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

Frontiers of Rhodopsin Science Pioneered by the Study of Novel Molecules

Principal Investigator	The University of Tokyo, Institute for Solid State Physics, Associate Professor INOUE Keiichi	Researcher Number : 90467001
Project Information	Project Number : 25H00424 Keywords : Rhodopsin, Optogenetics, Photochemistry, Photobiology, Advanced spectroscopy	Project Period (FY) : 2025-2029

Purpose and Background of the Research

●Outline of the Research

Rhodopsins are a photoreceptive membrane proteins using a retinal chromophore. In 20th century, the molecular mechanisms underlying their biological functions have been extensively studied in a few representative proteins, particularly visual rhodopsin of animals and H^+-pumping bacteriorhodopsin of archaea. However, with the rapid advances in genomic analysis, a growing number of molecules with novel functions that cannot be explained by existing theories have been discovered.

In this study, **we investigate these novel rhodopsins from four perspectives—function, structure, measurement, and theory—in a multifaceted manner. Through this effort, we seek to elucidate the molecular mechanisms** by which the isomerization of a single chemical bond in retinal can precisely regulate the structural dynamics of a 5,000-times larger protein moiety, across an extraordinary timescale spanning 19 orders of magnitude—from femtoseconds to days. By integrating the insights gained from various rhodopsins at a high level, we aim to uncover the fundamental principles that govern new molecular functions (Fig. 1).

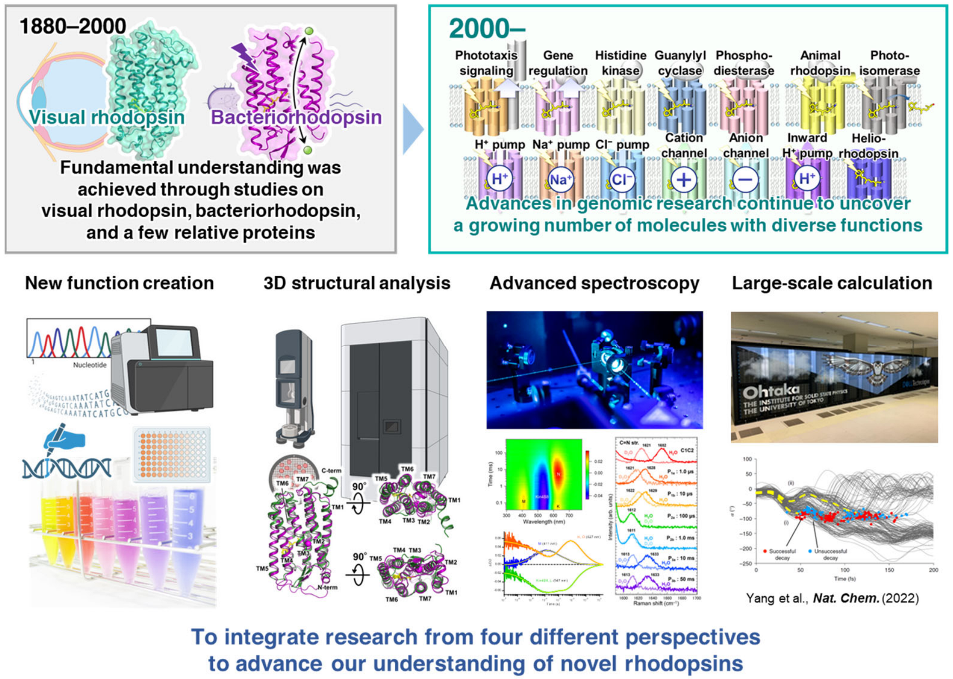


Figure 1. Outline of the research

●Research Framework

This study, led by **Inoue** (PI, Univ. Tokyo), aims to establish an international collaborative framework with **Kato** (Co-I, Univ. Tokyo), **Kuramochi** (Co-I, Osaka Univ.), **Béjà** (Technion), and **Olivucci** (Univ. Siena/Bowling Green State Univ.). The project seeks to achieve a fundamental understanding of the core molecular mechanisms underlying the biological function of diverse rhodopsins from four perspectives: function, structure, measurement, and theory (Fig. 2).

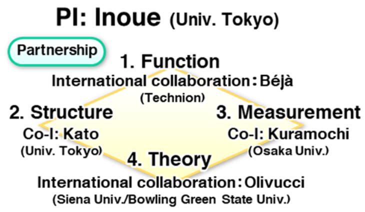


Figure 2. Research framework

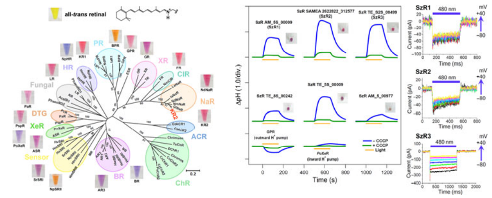
Expected Research Achievements

●Exploration and Development of Novel Functions

Advances in genome analysis have led to the discovery of new functional rhodopsins. In this study, we explore molecules with novel functionalities and establish a foundation for the development of highly applicable artificial rhodopsins (Fig. 3).

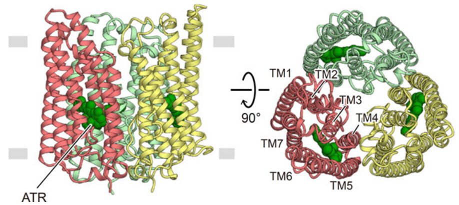
●Three-dimensional Analysis of New Rhodopsins

To understand the mechanisms underlying the photoreceptive functions of rhodopsins, we will determine the three-dimensional structures of rhodopsins with novel functions or properties at atomic resolution using cryo-electron microscopy (Fig. 4).



Karasuyama et al., ***Sci. Rep.*** (2018);
Inoue et al., ***Sci. Adv.*** (2020)

Figure 3. New molecule exploration/development



Kishi et al., ***Cell*** (2022); Tajima et al., ***Cell*** (2023)

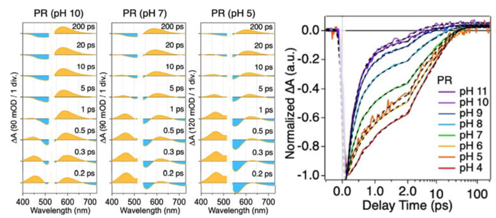
Figure 4. Three-dimensional structural analysis

●Advanced Spectroscopy

Rhodopsins exhibit photoreactions spanning a wide temporal range—from femto-seconds to days—following the retinal isomerization. We employ advanced spectro-scopy to observe dynamic events occurring at different structural levels (Fig. 5).

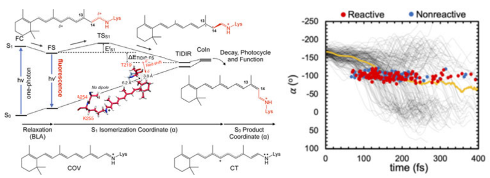
●Large-scale Theoretical Calculation

Based on the three-dimensional structural information revealed by cryo-EM, we will perform large-scale theoretical calculations to obtain insights that are difficult to access experimentally, thereby achieving a complementary understanding (Fig. 6).



Chang et al., ***Angew Chem Int. Ed.*** (2022)

Figure 5. Advanced spectroscopy of rhodopsins



Inoue et al., ***Nat. Commun.*** (2019);
Herasymenko et al., ***Chem. Sci.*** (2024)

Figure 6. Large-scale calculations of rhodopsins

Homepage Address, etc.	Lab homepage: https://inoue.issp.u-tokyo.ac.jp/ X (Twitter): https://x.com/LabInoue