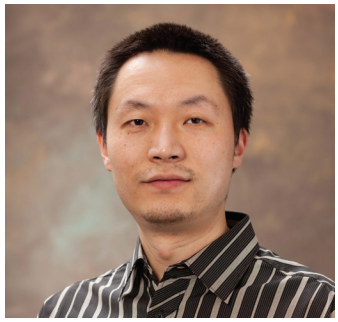


## Jian Hu

## Membrane Protein Structure-Function Characterization

**Associate Professor**

(b. 1974)

B.S., 1999,
Peking Univ.;

Ph.D., 2004,
Peking Univ.;

Postdoctoral Research Assoc., 2005-07,
Florida State Univ. and National High Magnetic Field Laboratory;

Postdoctoral Research Assoc., 2008-09,
Yale Univ.;

Associate Research Scientist, 2010-13,
Yale Univ.

517-353-8680


Selected Publications


*Structural insights of ZIP4 extracellular domain critical for optimal zinc transport*, Zhang, T., Sui, D., Hu, J., *Nature Communications* **2016**, *7*, 11979.

*Structural basis for regulation of human calcium-sensing receptor by magnesium ions and an unexpected tryptophan derivative co-agonist*, Zhang, C., Zhang, T., Zou, J., Miller1, C.L., Gorkhali1, R., Yang, J, Schilmiller, A., Wang, S., Huang, K., Brown, E.D., Moremen, K.W., Hu, J. and Yang, J.J., *Science Advances* **2016**, *2*, e1600241.

*Resolution of Structure of PIP5K1A Reveals Molecular Mechanism for Its Regulation by Dimerization and Disheveled*, Hu, J., Yuan, Q., Kang, X., Qin, Y., Li, L., Ha, Y., and Wu, D., *Nature Communications* **2015**, *6*, 8205.

*METALLOPROTEINS. A tethered niacin-derived pincer complex with a nickel-carbon bond in lactate racemase*, Desguin, B., Zhang, T., Soumillion, P., Hols, P., Hu, J., Hausinger, R.P., *Science* **2015**, *349(6243)*, 66-9.

*The Crystal Structure of GxGD Membrane Protease FlaK*, Hu, J., Xue, Y., Lee, S. and Ha, Y., *Nature* **2011**, *475(7357)*, 528-531.

*Ligands Binding on the Interhelical Loop of CorA, a Magnesium Transporter from* Mycobacterium Tuberculosis, Hu, J., Sharma, M., Qin, H., Gao, F.P. and Cross, T.A., *Journal of Biological Chemistry* **2009**, *284(23)*, 15619-15628.

*Structural Biology of Transmembrane Domains: Efficient Production and Characterization of Transmembrane Peptides by NMR*, Hu, J., Qin, H., Li, C., Sharma, M., Gao, F.P. and Cross, T.A., *Protein Science* **2007**, *16(10)*, 2153-65.


Hu laboratory has broad interest in structural biology of membrane proteins and biomolecules involved in metal homeostasis. By applying multidisciplinary approaches, including X-ray crystallography, NMR and other biochemical/biophysical/cell biological methods, we are aiming to clarify the detailed molecular mechanism of how the complicated biological system works at atomic level. Currently, we have two major projects and several collaborative projects ongoing.

***Zinc Transporter - ZIP family.*** Zirt-Irt like protein (ZIP) family consists of a group of integral membrane proteins playing crucial roles in zinc and iron transport across cell membrane. In human genome, the fourteen members are involved in a variety of biological processes and associated with human diseases. Our current research is focused on ZIP4, a representative member in the mammalian ZIP family. ZIP4 is exclusively responsible for zinc uptake from intestine under normal conditions and ZIP4 mutations lead to a lethal genetic disorder, Acrodermatitis enteropathica (AE). ZIP4 is also upregulated on pancreatic cancer cells and essential for the growth of these extremely aggressive cells. In this project, our aims include: (1) Solve the crystal structure of ZIP4; (2) Elucidate zinc transport mechanism; and (3) Clarify the molecular mechanism of zinc-induced ZIP4 endocytosis. This work will also provide a structural framework for rational drug design against pancreatic cancer and other relevant diseases. (***Figure 1***)

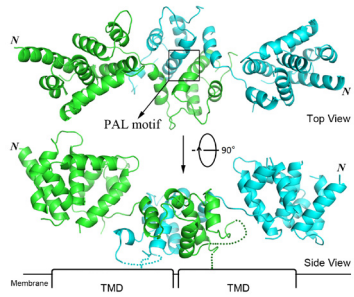


***Figure 1. Topology of ZIP4. The extracellular domain of ZIP4 is shown in cartoon mode. (PDB: 4X82)***

***Lipid Kinase – PIPK family.*** Phosphatidylinositol phosphate kinase (PIPK) family is a central player in the metabolism of phosphoinositides (e.g., PIP2), which are crucial signaling molecules in numerous biological processes. It has also been proposed that PIPKs are potential drug targets for human diseases, including a variety of cancers, diabetes, inflammations and chronic pain. The aim of our research is to establish the catalytic mechanism of the interfacial reaction, the molecular mechanism of substrate specificity, and particularly, the regulation mechanism by their binding partners and lipid molecules. We are also interested in structure-based drug design. (***Figure 2***)

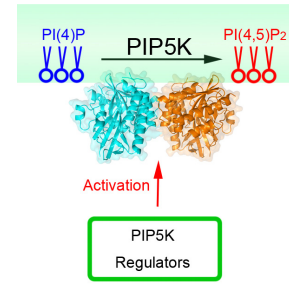


***Figure 2. Function and regulation of PIP5K.***

***Collaborative projects:***

***Lar proteins.*** LarA is a nickel-dependent racemase which catalyzes the inversion of the stereochemistry of lactic acid. The activity of LarA absolutely depends on a newly-discovered cofactor which is biosynthesized by LarB, LarC and LarE. We are working with Dr. Robert Hausinger at MMG to (1) clarify the catalytic mechanism of LarA; and (2) define the biosynthesis pathway of this novel Ni(II) pincer cofactor. (***Figure 3***).

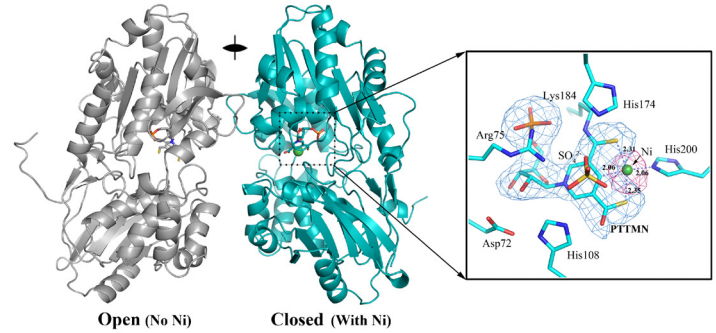


***Figure 3. Crystal structure of $LarA_{Lp}$ (left) and the Ni(II)-containing catalytic center (right). The Ni(II) pincer complex, composed of the organic compound PTTMN and a bound Ni(II), is a novel cofactor discovered recently. (PDB: 5HUQ)***

***Calcium Sensing Receptor.*** Calcium sensing receptor (CaSR) is a G protein-coupled receptor (GPCR) and a central player in calcium homeostasis in our body. Through collaboration with Dr. Jenny Yang (Georgia State University) and Dr. Edward Brown (Harvard University), we are conducting structural biology studies on CaSR, particularly on the extracellular domain (ECD) where metals/ligands bind and many disease-causing mutations occur. Our goal is to establish a structural framework for better understanding the activation mechanism by natural ligands, which is crucial for the design of agonist and antagonist of CaSR against severe human diseases. (***Figure 4***)

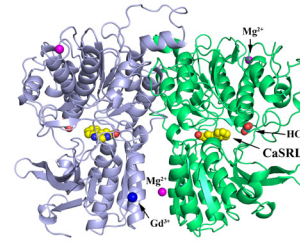


***Figure 4. Crystal structure of the extracellular domain of human Calcium Sensing Receptor. (PDB: 5FBK and 5FBH)***