BIOGRAPHICAL SKETCH

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NAME: Chen Shen

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POSITION TITLE: Postdoctoral Fellow in Boston Children's Hospital/Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yangzhou University, Yangzhou, China	B.Sc.	2010.7	Chemical Education
Peking University Shenzhen Graduate School, Shenzhen, China	PhD	2015.7	Physical Chemistry
Peking University Shenzhen Graduate School, Shenzhen, China	Postdoc	2017.1	Structural Biology

A. Personal Statement

After receiving his B.S. degree in chemical education, Chen was accepted into Peking University for graduate studies. From then on, He was attracted to the mysterious biological world and his Ph.D. research was aimed at structures and functions of regulatory proteins involved in tumor cell proliferation and tumor cell death. He solved the crystal structures of both caspase-8 death effector domain monomer and its domain-swapped dimer, which provide implications for the activation mechanism of this important initiator caspase. He received the Ph.D. degree in July of 2015 but stayed in his Ph.D. lab for a short period to complete a few manuscripts. After one year and a half, he arrived in Professor Hao Wu's laboratory in Boston in February of 2017. Here, he got good scientific environment to continue his studies related with innate immune research and death domain signaling. He extensively collaborated with postdocs and students in the lab to accomplish several papers involved in TLR signaling and NLR signaling. He initiated a new project on mechanistic studies for the activation of the multifaceted innate immune regulator NLRP6. He majorly focused on the structural study of auto-inhibited and activated NLRP6 inflammasome, as well as the molecular mechanisms of ligand and NLRP6 interaction in innate immune system.

B. Positions and Honors

2015-2017 Postdoctoral Fellow, Peking University Shenzhen Graduate School, Shenzhen, China
2017- Postdoctoral Fellow, Boston Children's Hospital and Harvard Medical School, Boston, MA

Honors

The progress of IKA scholarship (2014)
Outstanding Student of Peking University (2013)
First-class scholarship in YZU (2006-2009)
CRI Irvington Postdoctoral Fellowship (2019.1)

C. Contributions to Science

1. The Ph.D. period

Caspase-8 is a central molecule involved in different innate immune signaling pathways like extrinsic apoptosis, necroptosis, and inflammation. It is activated through a proximity-induced dimerization mechanism. Although the catalytic domain of caspase-8 is solved decades ago, the structural information of the pro-domain (tandem death effector domain - DED) is hindered by its highly aggregation propensity.

a. Chen solved the high-resolution crystal structure of the caspase-8 DED monomer. Based on sequence alignment with DED homologs like MC159 from the poxvirus Molluscum contagiosum *virus and* further analysis of solubility using bioinformatics tools, He performed rational site-directed mutagenesis on the caspase-8 DED domain. He identified the I128D mutant out of four candidate mutants that dramatically changed the solubility of caspase-8. With an additional F122A mutation, He was able to obtain high quality crystals to solve the monomeric caspase-8 DED structure. Besides its implication in death inducing signaling complex assembly, this work provided a general solution for dealing with the crystallization of low-solubility death domain superfamily proteins.

b. He solved the crystal structure of the caspase-8 DED domain-swapped dimer. Because a dimerized or oligomerized form of caspase-8 DED can provide insights into caspase-8 activation, He tried to figure out how the N-terminal DED induces proximity of the C-terminal caspase-8 catalytic domain. Despite the low expression level for the DED mutant construct F122A, He successfully obtained diffraction-quality crystals by extensive optimization of purification and crystallization steps. The dimeric structure of caspase-8 DED revealed an unprecedented domain-swapped form of a death effector domain, which may represent a new paradigm for activation of initiator caspases.

Chen Shen, Hong Yue, Jianwen Pei, Xiaomin Guo, Tao Wang, Junmin Quan. Crystal structure of the death effector domains of caspase-8. *BBRC* (Biochemical and Biophysical Research Communications). 2015, **463**, 297-302.

Chen Shen*, Jianwen Pei*, Xiaomin Guo*, Lu Zhou, Qinkai Li, Junmin Quan. Structural basis for the dimerization of caspase-8 death effector domains. *Sci Rep*. 2018, **8**, 16723.

2. The postdoctoral period

The nucleotide-binding domain and leucine rich repeat containing (NLR) family Pyrin domain (PYD) containing protein 6 (NLRP6) is a multifunctional protein in innate immune signaling. NLRP6 has been shown to sense metabolites from microbiota for inflammasome activation to shape the intestinal microenvironment. This protein can also regulate anti-viral signaling through sensing viral RNA with co-factor Dhx15. However the molecular mechanism still remains elusive due to the limited structural and biochemical studies of this protein. He solved the cryo-EM structure of the NLRP6 PYD domain filament. The study showed the full length NLRP6 inflammasome activation relies on the filamentous assembly of the N-terminal PYD domain. Simultaneously, N-terminal PYD also has symmetry compatibility with ASC Pyrin domain, indicating a unified assembly mechanism for NLRP inflammasomes. On the other hand, He was curious about the different assembly mode among different NLR proteins. He took part in the study of elucidating the molecular details of NLRC4 CARD and ASC CARD assembly.

Chen Shen, Alvin Lu, Wenjun Xie, Jianbin Ruan, Roberto Negro, Tian-Min Fu and Hao Wu. Molecular mechanisms for NLRP6 inflammasome assembly and activation. *PNAS*. 2019, **116**, 2052-2057.

Chen Shen, Humayun Sharif, Shiyu Xia, Hao Wu. Structural and mechanistic elucidation of inflammasome signaling by cryo-EM. *Curr. Opin. Struc. Biol*. 2019, https://doi.org/10.1016/j.sbi.2019.03.033.

Yang Li*, Tian-Min Fu*, Alvin Lu, Kristen Witt, Jianbin Ruan, **Chen Shen** and Hao Wu. Cryo-EM structures of ASC and NLRC4 CARD filaments reveal a unified mechanism of nucleation and activation of caspase-1. *PNAS*. 2018, **115**, 10845-10852.

Elucidation the signal transduction mechanism of Toll-like receptor pathway. Chen joined the structural study of the assembly of full length Myddosome. Meanwhile, he tried different biochemical approached to understand the ubiquitin transfer mechanisms facilitated by TRAF6.

Li Wang, Qi Qiao, Ryan Ferrao, **Chen Shen**, John M. Hatcher, Sara J. Buhrlage, Nathanael S. Gray and Hao Wu. Crystal structure of human IRAK1. *PNAS*. 2017, **114**, 13507-13512.

Tianmin Fu*, **Chen Shen***, Qiubai Li, Pengfei Zhang and Hao Wu. Mechanism of Ubiquitin Transfer Promoted by TRAF6. *PNAS*. 2018, **115**, 1783-1788. (* contribute equally)

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https://www.ncbi.nlm.nih.gov/myncbi/1DgCi89OgUJQW/bibliography/public/