【Grant-in-Aid for Specially Promoted Research】

Development of organic chemistry targeting biomolecules in live animals

Principal Investigator	Kyoto University, Graduate School of Engineering, Professor HAMACHI Itaru Researcher Number:90202259
Project Information	Project Number : 23H05405 Project Period (FY) : 2023-2027 Keywords : multimolecular crowding biosystems, biochemistry, brain organic chemistry, ligand-directed chemistry, chemical biology

Purpose and Background of the Research

●Outline of the Research

The purpose of this research project is to establish a rational approach to "organic chemistry in live animals " that enables analysis and functional control of proteins and lipids in their native habitats with minimal genetic manipulation. In particular, we attempt to develop new organic chemistry-based methods that can transform targeted biomolecules with high selectivity and efficiency in the animal brain and cancer tissues where a variety of molecules are mixed and distributed heterogeneously in multiple spatial compartments/domains such as intracellular organelles and distinct tissue areas (Fig. 1). Based on our previous achievements and preliminary findings relying on the originally developed ligand-directed chemistry (Fig. 2: Nature Chembio., 2009), we aim to construct valuable guidelines of a rational chemical strategy for selective labeling of proteins and lipids and create a new approach that allows the reaction-based fixation of information of target molecules (abundance, localization, interaction, etc.) for taking their snapshots in vivo. Using new findings gained from these efforts, we also challenge to develop novel covalent inhibitors targeting oncogenic proteins/enzymes. Overall, this is a unique and pioneering academic research that may promote a paradigm shift from traditional “organic chemistry in flasks” to “organic chemistry in multimolecular crowding bio-systems”. This research could also contribute to brain and neuroscience by providing innovative chemical biology tools and facilitate covalent drug discovery for cancer therapy.

Establishment of "organic chemistry in live animals" that enables analysis and functional control of proteins and lipids in their native habitats.

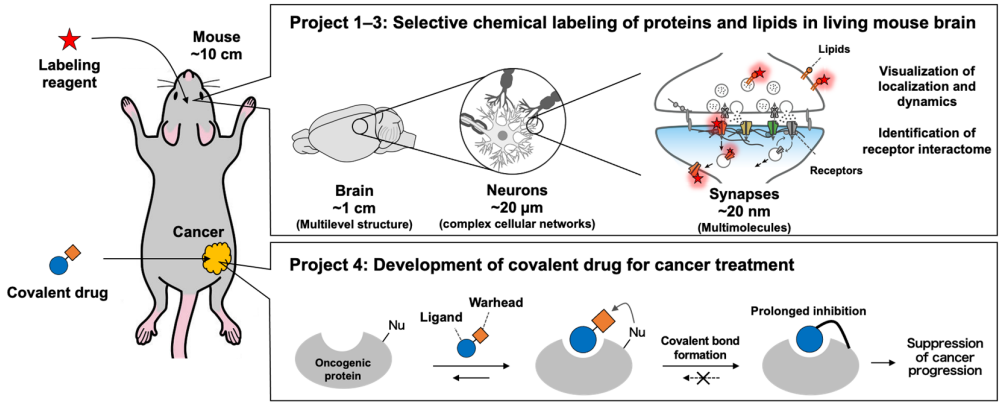

Figure 1. Conceptual illustration of this research project

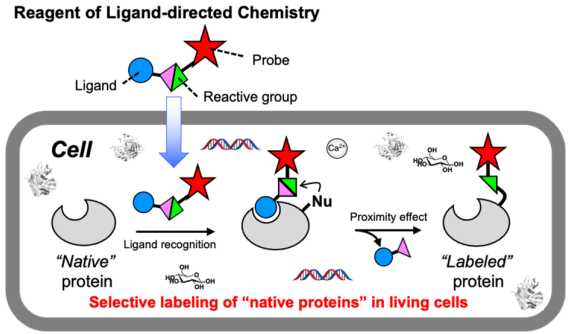

Figure 2. Ligand-directed chemistry

Expected Research Achievements

Proteins and lipids are key biomolecules that precisely regulate biological processes. Therefore, the analysis and control of their functions are of great importance not only in basic science, but also in medical applications and human health. With the recent advancement of molecular biology and chemical biology, it is now well recognized that in vitro analysis is not sufficient to decipher real figures of biomolecules due to the loss of their spatio-temporal information. Instead, high-precision analysis in their natural contexts, such as living cells, tissues, and organisms, is becoming increasingly important. In this research project, we carry out the following four projects, that is (i) Establishment of molecular design guideline of chemical reagents for neurotransmitter receptors labeling in live mouse brain via ligand-directed chemistry (Fig. 3), (ii) Development of a new proximity labeling method for comprehensive identification of proteome networks enabled in the live brain (Fig. 4), (iii) Selective lipid and its metabolites labeling in live cell and in vivo, and (iv) Development of new covalent drugs targeting cancer (Fig. 5). Thereafter, we plan to integrate the obtained experimental (both positive and negative) data and findings, so that we are able to establish a rational approach leading to in live animal organic chemistry.

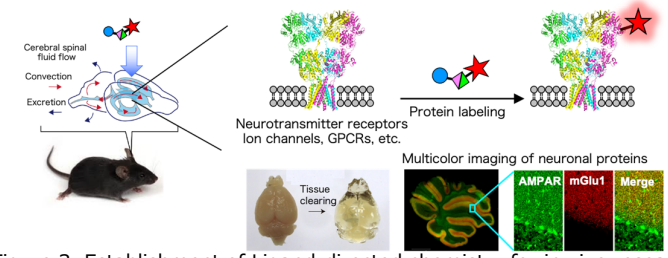

Figure 3. Establishment of Ligand-directed chemistry for in vivo research

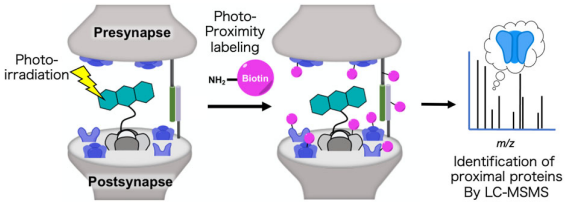

Figure 4. Photo-triggered proximity labeling

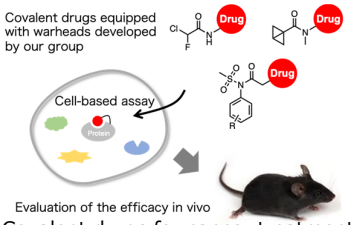

Figure 5. Covalent drugs for cancer treatment

Homepage Address, etc.	Hamachi Laboratory website http://www.sbchem.kyoto-u.ac.jp/hamachi-lab/