BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Peng, Shuxia

eRA COMMONS USER NAME (credential, e.g., agency login): S.PENG

POSITION TITLE: Senior Research Scientist

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Peking University Health Science Center, Beijing, China	Bachelor of Medicine	09/1999	07/2004	Nursing
Institute of Biophysics, Chinese Academy of Sciences (CAS), Beijing, China	Ph.D	09/2004	07/2011	Biochemistry and Molecular Biology
Oklahoma State University, Stillwater, OK, USA	Postdoctoral Fellow	03/2015	03/2019	Biochemistry and Molecular Biology

A. Personal Statement

With strong educational background and extensive experience in medicine and structural biology, I am always interested in the molecular mechanisms of the essential biological macromolecules how to perform functions in physiological process and human diseases. Therefore, my research has focused on the structures and functions of important biological macromolecules related to human health and diseases. I have determined dozens of three-dimensional structures of significant biomacromolecules, including proteins, as well as proteins in complex with lipids, nucleic acids and small molecule inhibitors. These proteins are from all kingdoms of life including virus, bacteria, yeast, plant and human, and most of these proteins are important for human health. These research projects have revealed the molecular mechanisms by which the proteins function and have provided foundametal structural basis for designing specific structure-based drugs to treat human diseases.
In my future research, I will continue to investigate the functional mechanisms of proteins involved in antivirus and anticancer activities within the human body, and to design innovative medicines based on protein structures to combat human diseases. My work will persist in exploring the structure and function of proteins and protein complexes relevant to human cancer or viral infections, using the methods of molecular biology, structural biology (X-ray crysatllograogy and cryo-EM), biochemistry, computational biology, and chemical biology to reveal the molecular mechanisms of significant biological macromolecules.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – Senior Research Scientist, Memorial Sloan-Kettering Cancer Center, NY, USA
2022 Associate Director, University of Oklahoma Health Sciences, OK, USA
2019 – 2022 Research Assistant Professor, Oklahoma State University, OK, USA
2011 – 2015 Research Associate, Institute of High Energy Physics, CAS, Beijing, China
2003 – 2004 Internship, Peking University First Hospital, Beijing, China

Honors

2004 – 2011 Full scholarship every year, CAS
2001 – 2003 The first-class scholarship for outstanding medical students, Peking University
2000 Federal Medical Education Award, Peking University Health Science Center

C. Contributions to Science

1. Structural basis of antitumor and antiviral proteins:

SAMD9 is a multi-domain protein playing significant roles in antivirus and antitumor response in human. The crystal structure of an effector domain in SAMD9 complex with dsDNA has been solved and several key residues for binding nucleic acids were identified. The biochemical experiments demonstrated that this dsNA-binding domain (DBD) is essential for antiviral and antiproliferative activities in both wild-type and gain-of-function SAMD9/9Lvariants. This research result has provided the fundamental structural basis of a potential therapeutic target for treating SAMD9/9L-associated human diseases.

A6 protein is an essential viral membrane assembly protein for vaccinia virus to form open-ended and crescent membranes. The crystal structure of A6 protein C-terminal domain from vaccinia virus was determined, which forms a unique cage that encloses multiple glycerophospholipids with a lipid bilayer-like configuration. This research result has revealed a protein modality for enclosing the lipid bilayer and provided molecular insight into a viral machinery involved in generating and/or stabilizing open-ended membranes of poxvirus.

a. **Peng S** et al. Structure and Function of an Effector Domain in Antiviral Factors and Tumor Suppressors SAMD9 and SAMD9L. *Proc Natl Acad Sci U S A*. 2022, 119(4):e2116550119.

b. Pathak PK, **Peng S** et al. Structure of a lipid-bound viral membrane assembly protein reveals a modality for enclosing the lipid bilayer, *Proc Natl Acad Sci U S A*. 2018, 115(27):7028-7032.

2. Identification of novel drug-binding pocket and structure-based drug design:

Hsp90 is a molecular chaperone and a potential drug target for treatment of cancer, neurodegenerative and infectious diseases. We identified the allosteric inhibitor binding site on the middle domain of Hsp90a molecular chaperone by determining the crystal structure of human Hsp90aMC labeled with a coumarin derivative. This research result provides the first direct visual insight into the mechanism of Hsp90a allosteric inhibitors and provides structural basis for designing new drugs.

By collaborating with Dr. Brain Blagg's lab in the University of Notre Dame, we have determined the structures of Hsp90 N-terminal domain complexed with isoform-specific inhibitors. Based on the crystal structures of Hsp90-inhibitor complexes, isoform-selective N-terminal inhibitors of Hsp90a, Hsp90β and TRAP1 have been developed respectively to overcome the detriments associated with pan-inhibition of Hsp90. Our research has provided fundamental structural basis for designing potential novel and less toxic drugs for cancer treatment.

a. **Peng S** et al. Structural basis of the key residue W320 responsible for Hsp90 conformational change. *J Biomol Struct Dyn*, 2022, Nov14:1-11.

b. **Peng S** et al. Crystal structure of the Hsp90α MC domain labeled with a coumarin-derivative reveals a potential allosteric binding site as a drug target. *Acta Crystallogr D Struct Biol*. 2022, 78 (Pt 5):571-585.

c. Merfeld T, **Peng S,** et al. Elucidation of novel TRAP1-Selective inhibitors that regulate mitochondrial processes. *European Journal of Medicinal Chemistry*, 2023, 258:115531

d. Mishra SJ, Reynolds TS, Merfeld T, Balch M, **Peng S**, Deng J, Matts R, Blagg BSJ. Structure-Activity Relationship Study of Tertiary Alcohol Hsp90α-Selective Inhibitors with Novel Binding Mode. *ACS Med Chem Lett.* 2022, 13(12):1870-1878.

e. Mishra S, Khandelwal A, Bannerjee M, Balch M, **Peng S**, Davis R, Merfeld T, Menthali V, Deng J, Matts R, Blagg B. Selective Inhibition of the Hsp90a isoform. *Angew Chem Int Ed Engl.* 2021, 60(19):10547-10551.

f. Khandelwal A, Kent CN, Balch M, **Peng S**, Mishra SJ, Deng J, Day VW, Liu W, SubramanianC, Cohen M, Holzbeierlein JM, Matts R, Blagg BSJ. Structure-guided design of an Hsp90β N-terminal isoform-selective inhibitor. *Nat Commun*. 2018, 9(1):425.

3. Structural and functional studies of enzymes:

Swt1 is an RNA endonuclease that plays an important role in quality control of nuclear messenger ribonucleoprotein particles (mRNPs) in eukaryotes. High-resolution crystal structure of the C-terminal domain of S. cerevisiae RNA endonuclease Swt1 reveals a HEPN (higher eukaryotes and prokaryotes nucleotide binding) Domain. The low-resolution architecture of Swt1 full-length in solution was analyzed using small angle X-ray scattering (SAXS) method. Our study provides the necessary structural information for detailed analysis of the functional role of Swt1 in the process of nuclear mRNP surveillance. As a principal investigator, this research is supported by National Natural Science Foundation of China (Youth Program).

During my PhD training, I have determined the crystal structure of Uroporphyrinogen III synthase (U3S) from Pseudomonas syringae pv. tomato DC3000 (psU3S) at 2.5Å resolution. U3S is one of the significant enzymes

in the biosynthesis of tetrapyrrole compounds. Based on mutation and activity analysis, a key residue, Arg219, was found to be important for the catalytic activity of psU3S. Our results provide the structural basis and biochemical evidence to further elucidate the catalytic mechanism of U3S.

a. **Peng S** et al. High-resolution crystal structure reveals a HEPN domain at the C-terminal region of S. cerevisiae RNA endonuclease Swt1. *Biochem Biophys Res Commun*. 2014, 453(4): 826-32.

b. **Peng S** et al. Crystal structure of uroporphyrinogen III synthase from Pseudomonas syringae pv. tomato DC3000. *Biochem Biophys Res Commun*. 2011, 408(4): 576-81.

4. Other contributions:

Apart from above mentioned areas, I have a key contribution in other projects related to mechanistic studies on DNA binding by STENOFOLIA homeodomain in plant, Ca^{2+} binding EF-hand protein in human pathogen Pseudomonas aeruginosa, etc.

a. Pathak PK[1], Zhang F[1], **Peng S[1]**, Niu L, Chaturvedi J, Tadege M, Deng J. Structure of the unique tetrameric STENOFOLIA homeodomain bound with DNA. *Acta Crystallogr D Struct Biol*. 2021, 77(Pt 8):1050-1063.

b. Kayastha B, Kubo A, Burch-Konda J, Rogers R, Dohmen R, **Peng S**, Chaudhary B, Mohanty S, Barbier M, Cook G, Deng J, Bevere J, Huckaby A, Witt W, Patrauchan M. EF-hand protein, EfhP, specifically binds Ca^{2+} and mediates Ca^{2+} regulation of virulence in a human pathogen Pseudomonas aeruginosa. *Scientific Reports*, 2022,12(1):8791.

c. Jia H, Xue S, Lei L, Fan M, **Peng S**, Li T, Nagarajan R, Carver B, Ma Z, Deng J, Yan L. A semi-dominant NLR allele causes whole-seedling necrosis in wheat. *Plant Physiol*. 2021, 186(1):483-496.