BIOGRAPHICAL SKETCH

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NAME: Wei Huang

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POSITION TITLE: Postdoctoral Researcher

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
Xi'an Jiaotong University (China)	B.E	07/2006	Bioengineering
Louisiana State University, Baton Rouge	Ph.D.	12/2011	Biochemistry; Structural Biology
Case Western Reserve University	Post-Doc	01/2012-06/2019	Structural biology; Pharmacology
Case Western Reserve University	Research Scientist	present	Biophysics, Biochemistry; Structural biology; Pharmacology

A. Personal Statement

My professional career has focused on understanding the molecular interactions involved in fundamental biological pathways. I have benefited from a diverse and complete training in a range of techniques, both computational and experimental, under the tutelage of several young and ambitious mentors. As a graduate student, I was trained in RNA biology, macromolecular biophysics, nuclear magnetic resonance spectroscopy and molecular dynamics simulations jointly under Dr. Fareed Aboul-ela (now at Zewail City of Science and Technology) and Dr. Shantenu Jha (now at Rutgers University). My graduate studies have focused on understanding the structure and functional dynamics of the SAM-I riboswitch under the modulation of small molecules, where I began the journey of integrating experimental data with computational simulations to synergetically improve the information obtained from experiments and theoretical calculations. After finishing my PhD, I continued this pathway of integrated structural biology under the guidance of Dr. Sichun Yang (Case Western Reserve University) to investigate structure dynamics of estrogen receptor using multifaceted techniques, including small angle X-ray scattering, hydroxyl radical protein footprinting and protein-protein association simulations. After my first round of postdoctoral training, I had worked Dr. Derek Taylor (Case Western Reserve University), a recipient of NIH Director's Innovation Award, who also revealed one of the first structures for complete detail eukaryotic 80S ribosomes, to investigate the structure and function of macromolecular assembly. In Dr. Taylor's lab with diverse and enriched scientific environment, not only I can continue to use previous techniques I was trained with, as well as expand to new ones, such as cryo-electron microscopy, to study the molecular interactions involved in macromolecular assemblies spanning the whole central dogma of biology. Currently, in Dr. Taylor's lab, I have assembled a well-established streamline of cryo EM resources, including the access to high-end microscopes and computational resources for imaging processing. Combined with the expertise accumulated over the years in biochemically optimizing the biological samples in the Taylor lab, we are well positioned to tackle more and more challenged biological complexes in the future.

B. Positions and Honors

Positions and Employment

2006-2007 Research Assistant, Institute for Cancer Research, Xi'an Jiaotong University, Xi'an, Shaanxi, P.R.China
2012-2015 Post-Doctoral Researcher, Center for Proteomics and Bioinformatics, Case Western Reserve University, Cleveland, Ohio
2016-2019 Post-Doctoral Researcher, Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio
2019-present Research Scientist, Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio

Other Experience and Professional Memberships

2007- Member, Chinese Society of Cell Biology
2007- Member, American Chemical Society
2009- Member, RNA society
2012- Member, Biophysical Society
2015- Editor, General Physiology and Biophysics
2016- Member, American Society for Biochemistry and Molecular Biology
2017- Member, American Heart Association

Honors

2006 Distinguished Undergraduate Thesis Award, Xi'an Jiaotong University, China
2009 LONI Graduate Fellowship, Louisiana State University, LA
2010 McDaniel Travel Award, Louisiana State University, LA
2016 Pharmacology Retreat Best Poster Award, Case Western Reserve University, OH
2017 ASBMB Travel Award
2017-2019 AHA postdoctoral fellowship

C. Contribution to Science

1. Our current primary project has elucidated the detail mechanism of actions for a small molecule activator of PP2A (SMAP), DT-061, to invigorate a specific PP2A holoenzyme. DT-06, binds to the heterotrimeric intersubunit interface formed in AB56αC complexes to stabilize and direct holoenzyme activity against B56α regulated substrates, including c-MYC. This insight demonstrates a strategy to target protein-protein interfaces by stabilizing the holoenzyme complex to selectively bias phosphatases against disease specific hyperphosphorylated substrates.
    a. Leonard D, **Huang W**, Izadmehr S, O'Connor CM, Wiredja DD, Wang ZZ, Zaware N, Chen YH, Schlatzer D, Kiselar J, Vasireddi N, Schuechner S, Perl A, Galsky MD, Xu WQ, Brautigan DL, Ogris E, Taylor DJ, Narla G. (2019) Selective PP2A enhancement through biased heterotrimer stabilization. Cell. https://doi.org/10.1016/j.cell.2020.03.038

2. My Ph.D. thesis focused on understanding the coupling of small molecule binding with the conformational rearrangement of the SAM-I riboswitch, an RNA structure element that fine-tunes gene expression levels in bacteria. I used molecular dynamics simulations to unveil the conformational fluctuations in RNA that cannot be directly observed in the crystal structure. With some of the longest trajectories at that time, we identified a transient formation, loss, and reformation of a distinct structural motif governing long range interactions, which was later revealed in another X-ray structure. Additionally, I also used molecular models for a "hybrid" state that possess characteristics of the "ON" and "OFF" states of a SAM-I riboswitch simultaneously, and performed several millisecond timescale molecular dynamics simulations with and without the small molecule. We observed the conversion of three base pairs from an anti-terminator helix, characteristic of the "ON" state, to a P1 helix characteristic of the "OFF" state, only in the presence of the small molecule. Finally,

I introduced computational methods to enable dynamic predictions for the formation of base pairings as the RNA is synthesized, leading to a new model for the "ON" state of the SAM-I riboswitch, and later verified experimentally by site-directed mutagenesis, nuclear magnetic resonance, RNA chemical probing and fluorescence spectroscopy.

a. **Huang W**, Kim J, Jha S, Aboul-ela F. (2009) A mechanism for S-adenosyl methionine assisted formation of a riboswitch conformation: a small molecule with a strong arm. Nucleic acids research, 37(19):6528-39. PMCID: PMC2770654
b. **Huang W**, Kim J, Jha S, Aboul-ela F. (2013) The impact of a ligand binding on strand migration in the SAM-I riboswitch. PLoS computational biology, 9(5):e1003069. PMCID: PMC3656099
c. **Huang W**, Kim J, Jha S, Aboul-Ela F. (2012) Conformational heterogeneity of the SAM-I riboswitch transcriptional ON state: a chaperone-like role for S-adenosyl methionine. Journal of molecular biology, 418(5):331-49. PMCID: PMC4767528
d. Boyapati VK, **Huang W**, Spedale J, Aboul-Ela F. (2012) Basis for ligand discrimination between ON and OFF state riboswitch conformations: the case of the SAM-I riboswitch. RNA, 18(6):1230-43. PMCID: PMC3358645
e. Aboul-ela F, **Huang W**, Abd Elrahman M, Boyapati V, Li P. (2015) Linking aptamer-ligand binding and expression platform folding in riboswitches: prospects for mechanistic modeling and design. Wiley interdisciplinary reviews. RNA, 6(6):631-50. PMCID: PMC5049679

3. In addition to using a range of techniques to address specific scientific problems as described above, I have also developed a series of methods to seamlessly integrate multifaceted techniques that can be applied to study protein complexes. First, we've built a coarse-grained model in conjunction with an enhanced sampling algorithm to achieve large scale unbiased simulations of protein-protein association. Secondly, we've implemented a software, specifically tailored for coarse-grained model, to unify the theoretical calculations of small angle X-ray scattering profiles in order to bridge the gap between a large pool of structures and experimental small angle X-ray scattering data. Moreover, we've established a quantitative relationship between modification rates measured by hydroxyl radical protein footprinting and protein topology features, improving the previous qualitative usage of such experimental information. These three individual components have already been adopted by other research groups to study their own systems. Finally, we've formulated a workflow, namely iSPOT, to tightly integrate multifaceted techniques, which are unreliable, low resolution and sparse on their own, to enable modeling structures approaching the crystal structure.

    a. Ravikumar KM, **Huang W**, Yang S. (2012) Coarse-grained simulations of protein-protein association: an energy landscape perspective. Biophysical journal, 103(4):837-45. PMCID: PMC3443792
    b. Ravikumar KM, **Huang W**, Yang S. (2013) Fast-SAXS-pro: a unified approach to computing SAXS profiles of DNA, RNA, protein, and their complexes. The Journal of chemical physics, 138(2):024112. PMID: 23320673
    c. **Huang W**, Ravikumar KM, Chance MR, Yang S. (2015) Quantitative mapping of protein structure by hydroxyl radical footprinting-mediated structural mass spectrometry: a protection factor analysis. Biophysical journal, 108(1):107-15. PMCID: PMC4286602
    d. **Huang W**, Ravikumar KM, Parisien M, Yang S. (2016) Theoretical modeling of multiprotein complexes by iSPOT: Integration of small-angle X-ray scattering, hydroxyl radical footprinting, and computational docking. Journal of structural biology, 196(3):340-349. PMCID: PMC5118146

4. My work also focused on understanding the structure and functional dynamics of human estrogen receptor in response to different know drugs. I was able to optimize the expression conditions and purify recombinant human estrogen receptor with known activities—specific DNA binding and recognition of LXXLL motifs on the co-regulators. Purified estrogen receptor has been used by other research groups to pull-down co-activators from the cell lines for functional study. Additionally, I employed the coarse-grained model we developed to simulate the interaction between individual domains of estrogen receptor, revealing novel domain-domain interfaces for further experimental function validations. Utilizing the same coarse-grained model, I also studied a mutation that is constitutively active identified from cancer patients, providing a mechanistic explanation from the structure dynamics perspective.

a. Khurana S, Chakraborty S, Zhao X, Liu Y, Guan D, Lam M, **Huang W**, Yang S, Kao HY. (2012) Identification of a novel LXXLL motif in α-actinin 4-spliced isoform that is critical for its interaction with estrogen receptor α and co-activators. The Journal of biological chemistry, 287(42):35418-29. PMCID: PMC3471738
b. **Huang W**, Greene GL, Ravikumar KM, Yang S. (2013) Cross-talk between the ligand- and DNA-binding domains of estrogen receptor. Proteins, 81(11):1900-9. PMID: 23737157
c. **Huang W**, Ravikumar KM, Yang S. (2014) A Newfound Cancer-Activating Mutation Reshapes the Energy Landscape of Estrogen-Binding Domain. Journal of chemical theory and computation, 10(8):2897-900. PMID: 26588264
d. **Huang W**, Peng Y, Kiselar J, Zhao X, Albaqami A, Mendez D, Chen Y, Chakravarthy S, Gupta S, Ralston C, Kao, H. Y, Yang S. (2018). Multidomain architecture of estrogen receptor reveals interfacial cross-talk between its DNA-binding and ligand-binding domains. Nature communications, 9(1), 3520. PMID: 30166540

5. We have established the single particle analysis cryo-EM pipeline to resolve structures for a wide spectrum of biomacromolecules, including ribosomes, membrane protein. Our work has not only benefit our own lab, but also assists our local structural biology community to adopt this latest revolutionary technique as their research tool.
    a. Scott H, **Huang W**, Bann JG, Taylor DJ. (2018). Advances in structure determination by cryo-EM to unravel membrane‐spanning pore formation. Protein Science, 27(9), 1544-1556. PMID: 30129169
    b. Morgan, C, **Huang W**, Rudin S, Taylor D, Kirby J, Bonomo R, Yu E. (2019) Cryo-EM structure of the Acinetobacter baumannii 70S ribosome and implications for new antibiotic development. mBio, 11(1). PMID:31964740
    c. Basak S, Gicheru Y, Samanta A, Molugu SK, **Huang W**, la de Fuente M, ... & Chakrapani S. (2018). Cryo-EM structure of 5-HT 3A receptor in its resting conformation. Nature communications, 9(1), 514. PMID: 29410406
    d. Su CC, Morgan C, Kambakam S, Rajavel M, Scott H, **Huang W**, Emerson C, Taylor D, Stewart P, Bonomo R, Yu E. (2019) Cryo-EM structure of an Acinetobacter baumannii multidrug efflux pump. mBio, 10(4), e01295-19. PMID: 31266873

6. We have done a number of studies focusing on the pharmacology of small molecule compounds with various targets, including telomerase, 15-hydroxyprostaglandin dehydrogenase, protein phosphatase 2A, etc.
    a. Hernandez-Sanchez W, **Huang W**, Plucinsky B, Garcia-Vazquez N, Robinson NJ, Schiemann W P., ... & Taylor DJ. (2019). A non-natural nucleotide uses a specific pocket to selectively inhibit telomerase activity. PLoS biology, 17(4), e3000204.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/wei.huang.6/bibliography/public/