Usage Report for Fiscal Year 2025

**Project Title:**

# Ligand-Protein, Protein-Lipid and Lipid-Lipid Interactions

**Name:**

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1. Background and purpose of the project, relationship of the project with other projects

Biological membranes form the primary interface between the intracellular milieu and the external environment, establishing a selective barrier that maintains cellular integrity and organization. In addition to this boundary function, lipid bilayers compartmentalize the cell into specialized regions, enabling spatial regulation of biochemical processes. While membrane-associated proteins mediate many functional activities, the structural framework of biological membranes consists of chemically diverse lipids that critically influence membrane properties and cellular function.

Cellular function requires regulated exchange of molecules and transmission of information across this lipid barrier. Membrane-embedded proteins, including receptors and transporters, mediate these processes through lipid–protein interactions that support signaling complexes. Lysophospholipids have emerged as important bioactive mediators that regulate cellular responses through receptor-dependent pathways, and their stereochemical configuration plays a key role in receptor recognition and downstream signal transduction.

2. Specific usage status of the system and calculation method

Quantum mechanics (QM) simulations utilizing the Gaussian 09 and Gaussian 16 software package have been performed. Molecular dynamics (MD) simulations were performed utilizing the NAMD software package and results were visualized with VMD.

3. Result and Conclusion

Molecular dynamics simulations revealed stereochemistry-dependent interactions of *lyso*-phosphatidyl-β-D-glucoside (LysoPtdGlc) with the GPR55 receptor. The G3P-configured *R*-LysoPtdGlc remained stably bound within the ligand-binding pocket of the GPR55–$G\alpha_{13}$ complex, whereas the S-configured stereoisomer did not exhibit stable binding. Functional assays demonstrated that *R*-LysoPtdGlc induced axonal chemorepulsion consistent with GPR55–$G\alpha_{13}$ signaling, while *S*-LysoPtdGlc unexpectedly triggered chemoattractive responses mediated through GPR55–$G\alpha_s$. In nociceptive neurons, these stereoisomer-specific effects translated into distinct physiological outcomes, as intrathecal administration of *R*-LysoPtdGlc increased mechanical sensitivity in a GPR55-dependent manner, whereas *S*-LysoPtdGlc showed no comparable effect. Together, these findings demonstrate that the stereochemical configuration of LysoPtdGlc determines receptor engagement, downstream signaling pathway selection, and functional biological responses.

4. Schedule and prospect for the future

To-date, the fundamental principles governing lipid–lipid and lipid–protein interactions remain incompletely characterized. To advance a detailed mechanistic understanding, we integrate QM and MD simulations with experimental data to elucidate the structural and dynamic features underlying these processes.

**Fiscal Year 2025 List of Publications Resulting from the Use of the supercomputer**

**[Paper accepted by a journal]**

- A.T. Guy, Y. Kohro, K. Kano, X. Huang, L. Chen, N. Ooashi, M. Inoue, N. Ishii, T. Yamashita, Y. Hirabayashi, I. Imayoshi, I. Matsuo, P. Greimel, M. Tsuda, H. Kamiguchi; "Lysophospholipid stereoisomers exert distinct GPR55-mediated functions via different Gα subunits" *The Journal of biological chemistry* **2025**, 301(7), 110324. doi: 10.1016/j.jbc.2025.110324

**[Conference Proceedings]**

**[Oral presentation]**

**[Poster presentation]**

**[Others (Book, Press release, etc.)]**