	Head Investigator	The University of Tokyo, Graduate School of Pharmaceutical Sciences, Professor MURATA Shigeo Researcher Number:20344070
	Research Area Information	Number of Research Area : 23A301 Project Period (FY) : 2023-2027 Keywords : protein degradation, mass spectrometry, TPD, ubiquitin

Purpose and Background of the Research

●Outline of the Research

Proteins are vital to living organisms, and the functions of cells and tissues are determined by the proteome, which consists of thousands of different proteins. Protein synthesis follows genetic information, but the correlation between mRNA, translation, and protein levels is weak. Post-translational regulation, especially proteolysis, plays a critical role. Proteins vary in lifetime, from minutes to years. Existing laws explain some protein lifetimes, but most remain elusive. The regulation of individual protein lifetime is extensively studied in key biological events, but only limited aspects of protein dynamics are observed. During major functional transformations, protein composition undergoes significant reconfiguration, affecting degradation and synthesis. The mechanisms behind selective and large-scale proteolysis in biological and pathological contexts are unknown. To unravel these mysteries, we'll explore new principles of protein lifetime regulation, establish techniques for in-depth lifetime measurements, and elucidate regulatory mechanisms that drive compositional changes. We'll integrate sequence, modification, and 3D structure information to study protein lifetime regulation factors. We'll also develop technologies for precise protein lifetime control and methods to manipulate cellular and tissue functions. This interdisciplinary research aims to understand, measure, and manipulate protein lifetime mechanisms to achieve a deep understanding of biological phenomena and pathological conditions.

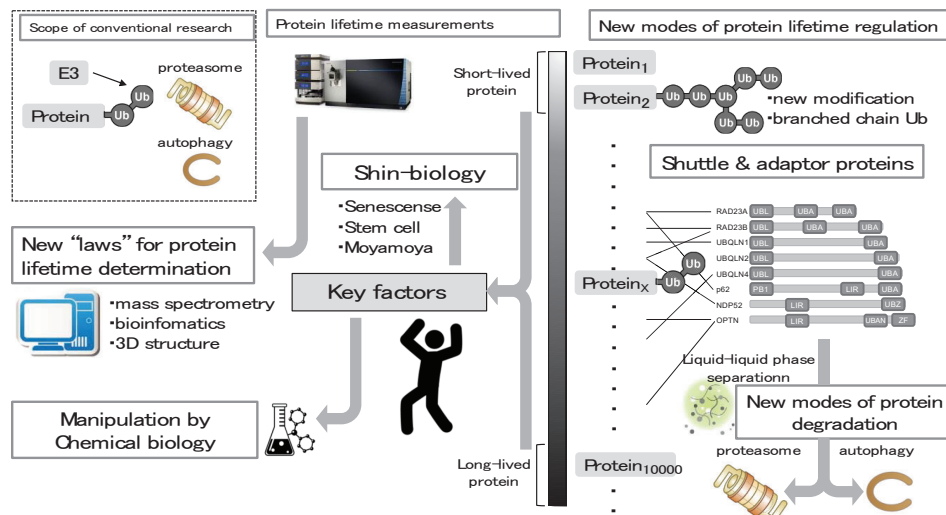


Figure 1. Schematic representation of our research concept

Expected Research Achievements

This research area brings together researchers in proteolysis, analytical chemistry, bioinformatics, and chemical biology to elucidate the molecular mechanisms that regulate protein lifetimes and understand the principles that govern protein lifetimes. The following three projects will be pursued.

- **Biology of Protein Lifetime Dynamics** When a cell undergoes a major change in function, it must undergo a major remodeling of its protein composition through protein degradation. A comprehensive understanding of protein half-life is an important clue to what events occur in cells. Proteome-wide measurement of protein lifetime, determination of the subsets that fluctuate, and elucidation of their regulatory mechanisms will lead to a new understanding of life phenomena.
- **Mechanisms of Protein Lifetime Determination** New modes of degradation, such as functional amplification by branched-chain ubiquitination, selection of degradation substrates by the diversity of shuttle molecules, and proteolysis enhancement by liquid-liquid phase separation, have been revealed, and it has become clear that protein lifetimes are regulated in a multilayered and complex manner.
- **Measurement and Manipulation of Protein Lifetime** We will establish techniques to measure protein lifetimes in high depth and elucidate the regulatory mechanisms of protein degradation that drive large-scale changes in protein composition in various physiological and pathological environments by integrating information. We will also create a new technology to control protein lifetimes.

The perspective of "protein lifetime studies" created in this research area will have a great impact not only on basic research but also on all life sciences and in the medical field, considering that protein lifetime regulation is involved in all life phenomena.

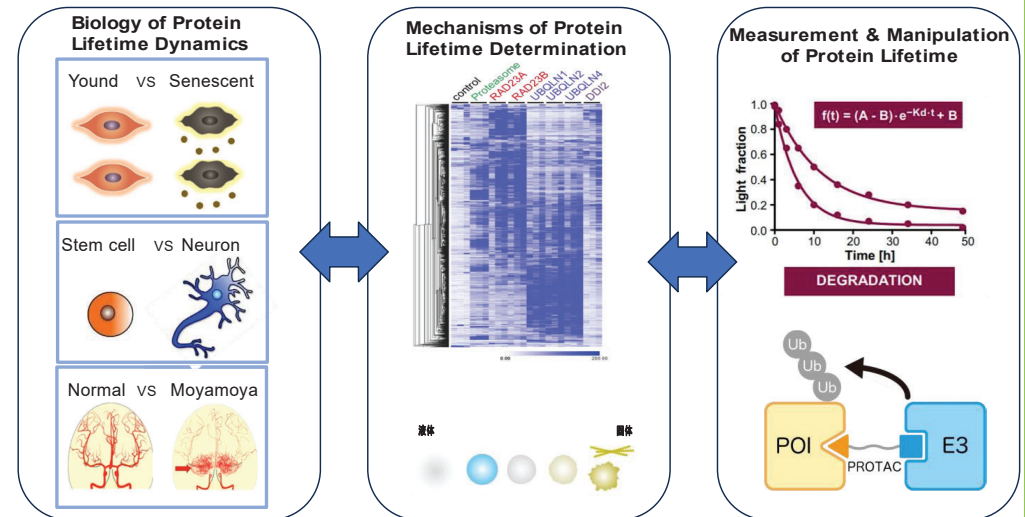


Figure 2. Strategies for "Protein lifetime studies"