BIOGRAPHICAL SKETCH

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NAME: **Jing-Yuan Liu**

eRA COMMONS USER NAME (credential, e.g., agency login): **JINGYUAN**

POSITION TITLE: **Associate Professor**

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
Shandong University, China	B.Sc.	07/1995	Biochemistry
Institute of Genetics, Chinese Academy of Sci.	M.Sc,	07/1998	Molecular Genetics
Indiana University School of Medicine, IN, USA	Ph.D.	10/2006	Structural Biology
Indiana University School of Medicine, IN, USA	Postdoc	11/2011	Computational Biology and Bioinformatics

A. Personal Statement

The major research focus of my laboratory at University of Toledo College of Medicine and Life Sciences (formally Medical College of Ohio) is to understand the interactions between protein-and-protein or between protein-and-compound for drug discovery using bioinformatics and computational approaches and then validate those findings by biophysical and biochemical methods and/or patient data mining such as electronic medical records. Protein-protein interactions are required for biological functions while small compounds that interact with proteins can alter, regulate or trigger protein functions. However, how proteins recognize each other and form a stable complex is not fully understood. Our research incorporates protein dynamics to understand how specific proteins function or interact with other proteins. In addition, we are developing new algorithms to visualize protein dynamics for a better understanding of these interactions via mining of the simulation data. I was trained both as a biochemist and as an X-Ray Crystallographer during my graduate studies and a computational biologist and bioinformatician during my postdoctoral training. I have collaborated successfully with many investigators since I became independent. The computational work of my group initially identified PPIs as potential inhibitors of FASN and we then conducted data mining of a breast cancer cohort to illustrate the potential effect of PPI usage on the outcome of breast cancer patients. Working with a group of PIs and clinicians, our initial findings have led to phase II clinical trials to repurpose proton pump inhibitors in breast cancer treatment (NCT02595372).

<u>Ongoing and completed projects</u>

1. R01 GM127656 (Liu) 2018-2024
   NIH/NIGMS
   Effective targeting survivin dimerization interface with small molecule inhibitors
   Role: PI
2. R01 CA276732 (Shi-He Liu) 2023-2028
   NIH/NCI
   Engineering of Exosomes for Pancreatic Cancer Targeting Therapy
   Role: Co-I
3. R21 CA277252A1 (J.T. Zhang) 2023-2026
   NIH/NCI
   Targeting FASN to eliminate metastatic breast cancer in the brain
   Role: Co-I
4. PC230068 (Shang Su) 2024-2025
   DoD
   Dabber: D-type peptide grabber for degradation of undruggable target proteins

in lethal prostate cancer
Role: Co-I

5. R01CA219342 (Yue Zou) 2017-2023
NIH/NCI
ATR isomerization in cellular response to UV damage of DNA
Role: Co-I.
6. R01 CA211904 (J.T. Zhang) 2017–2023
NIH/NCI
Molecular targeting the translational control axis in Wnt/β-catenin signaling pathway
Role: Co-I
7. BC150290 (J.T. Zhang) 2016-2018
DOD
Targeting FASN for breast cancer treatment by repositioning PPIs
Role: Co-I
8. No Number (Liu) 2015-2017
Showalter Research Trust
Characterization of newly synthesized lead analogs targeting survivin for cancer treatment
Role: PI

Citations:

1. Wang CJ, Li D, Danielson JA, Zhang EH, Dong Z, Miller KD, Li L, Zhang JT, **Liu JY**. Proton pump inhibitors suppress DNA damage repair and sensitize treatment resistance in breast cancer by targeting fatty acid synthase. Cancer Lett. 2021 Jul 1; 509:1-12.
2. Peery R, Kyei-Baffour K, Dong Z, Liu J, de Andrade Horn P, Dai M*, **Liu JY***, Zhang JT.* Synthesis and Identification of a Novel Lead Targeting Survivin Dimerization for Proteasome-Dependent Degradation. J Med Chem. 2020 Jul 9;63(13):7243-7251. (*corresponding authors)
3. Qi J, Dong Z, Liu J, Peery RC, Zhang S, **Liu JY*,** Zhang JT*. Effective Targeting of the Survivin Dimerization Interface with Small-Molecule Inhibitors. Cancer Res. 2016 Jan 15;76(2):453-62. (*corresponding authors)
4. Fako VE, Zhang JT, **Liu JY.** Mechanism of Orlistat Hydrolysis by the Thioesterase of Human Fatty Acid Synthase. ACS Catal. 2014 Oct 3;4(10):3444-3453.

B. Positions and Honors:

Positions and employment

2019–prst	Associate Professor, Department of Medicine, University of Toledo College of Medicine and Life Sciences (formally Medical College of Ohio), Toledo, OH
2012–2019	Assistant Professor, Department of Computer and Information Science, Indiana University Purdue University, Indianapolis, IN
2015–2019	Assistant Professor, Department of Pharmacology and Toxicology, IU School of Medicine, Indianapolis, IN
2013–2019	Member, Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, IN.

Other experiences and appointments

2011-prst	Associate Editorial Board Member, *Int. J. Biochem Mol Biol*
2013-prst	Editorial Advisory Board Member, *Current Cancer Drug Target*
2014-prst	Editorial Board Member, *Aperito Journal of Computer Science and Biology*
2015-prst	Editorial Board Member, *Journal of Bioinformatics and Comparative Genomics*

Honors

2002	Annual Outstanding Student Award, Shandong University, Jinan, China
2002	Outstanding Poster Presentation Award, Dept. of Biochem. & Mol. Biol., Indiana Univ. School of Medicine, Indianapolis, IN, USA
2004	Travel award, 10th SCBA International Meeting, Beijing, China.
2015-2016	Ralph W. and Grace M. Showalter Research Trust Young Investigator Award

C. Contributions to Science

a. ***Molecular Cloning and Structural Biology of Thiamin Pyrophosphokinase***

I started my research career by working on thiamin pyrophosphokinase (TPK), which has been implicated in Wernicke-Korsakoff syndrome (WKS), a neuro-disorder, and wet beriberi, a heart disease. TPK transfers two phosphate groups from ATP to the hydroxyl group of thiamin and produces thiamin pyrophosphophate (TPP), which is a cofactor for many key enzymes in cellular energy production. To further understand how TPK works, I cloned the mouse TPK (mTPK) gene and determined the crystal structure of apo mTPK enzyme. I was also able to determine the crystal structure of mTPK complexed with pyrithiamine and TPP at 1.9 and 1.7Å, respectively. In addition, I elucidated the inhibition mechanism of pyrithiamine, a potent inhibitor of thiamine metabolism that induces neurological symptoms similar to WKS, and showed that pyrithiamine, commonly believed not a substrate of TPK, can be phosphorylated by TPK based on analyses with enzymatic assays, X-Ray Crystallography and Mass Spectrometry. In addition, I worked on the structure and function of fumarylacetoacetate hydrolase (FAH) on the side and was exposed to a different protein and gained more experiences on enzymology and protein sciences.

1. Timm, DE; **Liu, J.Y.**; Baker, LJ; Harris, RA. Crystal structure of thiamin pyrophosphokinase. *J Mol Biol* 310(1): 195-204; 2001. PMID: 11419946.
2. **Liu, J.Y.**; Timm, DE; Harris, RA; Hurley, TD. Studies in the structure and function of thiamin pyrophosphokinase. In: Patel MS, Jordan F, editors. Thiamine: Catalytic mechanism and role in normal and disease states. New York: Marcel Dekker. 2002.
3. **Liu, J.Y.**; Timm, DE; Hurley, TD. Pyrithiamine as a substrate for thiamine pyrophosphokinase. *J Biol Chem* 281(10): 6601-6607; 2006. PMID: 16365036.
4. **Liu, J.Y.***; Hurley, TD. A new crystal form of mouse thiamin pyrophosphokinase. *Int J Biochem Mol Biol* 2:111-118; 2011. (*corresponding author) PMID: 21552434.

b. ***Study of Protein-Ligand and Protein-Protein Interactions using Molecular Dynamic Simulations***

As a structural biologist, I recognize that protein dynamics play an important role in their function that cannot be captured by conventional X-Ray Crystallography. Protein structures solved by X-Ray Crystallography are static snapshots of proteins and dynamic properties are mostly lost. Flexible regions are evasive from X-Ray Crystallography which results in incomplete structure entries in protein databank. In order to understand protein dynamics, I have gained experiences in molecular dynamic (MD) simulations in the study of estrogen receptor. I showed that the antagonism of ER ligands can be predictable by their dynamic properties. These findings provide insight in the mechanism of ER antagonism and in developing better drugs for breast cancer therapy. I also investigated the mechanism of orlistat hydrolysis by thioesterase of human fatty acid synthase (FASN) using MD simulations and showed that the hexyl tail of the covalently-bound orlistat undergoes a conformational transition, which is accompanied by destabilization of a hydrogen bond between a hydroxyl moiety of orlistat and the catalytic His^{2481} of TE that in turn leads to an increased hydrogen bonding between water molecules and His^{2481} and increased chance for water activation to hydrolyze the covalent bond between orlistat and Ser^{2308}. These findings suggest that stabilizing the hexyl tail of orlistat may lead to the design of more potent irreversible inhibitors that target FASN and block thioesterase activity with greater endurance. MD simulations have also been used to investigate the dimerization and dynamic natures of 14-3-3σ. I, for the first time, defined dimerization core and showed that a highly packed dimeraization core that has low water trafficking is a prerequisite for stable and specific protein-protein interactions. I also showed that the ligand-protein binding site of 14-3-3σ is constantly transitioning between the open and close conformation. These findings are not only important in helping us understand how protein recognizes each other, but also help identify critical residues as targeting site to disrupt or enhance protein-protein interaction in drug discovery

1. **Liu, J.Y.***; Li, Z.; Li, H.; Zhang, J.T.* A critical residue that promotes protein dimerization: a story of partially exposed Phe^{25} in 14-3-3σ. *J. Chem. Inf. Model*. 51:2612-25; 2011. (*corresponding authors). PMID: 21870863.
2. Li, Z.; Peng, H.; Qin, L.; Qi, J.; Zuo, X.; **Liu, J.Y.***; Zhang, J.T*. Determinants of 14-3-3σ dimerization and function in drug resistance. *J Biol Chem.* 1;288(44):31447-57; 2013 (*corresponding author). PMID: 24043626.
3. Hu, G.; **Liu, J.Y.*;** and Wang, J.***** Insight into conformational change for 14-3-3σ protein by molecular dynamics simulation. *Int. J. Mol. Sci.* 15(2), 2794-2810; 2014. (*corresponding authors). PMID: 24552877.
4. Fako, V.E.; Zhang, J.T.; and **Liu, J.Y.** Mechanism of Orlistat Hydrolysis by the Thioesterase of Human Fatty Acid Synthase. *ACS Catalysis* 4:3444-3453; 2014. PMID: 25309810.

c. *Drug Discovery*

With my experiences in both structural biology and computational biology, I have participated in and made major contributions to several drug discovery studies. I helped to build successfully an in-house compound library, which contains millions of compounds from NCI, asinex, chemstar, iflab, otava, shark, mdd, chembridge, specs, and chemdiv. Using these databases, I successfully performed in-silico screening and docking analysis targeting a DNA damage repair protein, XPA, fatty acid synthase, and STAT3. It is noteworthy that both XPA and STAT3 are considered "undruggable" because their active sites are DNA-binding domains, which lack known enzymatic activity and thought to be too flat for specific binding by small molecule compounds. With my deep understanding of protein structure and dynamics, I was able to design better approaches to target the DNA binding sites of the proteins and perform successful docking to identify potential inhibitors. These findings suggest that the previously dubbed "undruggable" DNA-binding sites may be druggable.

1. Huang, W.; Dong, Z.; Wang, F.; Peng, H.; **Liu, J.Y***.; Zhang, J.T.* A small molecule inhibitor targeting the "undruggable" DNA-binding site of human STAT3 inhibits cancer cell proliferation, migration, and invasion. *ACS Chem. Biol*. 9:1188-1196; 2014 (cover article). (*corresponding authors) PMID: 24661007.
2. Fako, V.E.; Wu, X.; Pflug, B.; **Liu, J.Y**.*; and Zhang, J.T.* Repositioning proton pump inhibitors as anti-cancer drugs by targeting the thioesterase domain of human fatty acid synthase. *J. Med. Chem*. 58:778-784; 2015 (cover article). (*corresponding authors) PMID: 25513712.
3. Qi, J; Dong, Z.; Liu, J.; Peery, R.C.; Zhang, S.; **Liu, J.Y**.; Zhang, J.T. Effective targeting of the survivin dimerization interface with small-molecule inhibitors. *Cancer Res*. 76:453-462; 2016. PMID: 26744521
4. Huang, W; Dong, Z.; Wang, F.; Chen, Y.; Wang, C.; He, Y.; Hangoc, G.; Pollok, K.; Sandusky, G.; Fu, X.Y.; Broxmeyer, H.; Zhang, Z.Y**.; Liu, J.Y**.; Zhang, J.T. Novel lead inhibitors targeting the DNA-binding domain of STAT3 suppresses tumor growth and STAT3 target gene expression in vivo. *Oncogene* 76:453-462. PMID: 26073084

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1PKNTjnAvg-5mE/bibliography/public/