

ZIWEI DAI

Department of Biology ◊ Southern University of Science and Technology

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EDUCATION

Peking University, Beijing, China

Sep 2010 - Jan 2016

Ph.D. in Physical Chemistry

Dissertation title: **Dynamics and Steady State Modeling of Disease Networks**

Advisor: Dr. Luhua Lai

Peking University, Beijing, China

Sep 2006 - Jul 2010

B.S. in Applied Mathematics

Dissertation title: **Dynamic Simulation and Regulation of Human Arachidonic Acid Metabolic Network**

Advisor: Dr. Luhua Lai and Dr. Tiejun Li

EMPLOYMENT

Southern University of Science and Technology, Shenzhen, China

Jan 2021 -

Assistant professor

Duke University, Durham, USA

Jun 2016 - Dec 2020

Postdoctoral associate

Advisor: Dr. Jason W. Locasale

RESEARCH EXPERIENCE

- **Understanding how methionine metabolism affects genomic architecture of histone methylation and gene expression**

We used the epigenetic mark histone H3 lysine 4 trimethylation (H3K4me3) as a model to study its responses to methionine restriction in cancer cells and liver of mice under normal and methionine-restricted conditions. Using quantitative metrics I developed, I found that changes in H3K4me3 width were strongly associated with cell type specific biological functions, cell identity-related transcription factor (TF) binding motifs, and changes in gene expression. These results demonstrate that changes in methionine metabolism lead to changes in H3K4me3 peak width that encode both gene expression dynamics and cell identity information.

1. **Ziwei Dai**, Samantha J Mentch, Xia Gao, Sailendra N Nichenametla, Jason W Locasale*. Methionine metabolism influences the genomic architecture of H3K4me3 with the link to gene expression encoded in peak width. **Nat Commun.** 2018 May 16;9(1):1955.
 2. Michael A Reid, **Ziwei Dai**, Jason W Locasale*. The impact of cellular metabolism on chromatin dynamics and epigenetics. **Nat Cell Biol.** 2017 Nov;19(11):1298-1306.
- **Characterizing intratumoral metabolic heterogeneity using single-cell RNA-seq**

To dissect the metabolic landscape of the tumor microenvironment at the single-cell resolution, we developed a computational pipeline and applied it to single-cell RNA-seq datasets for two human tumor types including melanoma and head and neck. We found that single tumor cells exhibit higher metabolic activity and variation compared to single non-malignant cells and bulk tumors, and identified mitochondrial metabolism as the essential contributor to metabolic heterogeneity in both malignant and non-malignant cells.

1. Zhengtao Xiao, **Ziwei Dai***, Jason W Locasale*. Metabolic landscape of the tumor microenvironment at single cell resolution. **Nat Commun.** 2019 Aug 21;10(1):3763.

- **Quantifying the impacts of dietary methionine restriction on cancer outcomes**

We studied the effects of dietary methionine restriction on metabolism and cancer outcomes in mouse tumor models including patient-derived xenograft model and sarcoma model. I used computational approaches including singular value decomposition and analysis of genome-scale metabolic network to show that dietary methionine restriction specifically targets one carbon metabolism in multiple tissues to mediate anti-tumor effects, and that similar changes in plasma metabolite profiles can be achieved in humans through dietary methionine restriction.

1. Xia Gao, Sydney M Sanderson, **Ziwei Dai**, Michael A Reid, Daniel E Cooper, Min Lu, John P Richie, Amy Ciccarella, Ana Calcagnotto, Peter G Mikhael, Samantha J Mentch, Juan Liu, Gene Ables, David G Kirsch, David S Hsu, Sailendra N Nichenametla, Jason W Locasale*. Methionine metabolism links diet and nutrition to the efficacy of cancer therapies. **Nature.** 2019 Aug;572(7769):397-401.
2. Sydney M Sanderson, Xia Gao, **Ziwei Dai**, Jason W Locasale*. Methionine Metabolism in Health and Cancer: A Nexus of Diet and Targeted Medicine. **Nat Rev Cancer.** 2019 Sep 12.

- **Computational modeling of the Warburg Effect**

To investigate possible mechanisms that cause the Warburg Effect (WE) in cancer cells, I developed a flux balance model of glycolysis to demonstrate that the extent of WE in cancer cells is determined by cellular demands of redox balancing, energy and biomass. I then developed a more detailed ODE model for glycolysis and simulated this model to identify the enzyme GAPDH as the rate-limiting step of glycolysis in cells with higher WE. The prediction was validated by experiments in cancer cells and mouse xenograft tumor models which showed that KA, an inhibitor of GAPDH, selectively killed cancer cells with higher WE and reduced tumor growth *in vivo*.

1. **Ziwei Dai**, Alexander A Shestov, Luhua Lai, Jason W Locasale*. A Flux Balance of Glucose Metabolism Clarifies the Requirements of the Warburg Effect. **Biophys J.** 2016 Sep 6;111(5):1088-100.
2. **Ziwei Dai***, Jason W Locasale*. Thermodynamic constraints on the regulation of metabolic fluxes. **J Biol Chem.** 2018 Dec 21;293(51):19725-19739.
3. Maria V Liberti, **Ziwei Dai**, Suzanne E Wardell, Joshua A Baccile, Xiaojing Liu, Xia Gao, Robert Baldi, Mahya Mehrmohamadi, Marc O Johnson, Neel S Madhukar, Alexander A Shestov, Iok I Christine Chio, Olivier Elemento, Jeffrey C Rathmell, Frank C Schroeder, Donald P McDonnell, Jason W Locasale*. A Predictive Model for Selective Targeting of the Warburg Effect through GAPDH Inhibition with a Natural Product. **Cell Metab.** 2017 Oct 3;26(4):648-659.

- **Development of computational models for 13C-metabolic flux analysis**

I and Shiyu Liu, a graduate student that I've been mentoring, applied 13C-metabolic flux analysis to study the effects of PHGDH inhibition on fluxes in central carbon metabolism. We found that PHGDH inhibition leads to simultaneous alterations of fluxes in pentose phosphate pathway, TCA cycle and serine, glycine and one carbon (SGOC) metabolism, resulting in impairment of nucleotide synthesis and cell toxicity. I also developed kinetic flux profiling models to quantitate glycolytic fluxes in different cell lines under KA treatment.

1. **Ziwei Dai**, Jason W Locasale*. Understanding metabolism with flux analysis: From theory to application. **Metab Eng.** 2017 Sep;43(Pt B):94-102.

2. Michael A Reid, Annamarie E Allen, Shiyu Liu, Maria V Liberti, Pei Liu, Xiaojing Liu, **Ziwei Dai**, Xia Gao, Qian Wang, Ying Liu, Luhua Lai, Jason W Locasale*. Serine synthesis through PHGDH coordinates nucleotide levels by maintaining central carbon metabolism. *Nat Commun.* 2018 Dec 21;9(1):5442.
 3. Maria V Liberti, **Ziwei Dai**, Suzanne E Wardell, Joshua A Baccile, Xiaojing Liu, Xia Gao, Robert Baldi, Mahya Mehrmohamadi, Marc O Johnson, Neel S Madhukar, Alexander A Shestov, Iok I Christine Chio, Olivier Elemento, Jeffrey C Rathmell, Frank C Schroeder, Donald P McDonnell, Jason W Locasale*. A Predictive Model for Selective Targeting of the Warburg Effect through GAPDH Inhibition with a Natural Product. *Cell Metab.* 2017 Oct 3;26(4):648-659.
- **Parameter estimation and computer simulation of biological networks**

In my PhD thesis, I developed a computer algorithm for parameter estimation of biological network models based on experimental data. The algorithm, named differential simulated annealing (DSA), uses information about the geometry of the parameter space to accelerate the convergence of the simulated annealing algorithm. Compared to other algorithms, DSA was able to reach parameter sets that better fit experimental data in shorter time. I also collaborated with other researchers in our group to apply DSA in several biological network models they developed.

1. **Ziwei Dai**, Luhua Lai*. Differential simulated annealing: a robust and efficient global optimization algorithm for parameter estimation of biological networks. *Mol Biosyst.* 2014 Jun;10(6):1385-92.

COMPLETE PUBLICATION LIST

1. **Ziwei Dai**, Vijyendra Ramesh, Jason W Locasale. The evolving metabolic landscape of chromatin biology and epigenetics. *Nat Rev Genet.* 2020 Dec;21(12):737-753.
2. Shiyu Liu, **Ziwei Dai**, Daniel E Cooper, David G Kirsch, Jason W Locasale. Quantitative Analysis of the Physiological Contributions of Glucose to the TCA Cycle. *Cell Metab.* 2020 Oct 6;32(4):619-628.e21.
3. **Ziwei Dai***, Jason W Locasale*. Cooperative virus propagation underlies COVID-19 transmission dynamics. *medRxiv [Preprint]*. 2020 May 7:2020.05.05.20092361.
4. Lake-Ee Quek*, James R Krycer, Satoshi Ohno, Katsuyuki Yugi, Daniel J Fazakerley, Richard Scalzo, Sarah D Elkington, **Ziwei Dai**, Akiyoshi Hirayama, Satsuki Ikeda, Futaba Shoji, Kumi Suzuki, Jason W Locasale, Tomoyoshi Soga, David E James*, Shinya Kuroda*. Dynamic 13C flux analysis captures the reorganisation of adipocyte glucose metabolism in response to insulin. *iScience.* 2020 Jan 21.
5. Zhengtao Xiao*, Jason W Locasale, **Ziwei Dai**. Metabolism in the tumor microenvironment: insights from single-cell analysis. *OncoImmunology.* 2020 Jan 1.
6. Maria V Liberti*, Annamarie E Allen, Vijyendra Ramesh, **Ziwei Dai**, Katherine R Singleton, Zufeng Guo, Jun O Liu, Kris C Wood, Jason W Locasale. Evolved resistance to partial GAPDH inhibition results in loss of the Warburg effect and in a different state of glycolysis. *J Biol Chem.* 2019 Nov 20.
7. **Ziwei Dai**, Shiyu Yang, Liyan Xu, Hongrong Hu, Kun Liao, Jianghuang Wang, Qian Wang, Shuaishi Gao, Bo Li*, Luhua Lai*. Identification of cancer-associated metabolic vulnerabilities by modeling multi-objective optimality in metabolism. *Cell Commun Signal.* 2019 Oct 10;17(1):124.
8. Sydney M Sanderson, Xia Gao, **Ziwei Dai**, Jason W Locasale*. Methionine Metabolism in Health and Cancer: A Nexus of Diet and Targeted Medicine. *Nat Rev Cancer.* 2019 Sep 12.

9. Xia Gao, Sydney M Sanderson, **Ziwei Dai**, Michael A Reid, Daniel E Cooper, Min Lu, John P Richie, Amy Ciccarella, Ana Calcagnotto, Peter G Mikhael, Samantha J Mentch, Juan Liu, Gene Ables, David G Kirsch, David S Hsu, Sailendra N Nichenametla, Jason W Locasale*. Methionine metabolism links diet and nutrition to the efficacy of cancer therapies. **Nature**. 2019 Aug;572(7769):397-401.
10. Sydney M Sanderson, Peter G Mikhael, Vijyendra Ramesh, **Ziwei Dai**, Jason W Locasale*. Nutrient availability shapes methionine metabolism in p16/MTAP-deleted cells. **Sci Adv**. 2019 Jun26;5(6):eaav7769.
11. Zhengtao Xiao, **Ziwei Dai***, Jason W Locasale*. Metabolic landscape of the tumor microenvironment at single cell resolution. **Nat Commun**. 2019 Aug 21;10(1):3763.
12. **Ziwei Dai***, Jason W Locasale*. Thermodynamic constraints on the regulation of metabolic fluxes. **J Biol Chem**. 2018 Dec 21;293(51):19725-19739.
13. Michael A Reid, Annamarie E Allen, Shiyu Liu, Maria V Liberti, Pei Liu, Xiaojing Liu, **Ziwei Dai**, Xia Gao, Qian Wang, Ying Liu, Luhua Lai, Jason W Locasale*. Serine synthesis through PHGDH coordinates nucleotide levels by maintaining central carbon metabolism. *Nat Commun*. 2018 Dec 21;9(1):5442.
14. **Ziwei Dai**, Samantha J Mentch, Xia Gao, Sailendra N Nichenametla, Jason W Locasale*. Methionine metabolism influences the genomic architecture of H3K4me3 with the link to gene expression encoded in peak width. **Nat Commun**. 2018 May 16;9(1):1955.
15. Hu Meng, **Ziwei Dai**, Weilin Zhang, Ying Liu, Luhua Lai*. Molecular mechanism of 15-lipoxygenase allosteric activation and inhibition. **Phys Chem Chem Phys**. 2018 May 30;20(21):14785-14795.
16. Michael A Reid, **Ziwei Dai**, Jason W Locasale*. The impact of cellular metabolism on chromatin dynamics and epigenetics. **Nat Cell Biol**. 2017 Nov;19(11):1298-1306.
17. Maria V Liberti, **Ziwei Dai**, Suzanne E Wardell, Joshua A Baccile, Xiaojing Liu, Xia Gao, Robert Baldi, Mahya Mehrmohamadi, Marc O Johnson, Neel S Madhukar, Alexander A Shestov, Iok I Christine Chio, Olivier Elemento, Jeffrey C Rathmell, Frank C Schroeder, Donald P McDonnell, Jason W Locasale*. A Predictive Model for Selective Targeting of the Warburg Effect through GAPDH Inhibition with a Natural Product. **Cell Metab**. 2017 Oct 3;26(4):648-659.
18. **Ziwei Dai**, Jason W Locasale*. Understanding metabolism with flux analysis: From theory to application. **Metab Eng**. 2017 Sep;43(Pt B):94-102.
19. **Ziwei Dai**, Jason W Locasale*. Metabolic pattern formation in the tumor microenvironment. **Mol Syst Biol**. 2017 Feb 9;13(2):915.
20. **Ziwei Dai**, Alexander A Shestov, Luhua Lai, Jason W Locasale*. A Flux Balance of Glucose Metabolism Clarifies the Requirements of the Warburg Effect. **Biophys J**. 2016 Sep 6;111(5):1088-100.
21. Hu Meng, Christopher L McClendon, **Ziwei Dai**, Kenan Li, Xiaoling Zhang, Shan He, Erchang Shang, Ying Liu, Luhua Lai*. Discovery of Novel 15-Lipoxygenase Activators To Shift the Human Arachidonic Acid Metabolic Network toward Inflammation Resolution. **J Med Chem**. 2016 May 12;59(9):4202-9.
22. Youjun Xu, **Ziwei Dai**, Fangjin Chen, Shuaishi Gao, Jianfeng Pei, Luhua Lai*. Deep Learning for Drug-Induced Liver Injury. **J Chem Inf Model**. 2015 Oct 26;55(10):2085-93.
23. Yiran Wu, Xiaolong Zhuo, **Ziwei Dai**, Xiao Guo, Yao Wang, Chuanmao Zhang, Luhua Lai*. Modeling the mitotic regulatory network identifies highly efficient anti-cancer drug combinations. **Mol Biosyst**. 2015 Feb;11(2):497-505.

24. **Ziwei Dai**, Luhua Lai*. Differential simulated annealing: a robust and efficient global optimization algorithm for parameter estimation of biological networks. **Mol Biosyst.** 2014 Jun;10(6):1385-92.
25. Cheng Zhu, **Ziwei Dai**, Huanhuan Liang, Tao Zhang, Feng Gai, Luhua Lai*. Slow and bimolecular folding of a de novo designed monomeric protein DS119. **Biophys J.** 2013 Nov 5;105(9):2141-8.

Contributed as member of consortium:

26. Guinney J, Wang T, Laajala TD, Winner KK, Bare JC, Neto EC, Khan SA, Peddinti G, Airola A, Pahikkala T, Mirtti T, Yu T, Bot BM, Shen L, Abdallah K, Norman T, Friend S, Stolovitzky G, Soule H, Sweeney CJ, Ryan CJ, Scher HI, Sartor O, Xie Y, Aittokallio T, Zhou FL, Costello JC; **Prostate Cancer Challenge DREAM Community.** Prediction of overall survival for patients with metastatic castration-resistant prostate cancer: development of a prognostic model through a crowdsourced challenge with open clinical trial data. **Lancet Oncol.** 2017 Jan;18(1):132-142.
27. Eduati F, Mangravite LM, Wang T, Tang H, Bare JC, Huang R, Norman T, Kellen M, Menden MP, Yang J, Zhan X, Zhong R, Xiao G, Xia M, Abdo N, Kosyk O; **NIEHS-NCATS-UNC DREAM Toxicogenetics Collaboration.**, Friend S, Dearth A, Simeonov A, Tice RR, Rusyn I, Wright FA, Stolovitzky G, Xie Y, Saez-Rodriguez J. Prediction of human population responses to toxic compounds by a collaborative competition. **Nat Biotechnol.** 2015 Sep;33(9):933-40.

AWARDS & HONORS

- **Robert J. Fitzgerald Scholar Award**, 2018
Department of Pharmacology and Cancer Biology, Duke University
10 out of 100 students and postdocs in the department got this award.
- **National Fellowship for Graduate Students**, 2014
Ministry of Education and Ministry of Finance of China
7 out of 150 students in the department received this fellowship.
- **President Fellowship for Graduate Students**, 2014
Peking University, China
8 out of 50 students in the program received this fellowship.

INVITED TALKS

- **Works-in-progress seminar of pharmacology and cancer biology**
Duke University, Durham, NC
January, 2019
- **Scientific retreat of pharmacology and cancer biology**
Duke University, Durham, NC
September, 2018
- **Duke epigenetics seminar**
Duke University, Durham, NC
January, 2017

MENTORING EXPERIENCE

- **Chuping Qiu** (graduate student, 2018-)
- **Zhengtao Xiao, PhD** (postdoc, 2017-) Dr. Xiao has published two first-author papers in high-impact journals with me, including one in *Nature Communications* and one in *Oncoimmunology*.

- **Shiyu Liu** (graduate student, 2016-) Shiyu has successfully passed his preliminary examination and completed a first-author paper with me. The paper is currently in revision in *Cell Metabolism*.
- **Luke Hayden** (rotation student, 2017)
- **Young-sook Kim** (rotation student, 2016)
- **Peter Mikhael** (undergraduate student, 2016-2019) Peter has co-authored two papers with me, including one in *Nature* and one in *Science Advances*.

EDITORIAL EXPERIENCE

Ad hoc reviewer (journals): Trends Endocrinol Metab, Clin Cancer Res, PLoS Biol, Sci Rep, BMC Syst Biol, BMC Bioinformatics, Wiley Interdiscip Rev Syst Biol Med, Open Biol, Molecules

Ad hoc reviewer (funding agency): FONDECYT Initiation (Chile)