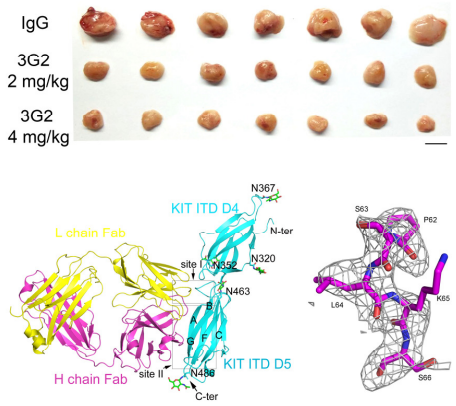
# Structural pharmacology of cell surface receptors: from the structure and beyond the structure

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## Abstract (300 word limit)

Our research marches towards a newly emerging field in pharmacology—structural pharmacology, and focuses on structural pharmacology of cell surface receptors (CSRs) that are associated with cancer and neuropsychiatric diseases, such as receptor protein tyrosine phosphatases (RPTPs) [1, 2], CASPR2 [3], plexins [4], receptor tyrosine kinases (RTKs) [5, 6], and *etc*. The term of *structural pharmacology* is seen in some web pages, but seldom used in peer-reviewed journals. The usage of *structural pharmacology* in the title of a very recent research article, jointly published by Harvard Medical School and University of Oxford (*Nature.* 2019 Jan; 565(7740):454-459), may signify the beginning of new era in the field of structural pharmacology. In this talk, I would like to share our two research stories. One is about signaling mechanism of autism-associated signal complex SALM/LAR-RPTP. Recently, we have reported crystal structures of human SALM5 LRR-Ig in isolation and in complex with human PTPδ Ig1–3 (with mini exon insert MeA deleted) [1, 2]. Our study presents a structural template for the SALM family and first time reveals a mechanism underlying how a synaptic adhesion molecule directly induces *cis*-dimerization of LAR-RPTPs into higher-order signaling assembly. Our structural study also opens an avennue for screening molecular tool modulators targeting the SALM/LAR-RPTP signaling complex[1]. The other one is about KIT ITD$^{502\text{-}503}$, an oncogenic mutant with internal tandem duplication (ITD) of Ala502 and Tyr503 in KIT ectodomain, which occurs in 10% of gastrointestinal stromal tumor patients. Based on structural mechanism of KIT and other class III RTKs' signaling, we have found 3G2, a monoclonal antibody that selectively recognizes KIT ITD$^{502\text{-}503}$ and exhibits high potency in inhibiting growth of KIT ITD$^{502\text{-}503}$-transformed cells *in vitro* and in vivo. Our crystal structure of KIT ITD$^{502\text{-}503}$ in complex with 3G2 (PDB entry: 6A14) clearly shows that KIT ITD$^{502\text{-}503}$ is a druggable target.

## Image




## Recent Publications

1. **Liu Heli***. Synaptic organizers: synaptic adhesion-like molecules (SALMs). ***Current Opinion in Structural Biology***. 2019 Feb 8; 54:59-67. (Invited review) (hereinafter *corresponding author)
2. Lin Z, Liu J, Ding H, Xu F, **Liu Heli***. Structural basis of SALM5-induced PTPδ dimerization for synaptic differentiation. ***Nature Commun.*** 2018 Jan 18; 9(1):268
3. Liang W#, Zhang J#, Saint-Martin M#, Xu F, Noraz N, Liu J, Honnorat J*, **Liu Heli***. Structural mapping of hot spots within human CASPR2 discoidin domain for autoantibody recognition. ***J Autoimmun.*** 2019 Jan; 96:168-177 (#equal contribution)
4. **Liu Heli**, Juo ZS, Shim AH, Focia PJ, Chen X, Garcia KC, He X*. Structural basis of Semaphorin-Plexin recognition and viral mimicry from Sema7A and A39R complexes with PlexinC1. ***Cell***. 2010 Sep 3; 142(5):749-61
5. **Liu Heli**, Leo C, Chen X, Wong BR, Williams LT, Lin H, He X*. The mechanism of shared but distinct CSF-1R signaling by the non-homologous cytokines IL-34 and CSF-1. ***Biochim Biophys Acta***. 2012 Jul; 1824(7):938-45
6. **Liu Heli**#, Chen X#, Focia PJ, He X*. Structural basis for stem cell factor-KIT signaling and activation of class III receptor tyrosine kinases, ***The EMBO Journal***, 2007.2.7, 26(3): 891-901 (#equal contribution)



## Biography (150 word limit)

Heli Liu focuses on structural pharmacology of cell surface receptors and tries to solve pharmacological problems, such as target validation, at the structural level. On one hand, using a range of methodologies including X-ray crystallography, molecular biology and biophysics, he tries to answer some basic scientific questions, i.e., how CSRs (potential drug targets) perform their transmembrane signaling process at the atomic resolution level, how their cross-talk constitutes a complex signaling network for cellular events such as synaptic formation, and how their dysfunction is associated with human diseases. On the other hand, resorting to structural biology, chemical genetics and conventional hybridoma technologies, he endeavors to develop powerful antagonistic or agonistic small molecules or proteins (including monoclonal antibodies) that serve as tool modulators to fulfill target validation for CSRs. Our research aims to validate new drug targets and promote "precision medicine" development. Email: liuheli@hsc.pku.edu.cn