BIOGRAPHICAL SKETCH

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NAME: Zhang, Haoming

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

POSITION TITLE: Research Associate Professor of Pharmacology

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
Hubei University, China	BS	07/1984	Chemistry
Wuhan University, China	MS	07/1991	Physical Chemistry
Australian National University, Australia	PhD	03/1998	Biophysical Chemistry
University of British Columbia, Canada	Postdoctoral	07/2000	Biochemistry

A. Personal Statement

My research experience has been in the area of protein structure and function since the start of my graduate study in 1994. Initially trained as a biophysical chemist, I used time-resolved Fourier transform infrared spectroscopy to investigate electron transfer in PSII, a multi-subunit protein complex responsible for splitting water molecules to dioxygen in photosynthesis. As an NSERC research fellow, I took a multidisciplinary approach to investigate the structure and function of hemoprotein. Cytochrome P450 enzyme has been the focus of my research since 2000. In the past 21 years I have made scientific contributions to the field of drug metabolism by providing functional and structural understandings of: 1) the complex of P450 with its redox partners, P450 oxidoreductase (POR) and cyt b5; 2) the mechanism-based inactivation of P450s; 3) the role of the conformational dynamics on substrate recognition; and 4) the molecular architectures of P450 BM3 and the P450/POR complex incorporated in amphipols. My research on the role of cyt b5 contributed to the competitive model of cyt b5 and POR in binding to P450 2B4. In collaboration with Dr. James Halper, we published the very first crystal structure of P450 2B4 where the active site Thr302 is covalently bound to a mechanism-based inactivator. Since 2017, my research has been focused on elucidation of the structures of P450 complexes using transmission electron microscopy (TEM), which led to publication of three peer-reviewed articles on the structure of P450 complexes (see below). In collaboration with Dr. Yoichi Osawa, we remain as the leading investigators in utilization of cryo-EM to study P450 enzymes. Over the course of my career, I have published over 60 peer-reviewed articles on drug metabolism by P450s and acquired a variety of biophysical and biochemical expertise including TEM to tackle the challenging problems of understanding the structure and function of P450s. Through obtaining intramural and extramural research grants, I have demonstrated the ability to conduct independent research and manage research projects. My proven record of productivity and over 20 years of experience with metalloprotein will contribute greatly to the proposed research project. Below are three of my articles that highlight my contributions to the field of drug metabolism by P450 enzymes.

1. Cheng S, Bo Z, Hollenberg P, Osawa Y, Zhang H: Amphipol-facilitated elucidation of the functional tetrameric complex of full-length cytochrome P450 CYP2B4 and NADPH-Cytochrome-P450 oxidoreductase. J Biol Chem: 100645, 2021. PM33839156/PMC8113742.

2. Su M, Chakraborty S, Osawa Y, Zhang H: Cryo-EM reveals the architecture of the dimeric cytochrome P450 CYP102A1 enzyme and conformational changes required for redox partner recognition. J Biol Chem 295(6): 1637-1645, 2020. PM31901079/PMC7008367.

3. Zhang H, Yokom AL, Cheng S, Su M, Hollenberg PF, Southworth DR, Osawa Y: The full-length cytochrome P450 enzyme CYP102A1 dimerizes at its reductase domains and has flexible heme domains for efficient catalysis. J Biol Chem 293(20): 7727-7736, 2018. PM29618513.

B. Positions, Scientific Appointments, and Honors

1984 - 1988 Lecturer, Chemistry, Hubei University, China
1991 - 1994 Sr. Lecturer, Chemistry, Hubei University, China
1998 - 2000 Research Fellow, Biochemistry and Molecular Biology, University of British Columbia
2000 - 2004 Sr. Research Associate, Anesthesiology, University of Michigan Medical School
2004 - 2007 Research Investigator, Anesthesiology, University of Michigan Medical School
2007 - 2012 Research Investigator, Pharmacology, University of Michigan Medical School
2012 - 2019 Research Assistant Professor, Pharmacology, University of Michigan Medical School
2019 - Research Associate Professor, Pharmacology, University of Michigan Medical school

C. Contributions to Science

1. My early publications addressed the controversy surrounding the redox intermediates in the electron transfer chain of PSII, a multi-subunit protein complex that carries out light-driven oxidation of water to dioxygen molecules. Due to the presence of multiple intermediate species under constant illumination, it was difficult to discern the contribution of individual species. I took an innovative approach to publish the very first time-resolved vibrational spectrum of PSII obtained after a single flash and was able to differentiate individual contributions of two redox plastoquinones and a tyrosyl radical based on their differences in kinetic decay. My assignments for the vibrational spectra of plastoquinones and the tyrosyl radical were unequivocal, which resolved the controversy on the origin of the 1478 cm^{-1} band and discovered new vibrational signals from the tyrosyl radical. I was the corresponding author on two related articles.

a. Zhang HM, Razeghifard MR, Fischer G, Wydrzynski T. A time-resolved FTIR difference study of the plastoquinone Q_A and redox-active tyrosine Y_Z interactions in photosystem II. Biochemistry. 1997;36(39):11762-8.
b. Zhang HM, Fischer G, Wydrzynski T. Room-temperature vibrational difference spectrum for $S_2Q_B^-/S_1Q_B$ of photosystem II determined by time-resolved Fourier transform infrared spectroscopy. Biochemistry. 1998;37(16):5511-7.

2. I shifted my research focus to drug-metabolizing cytochrome P450 enzymes in 2000 when I finished my postdoctoral training. I have published over 60 peer-reviewed articles in this field. These articles addressed important questions regarding the structure, function and dynamics of P450s. In collaboration with Dr. James Halpert, I published the first two crystal structures of covalently modified P450 2B4, which provided critical insights on covalent modification of a key Thr residue in the active site of P450 2B4. Catalytic function of P450 sometimes depends on the presence of cyt b5, but the role of cyt b5 in P450 catalysis is controversial. By a combination of biochemical and kinetic approaches I proposed a competitive model for the interactions of cyt b5 with P450 2B4. This finding detailed in Ref d was selected in the JBC Special Collections for Cytochrome P450 Research as one of the most significant findings in the field of P450 research over the last decade. My research also addressed the question how protein dynamics affect P450 function. By introduction of de novo disulfide bonds and molecular dynamic simulation, we documented the changes in substrate ingress/egress channels and their effects on metabolism. These studies have contributed to the fundamental understanding of P450 functions.

a. Zhang H, Gay SC, Shah M, Foroozesh M, Liu J, Osawa Y, Zhang Q, Stout CD, Halpert JR, Hollenberg PF. Potent mechanism-based inactivation of cytochrome P450 2B4 by 9-ethynylphenanthrene: implications for allosteric modulation of cytochrome P450 catalysis. Biochemistry. 2013;52(2):355-64. PMCID: 3568706.

b. Gay SC, Zhang H, Wilderman PR, Roberts AG, Liu T, Li S, Lin HL, Zhang Q, Woods VL, Jr., Stout CD, Hollenberg PF, Halpert JR. Structural analysis of mammalian cytochrome P450 2B4 covalently bound to the mechanism-based inactivator tert-butylphenylacetylene: insight into partial enzymatic activity. Biochemistry. 2011;50(22):4903-11. PMCID: 3105221.
c. Zhang H, Kenaan C, Hamdane D, Hoa GH, Hollenberg PF. Effect of conformational dynamics on substrate recognition and specificity as probed by the introduction of a de novo disulfide bond into cytochrome P450 2B1. J Biol Chem. 2009;284(38):25678-86. PMCID: 2757969.
d. Zhang H, Hamdane D, Im SC, Waskell L. Cytochrome b5 inhibits electron transfer from NADPH-cytochrome P450 reductase to ferric cytochrome P450 2B4. J Biol Chem. 2008;283(9):5217-25.

3. My recent research focus includes:1) application of single particle cryo-EM to determine the structural organization of mammalian P450 with POR and cyt b5; 2) development of new therapeutic anti-platelet drug to minimize P450-mediated metabolism for improved efficacy. Using negative stain and cryo-EM, we determined the molecular architecture of P450 BM3 and the complex of P450/POR. These studies reveal the critical conformational changes required for electron transfer from the reductase to P450s. My research on the clopidogrel conjugates have demonstrated the promising therapeutic potential of this class of compounds for higher efficacy and lower bleeding risk in anti-platelet therapy compared with existing drugs. This project is a natural extension of my previous research on the metabolism of clopidogrel by P450 enzymes.

1. Cheng S, Bo Z, Hollenberg P, Osawa Y, Zhang H: Amphipol-facilitated elucidation of the functional tetrameric complex of full-length cytochrome P450 CYP2B4 and NADPH-cytochrome-P450 oxidoreductase. J Biol Chem: 100645, 2021. PM33839156/PMC8113742.
2. Su M, Chakraborty S, Osawa Y, Zhang H: Cryo-EM reveals the architecture of the dimeric cytochrome P450 CYP102A1 enzyme and conformational changes required for redox partner recognition. J Biol Chem 295(6): 1637-1645, 2020. PM31901079/PMC7008367.
3. Sun Y, Venugopal J, Guo C, Fan Y, Li J, Gong Y, Chen YE, Zhang H, Eitzman DT: Clopidogrel resistance in a murine model of diet-Induced obesity Is mediated by the Interleukin-1 receptor and overcome with DT-678. Arterioscler Thromb Vasc Biol: ATVBAHA120314146, 2020. PM32268786.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1l5Y2LRNkrzQl/bibliography/46697763/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

R21 ES030791-02 (Zhang and Su) 05/2020-04/2022
NIH, NIEHS
Structural basis for detoxification of environmental pollutants by native complexes of CYP2B family with its redox partners
The objective is to elucidate the structure of CYP2B4 and cyt b5 complex by cryo-EM
Role: PI

R01 GM077430 (Osawa and Zhang) 05/2019-04/2023
NIH, NIGMS
P450 and NO synthase regulation by multiprotein complexes
The major goal is to elucidate the structure and function of regulation of the multiprotein complexes of P450 and NO synthase. The major focus is to determine the structure of the protein complexes by cryo-EM.
Role: Co-PI

UMHS-PUHSC Joint Institute (Eitzman, Zhang) 09/2018-12/2021
Overcoming interpatient variability in antiplatelet therapy
The objective of this project is to determine the efficacy of novel conjugates of clopidogrel in obese mouse model and human blood samples in preventing platelet aggregation.

Role: PI

R01 NS055746-11 (Lieberman, Osawa and Southworth) 07/01/17 – 06/30/22
NIH, NINDS
Mechanisms of motor neuron toxicity in Kennedy disease
The overall goal is to understand the pathogenesis of neuromuscular degeneration in Kennedy disease to facilitate identification of new therapeutic approaches. The objective of this application is to define the role of the Hsp90/Hsp70-based chaperone machinery in the protein quality control decisions that govern degradation of the full-length polyQ AR, which causes Kennedy disease.
Role: Co-I