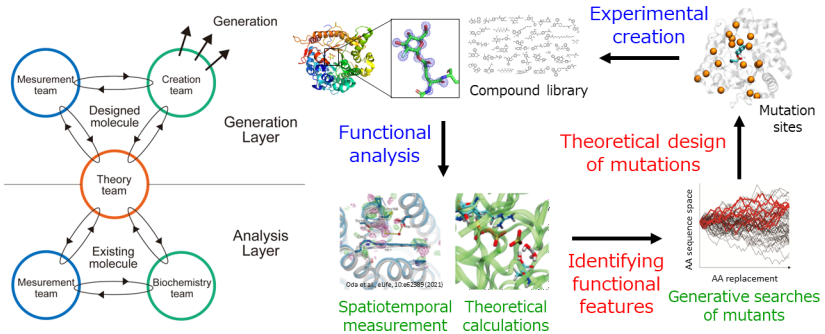

Figure 2 Diagram of researches in the area. Researches are conducted in two layers: the analytical layer and the generative one. In the analysis layer, functional features are identified. We then design theoretical modifications and generate new functions in the generative layer.

Expected Research Achievements

We will address three strategic aims where protein molecular function design is a core value in the field of biotechnology, as well as a seminal challenging aim that will greatly expand the scope of protein molecular design in the future (Figure 3).

- **Strategic aim 1: Drug discovery** Chemogenetic receptor proteins that can regulate cellular functions with approved drugs that have few side effects, and intrinsically disordered proteins involved in circadian rhythm abnormalities will be designed.
- **Strategic aim 2 : Biological protein tools** We will generate novel fluorescent sensor proteins for measurement of intracellular bioactive substances and tool proteins used in optogenetics for optical regulation of brain function.
- **Strategic aim 3 : Enzymes for new substance production** We will establish a method to design functionally more efficient carbohydrate-related enzymes that contribute to solving food problems and maintaining human health.
- **Challenging aim : Creation of protein functions from scratch** We will challenge creation of functions from scratch to artificially designed proteins, which do not exist in nature, to revolutionize the utilization of protein molecules.

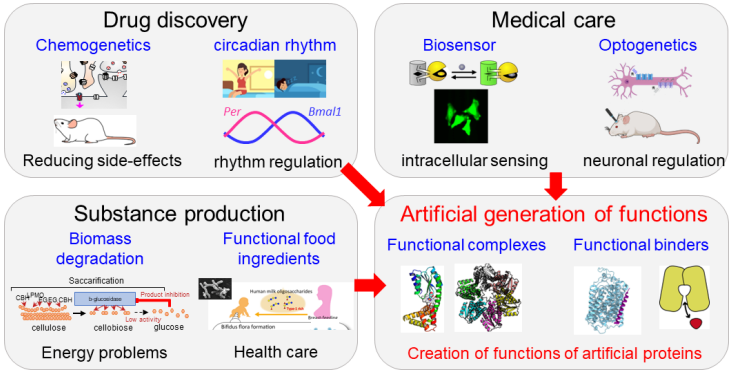

Figure 3 Research aims of the area

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