BIOGRAPHICAL SKETCH

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NAME: **Wu, Sihan**

POSITION TITLE: Assistant Professor, Children's Research Institute at UT Southwestern

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)	END DATE MM/YYYY	FIELD OF STUDY
Sun Yat-sen University, Guangzhou, Guangdong	BS	07/2009	Biotechnology
Sun Yat-sen University, Guangzhou, Guangdong	PHD	07/2014	Pharmacology

A. Personal Statement

My lab focuses on understanding the molecular function and dependency of extrachromosomal DNA (ecDNA) in human cancer and leveraging this knowledge to develop effective therapeutic strategies to treat ecDNA-driven cancer. In cancer, oncogene-containing DNA segments frequently jump off the chromosome and form circular ecDNA particles, especially in the most aggressive cancer types, including brain, lung, and breast cancers. Given the prevalence of ecDNA in cancer, my lab seeks to interrogate the molecular function of ecDNA and the molecular mechanism that maintains the ecDNA population in the cancer genome. By integrating high-resolution imaging and modern sequencing technologies, we have begun to understand how the structure of ecDNA impacts oncogene function, including how its circular shape and hyper-accessible chromatin promotes massive oncogene expression. Further, by revealing its unequal segregation behavior during mitosis, we show that ecDNA enables rapid oncogene copy number gain and facilitates genetic heterogeneity, therefore driving tumor evolution and therapeutic resistance. My lab is also interested in revealing the mechanism supporting ecDNA function, including how it replicates, transcribes, and repairs. This information may allow us to therapeutically target ecDNA, undermining the expression of amplified oncogenes, including the ones that still cannot be targeted through traditional pharmacological approaches.

Selected publications (* First & co-first author; † Corresponding & co-corresponding author)

1. **Wu S***, Bafna V, Mischel PS. Extrachromosomal DNA (ecDNA) in cancer pathogenesis. ***Current Opinion in Genetics & Development.*** 2021 Feb;66:78-82.
2. Kim H, Nguyen N, Turner K, **Wu S**, Gujar A, Luebeck J, Liu J, Deshpande V, Rajkumar U, Namburi S, Amin S, Yi E, Menghi F, Schulte J, Henssen A, Chang H, Beck C, Mischel P, Bafna V, Verhaak R. Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers. ***Nature Genetics.*** 2020 August 17; 52(9):891-897.
3. **Wu S***, Turner KM*, Nguyen N*, Raviram R, Erb M, Santini J, Luebeck J, Rajkumar U, Diao Y, Li B, Zhang W, Jameson N, Corces MR, Granja JM, Chen X, Coruh C, Abnousi A, Houston J, Ye Z, Hu R, Yu M, Kim H, Law JA, Verhaak RGW, Hu M, Furnari FB, Chang HY, Ren B, Bafna V, Mischel PS. Circular ecDNA promotes accessible chromatin and high oncogene expression. ***Nature.*** 2019 Nov;575(7784):699-703.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 - Assistant Professor, Children's Research Institute, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX

2021 - 2021 Basic Life Research Scientist, Stanford University, Stanford, CA

2020 - 2021	Senior Staff Research Associate, University of California, San Diego, La Jolla, CA
2014 - 2020	Postdoc, Ludwig Institute for Cancer Research San Diego Branch, La Jolla, CA
2009 - 2014	Ph.D. candidate, Laboratory of Guangmei Yan, Sun Yat-sen University, Guangzhou
2007 - 2009	Undergraduate Researcher, Laboratory of Guangmei Yan, Sun Yat-sen University, Guangzhou

Honors

2021	CPRIT Scholar, Cancer Prevention and Research Institute of Texas
2020	Zhi-Liao Award, Zhihu & Chinese Academy of Sciences
2019	Ludwig Institute Kerr Award, Ludwig Institute for Cancer Research
2019	Award of Excellence, poster session, UC San Diego Moore Cancer Center
2012	National Award for Academic Star of Doctoral Candidate, Ministry of Education of China
2012	National Scholarship for Graduated Student, Ministry of Education of China

C. Contribution to Science

1. **The molecular function of extrachromosomal DNA (ecDNA) in human cancer.** The ecDNA-based oncogene amplification is surprisingly prevalent in human cancer. Our lab first provides the most definitive proof showing the circular shape of ecDNA, driving massive oncogene expression due to its high copy number and hyper-accessible chromatin, forming new gene regulatory circuits, and associating with worse clinical outcomes.

    a. **Wu S***, Bafna V, Mischel PS. Extrachromosomal DNA (ecDNA) in cancer pathogenesis. ***Current Opinion in Genetics & Development.*** 2021 Feb;66:78-82.

    b. Kim H, Nguyen N, Turner K, **Wu S**, Gujar A, Luebeck J, Liu J, Deshpande V, Rajkumar U, Namburi S, Amin S, Yi E, Menghi F, Schulte J, Henssen A, Chang H, Beck C, Mischel P, Bafna V, Verhaak R. Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers. ***Nature Genetics.*** 2020 August 17; 52(9):891-897

    c. **Wu S***, Turner KM*, Nguyen N*, Raviram R, Erb M, Santini J, Luebeck J, Rajkumar U, Diao Y, Li B, Zhang W, Jameson N, Corces MR, Granja JM, Chen X, Coruh C, Abnousi A, Houston J, Ye Z, Hu R, Yu M, Kim H, Law JA, Verhaak RGW, Hu M, Furnari FB, Chang HY, Ren B, Bafna V, Mischel PS. Circular ecDNA promotes accessible chromatin and high oncogene expression. ***Nature.*** 2019 Nov;575(7784):699-703.

2. **Metabolic co-dependencies in cancer.** Altered cellular metabolism is one of the most characteristic phenotypic changes that occurs during the process of tumor formation, progression, and drug resistance. We identify that glycolytic and membrane lipid metabolisms are reprogrammed in glioblastoma, and in turn, addict to these pathways, rendering a unique therapeutic window to specifically target glioblastoma by tackling metabolic pathways.

    a. Bi J*, Chowdhry S*, **Wu S***, Zhang W, Masui K, Mischel P. Altered cellular metabolism in gliomas — an emerging landscape of actionable co-dependency targets. ***Nature Reviews Cancer.*** 2019 December 05; 20(1):57-70.

    b. Bi J, Ichu T, Zanca C, Yang H, Zhang W, Gu Y, Chowdhry S, Reed A, Ikegami S, Turner K, Zhang W, Villa G, **Wu S**, Quehenberger O, Yong W, Kornblum H, Rich J, Cloughesy T, Cavenee W, Furnari F, Cravatt B, Mischel P. Oncogene Amplification in Growth Factor Signaling Pathways Renders Cancers Dependent on Membrane Lipid Remodeling. ***Cell Metabolism.*** 2019 September; 30(3):525-538.e8.

    c. Bi J*, **Wu S***, Zhang W*, Mischel P. Targeting cancer's metabolic co-dependencies: A landscape shaped by genotype and tissue context. ***Biochimica et Biophysica Acta (BBA) - Reviews on Cancer.*** 2018 August; 1870(1):76-87.

    d. Xing F, Luan Y, Cai J, **Wu S**, Mai J, Gu J, Zhang H, Li K, Lin Y, Xiao X, Liang J, Li Y, Chen W, Tan Y, Sheng L, Lu B, Lu W, Gao M, Qiu P, Su X, Yin W, Hu J, Chen Z, Sai K, Wang J, Chen F, Chen Y, Zhu

S, Liu D, Cheng S, Xie Z, Zhu W, Yan G. The Anti-Warburg Effect Elicited by the cAMP-PGC1α Pathway Drives Differentiation of Glioblastoma Cells into Astrocytes. ***Cell Reports.*** 2017 January; 18(2):468-481.

3. **Molecular pathology of glioma.** Glioma is one of the most lethal human cancer with a dismal clinical outcome despite extensive treatment. We sought to understand the molecular alterations in glioma, revealing how microRNA, protein kinase A pathway, and NF-kappa B pathway link to the growth, invasion, and drug resistance of glioma, providing new angles to develop therapeutic strategies.

   a. Zanca C, Villa G, Benitez J, Thorne A, Koga T, D'Antonio M, Ikegami S, Ma J, Boyer A, Banisadr A, Jameson N, Parisian A, Eliseeva O, Barnabe G, Liu F, **Wu S**, Yang H, Wykosky J, Frazer K, Verkhusha V, Isaguliants M, Weiss W, Gahman T, Shiau A, Chen C, Mischel P, Cavenee W, Furnari F. Glioblastoma cellular cross-talk converges on NF-κB to attenuate EGFR inhibitor sensitivity. ***Genes & Development.*** 2017 June 15; 31(12):1212-1227.

   b. Zhou Y*, **Wu S***, Liang C*, Lin Y, Zou Y, Li K, Lu B, Shu M, Huang Y, Zhu W, Kang Z, Xu D, Hu J, Yan G. Transcriptional upregulation of microtubule-associated protein 2 is involved in the protein kinase A-induced decrease in the invasiveness of glioma cells. ***Neuro-Oncology.*** 2015 December; 17(12):1578-1588.

   c. **Wu S***, Lin Y*, Xu D, Chen J, Shu M, Zhou Y, Zhu W, Su X, Zhou Y, Qiu P, Yan G. MiR-135a functions as a selective killer of malignant glioma. ***Oncogene.*** 2012 Aug 23;31(34):3866-74.

   d. Shu M*, Zheng X*, **Wu S***, Lu H, Leng T, Zhu W, Zhou Y, Ou Y, Lin X, Lin Y, Xu D, Zhou Y, Yan G. Targeting oncogenic miR-335 inhibits growth and invasion of malignant astrocytoma cells. ***Molecular Cancer.*** 2011 May 19;10:59.

4. **Defective innate immunity in cancer.** Avoiding immune destruction is essential for tumorigenesis. We identified a zinc-finger antiviral protein ZAP, a core component of innate immunity that restricts viral infection, is commonly downregulated in a panel of clinical cancer specimens. We further demonstrate that loss-of-function of ZAP synergizes with APC-deficiency to drive colorectal cancer, and renders selective vulnerability to oncolytic alphavirus M1.

   a. Cai J, Liu W, Wong CW, Zhu W, Lin Y, Hu J, Xu W, Zhang J, Sander M, Wang Z, Dan J, Zhang J, Liu Y, Guo L, Qin Z, Liu X, Liu Y, Yan G, **Wu S**†, Liang J†. Zinc-finger antiviral protein acts as a tumor suppressor in colorectal cancer. ***Oncogene.*** 2020 Sep;39(37):5995-6008.

   b. Lin Y, Zhang H, Liang J, Li K, Zhu W, Fu L, Wang F, Zheng X, Shi H, **Wu S**, Xiao X, Chen L, Tang L, Yan M, Yang X, Tan Y, Qiu P, Huang Y, Yin W, Su X, Hu H, Hu J, Yan G. Identification and characterization of alphavirus M1 as a selective oncolytic virus targeting ZAP-defective human cancers. ***Proceedings of the National Academy of Sciences.*** 2014 October 21; 111(42):E4504-E4512.