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

Catalysts participating in chemical orders of living organisms

Principal Investigator	The University of Tokyo, Graduate School of Pharmaceutical Sciences, Professor KANAI Motomu Researcher Number:20243264
Project Information	Project Number : 23H05466 Project Period (FY) : 2023-2027 Keywords : catalyst, epigenetics, amyloid, Alzheimer disease, catalysis medicine

Purpose and Background of the Research

●Outline of the Research

The objective of this research is to create chemical catalysts that transform and manipulate the structure and function of proteins and other biomolecules in living organisms (Figure 1). This will create the basis for new biological research tools and medicinal concepts, as well as a new trend in catalysis that links physical and life sciences. Specifically, we aim to develop two catalytic systems in living cells and animals: 1) chemical catalysts that intervene in chromatin epigenetics, and 2) catalytic systems that degrade and remove toxic amyloid proteins. To carry out this research, it is essential to dramatically improve the reactivity and selectivity of chemical catalysts, which have been developed for reactions in flasks, and to ensure their biocompatibility. Complementary to genetic code expansion and editing technologies, this research will enable the artificial manipulation of biological functions through upstream to downstream, and will have wide-ranging ripple effects on basic and applied fields of chemistry and life sciences.

●Research objective

Life phenomena emerge from an ordered, dynamic network composed of biomolecules and chemical reactions. Biomolecules are the hardware of life, and their blueprints are encoded in DNA. Genetic code expansion (Schultz, Science 2001, 292, 498) and gene editing (Charpentier & Doudna, 2020 Nobel Prize in Chemistry) have made it possible to artificially rewrite this hardware at the animal/plant level, leading to major innovations in the life science. On the other hand, protein function is also determined by chemical reactions, called post-translational modifications (PTMs). PTMs can be regarded as the software of life.

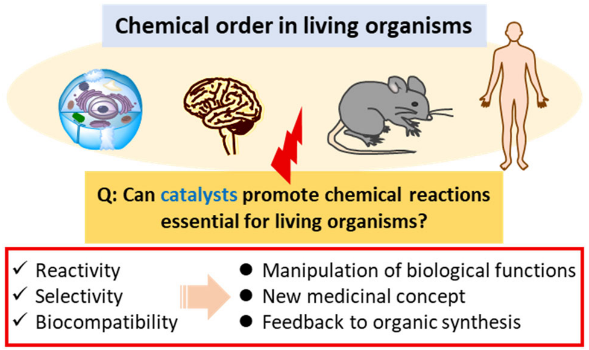

Figure 1. Research outline

If we can create chemical catalysts that substitute, complement, or even surpass enzyme functions in the biological environment, we will be able to directly manipulate the chemical order in living organisms, which will lead to the creation of new fundamental technologies in chemical biology, and ultimately to the concept of disease treatment (Figure 1). Current PTM manipulation relies on enzyme inhibitors (e.g., kinase inhibitors) and is highly restricted. When the target catalysis technology is obtained in this research, it will be possible to manipulate the flow of life from upstream (gene sequence and transcriptional control) through midstream (protein function control) to downstream (protein degradation) as desired and improve biological functions in a manner complementary to genetic code expansion and gene editing. Chemistry, especially catalysis, is a powerful tool for establishing this unexplored technology.

The purpose of this research is to create chemical catalysts that directly intervene in the chemical order of living organisms, and to create technologies for manipulating biological functions and medicinal concepts using these catalysts (Figure 1). The design and principle of the chemical catalysts established in this research will also dramatically advance synthetic organic chemistry in flasks. Therefore, this research will open up new fields of science in both physical and life sciences through the creation of chemical catalysts that work in the biological environment.

Expected Research Achievements

● Chemical catalysts that intervene in chromatin epigenetics

Chromatin is composed of DNA and histone proteins, which undergo various PTMs such as acetylation, methylation, phosphorylation, and glycosylation to regulate DNA transcription (chromatin epigenetics, Figure 2-1). Considering the unique effects of various PTMs introduced into each amino acid residue and the synergistic effects of PTMs, the chemical order of PTMs (epigenome) is responsible for the diverse gene expression patterns of organisms. In this research theme, we aim to develop chemical catalysts that intervene in epigenetics in living cells and animals, and to develop transcriptional regulation and anti-tumor effects by these catalysts.

● Chemical catalysts that degrade and remove amyloid proteins

Amyloid diseases such as Alzheimer disease (AD) and TTR amyloidosis (TTRA) are thought to be caused by the toxicity of amyloids, abnormal protein aggregates. We will create chemical catalysts that can degrade and remove amyloids accumulated in the animal body (Figure 2-2). Utilizing the knowledge of Aβ amyloid-selective photooxygenation catalysts already developed (reviewed in Org. Biomol. Chem. 2021, 19, 10017), we will extend its application to tau and TTR amyloids. This will establish the foundation for small molecule drugs for amyloid diseases.

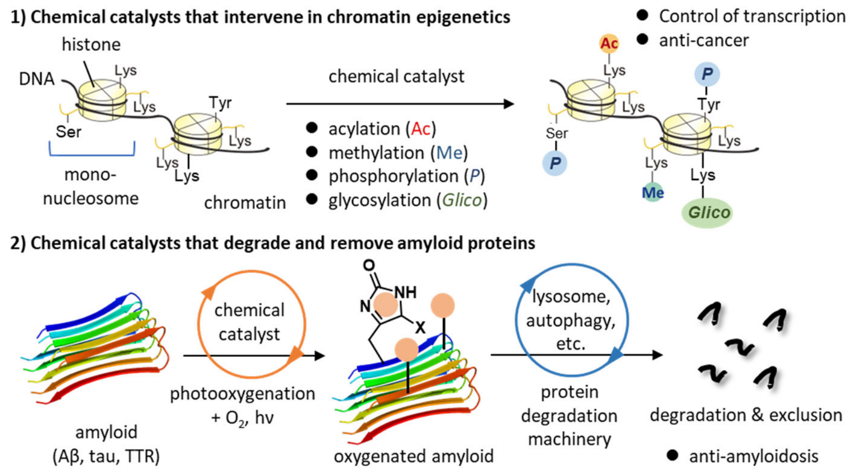

Figure 2. Our goal

Our research aims to build a molecular technology platform to realize a future society in which everyone in the world has equal access to treatment for quality of life and against life-threatening diseases by introducing the concept of catalysis in medicine.

Homepage Address, etc.	https://gousei.f.u-tokyo.ac.jp/index.html