BIOGRAPHICAL SKETCH

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NAME: Wu, Sihan

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

POSITION TITLE: Assistant 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)	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
Ludwig Institute for Cancer Research, San Diego, California	Postdoctoral Fellow	08/2020	Cancer genetics
University of California, San Diego, San Diego, California	Fellow	03/2021	Cancer genetics
Stanford University, Stanford, California	Fellow	06/2021	Cancer genetics

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 promote 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.

1. Lange JT, Rose JC, Chen CY, Pichugin Y, Xie L, Tang J, Hung KL, Yost KE, Shi Q, Erb ML, Rajkumar U, **Wu S**, Taschner-Mandl S, Bernkopf M, Swanton C, Liu Z, Huang W, Chang HY, Bafna V, Henssen AG, Werner B, Mischel PS. The evolutionary dynamics of extrachromosomal DNA in human cancers. **Nat Genet.** 2022 Oct;54(10):1527-1533. PubMed Central PMCID: PMC9534767.
2. Hung KL, Yost KE, Xie L, Shi Q, Helmsauer K, Luebeck J, Schöpflin R, Lange JT, Chamorro González R, Weiser NE, Chen C, Valieva ME, Wong IT, **Wu S**, Dehkordi SR, Duffy CV, Kraft K, Tang J, Belk JA, Rose JC, Corces MR, Granja JM, Li R, Rajkumar U, Friedlein J, Bagchi A, Satpathy AT, Tjian R, Mundlos S, Bafna V, Henssen AG, Mischel PS, Liu Z, Chang HY. ecDNA hubs drive cooperative intermolecular oncogene expression. **Nature.** 2021 Dec;600(7890):731-736. PubMed Central PMCID: PMC9126690.
3. Kim H, Nguyen NP, Turner K, **Wu S**, Gujar AD, Luebeck J, Liu J, Deshpande V, Rajkumar U, Namburi S, Amin SB, Yi E, Menghi F, Schulte JH, Henssen AG, Chang HY, Beck CR, Mischel PS, Bafna V, Verhaak RGW. Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers. **Nat Genet.** 2020 Sep;52(9):891-897. PubMed Central PMCID: PMC7484012.
4. **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. PubMed Central PMCID: PMC7094777.

Ongoing Research Support

RR210034 Wu (PI) 06/01/2021 - 05/31/2026
Cancer Prevention and Research Institute of Texas (CPRIT)
Recruitment of First-Time, Tenure-Track Faculty Members
Deciphering the replication of extrachromosomal DNA in cancer
The goals of this proposal are to identify cancer cell lines that carry ecDNAs and to generate genomic maps of the ecDNAs in each line, to characterize ecDNA replication, and to model ecDNA formation in genetically engineered mice.

CGCFUL-2021\100011 Mischel (PI), Chen (Co-PI), Wu (Young Investigator) 06/2022 – 05/2027
Cancer Research UK & National Cancer Institute
Cancer Grand Challenge
WP6-ecDNA sensing and immune response
The major goal of this project is to determine whether and how extrachromosomal DNA is detected by cGAS to trigger innate immune responses, how some cancer cells evade detection of ecDNA by cGAS and how to reinvigorate antitumor immune responses by harnessing the cGAS-STING pathway to detect ecDNA specifically in cancer cells.

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
2021	Forbeck Scholar, William Guy Forbeck Research Foundation
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. Lange JT, Rose JC, Chen CY, Pichugin Y, Xie L, Tang J, Hung KL, Yost KE, Shi Q, Erb ML, Rajkumar U, **Wu S**, Taschner-Mandl S, Bernkopf M, Swanton C, Liu Z, Huang W, Chang HY, Bafna V, Henssen AG, Werner B, Mischel PS. The evolutionary dynamics of extrachromosomal DNA in human cancers. **Nat Genet.** 2022 Oct;54(10):1527-1533. PubMed Central PMCID: PMC9534767.

    b. Hung KL, Yost KE, Xie L, Shi Q, Helmsauer K, Luebeck J, Schöpflin R, Lange JT, Chamorro González R, Weiser NE, Chen C, Valieva ME, Wong IT, **Wu S**, Dehkordi SR, Duffy CV, Kraft K, Tang J, Belk JA,

Rose JC, Corces MR, Granja JM, Li R, Rajkumar U, Friedlein J, Bagchi A, Satpathy AT, Tjian R, Mundlos S, Bafna V, Henssen AG, Mischel PS, Liu Z, Chang HY. ecDNA hubs drive cooperative intermolecular oncogene expression. **Nature.** 2021 Dec;600(7890):731-736. PubMed Central PMCID: PMC9126690.

c. Kim H, Nguyen NP, Turner K, **Wu S**, Gujar AD, Luebeck J, Liu J, Deshpande V, Rajkumar U, Namburi S, Amin SB, Yi E, Menghi F, Schulte JH, Henssen AG, Chang HY, Beck CR, Mischel PS, Bafna V, Verhaak RGW. Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers. **Nat Genet.** 2020 Sep;52(9):891-897. PubMed Central PMCID: PMC7484012.

d. **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. PubMed Central PMCID: PMC7094777.

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 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, Khan A, Tang J, Armando AM, **Wu S**, Zhang W, Gimple RC, Reed A, Jing H, Koga T, Wong IT, Gu Y, Miki S, Yang H, Prager B, Curtis EJ, Wainwright DA, Furnari FB, Rich JN, Cloughesy TF, Kornblum HI, Quehenberger O, Rzhetsky A, Cravatt BF, Mischel PS. Targeting glioblastoma signaling and metabolism with a re-purposed brain-penetrant drug. **Cell Rep.** 2021 Nov 2;37(5):109957. PubMed Central PMCID: PMC8856626.

   b. Bi J, Chowdhry S, **Wu S**, Zhang W, Masui K, Mischel PS. Altered cellular metabolism in gliomas - an emerging landscape of actionable co-dependency targets. **Nat Rev Cancer.** 2020 Jan;20(1):57-70. PubMed PMID: 31806884.

   c. Bi J, Ichu TA, Zanca C, Yang H, Zhang W, Gu Y, Chowdhry S, Reed A, Ikegami S, Turner KM, Zhang W, Villa GR, **Wu S**, Quehenberger O, Yong WH, Kornblum HI, Rich JN, Cloughesy TF, Cavenee WK, Furnari FB, Cravatt BF, Mischel PS. Oncogene Amplification in Growth Factor Signaling Pathways Renders Cancers Dependent on Membrane Lipid Remodeling. **Cell Metab.** 2019 Sep 3;30(3):525-538.e8. PubMed Central PMCID: PMC6742496.

   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 Rep.** 2017 Jan 10;18(2):468-481. PubMed Central PMCID: PMC5926788.

3. **Genetic and epigenetic reprograming of gene transcription in cancer.** Disrupted gene regulation is a major cause of human diseases, including cancer. Gene transcription is dictated by DNA sequence, epigenetic codes, and transcription regulatory proteins. In cancer, these elements are often reprogrammed to fuel cancer growth and adapt to the ever-changing tumor microenvironment. We show how microRNAs, protein kinase A pathway, and NF-kappa B pathway link to the growth, invasion, and drug resistance of cancer, providing new angles to develop therapeutic strategies.

   a. Chen PB, Fiaux PC, Zhang K, Li B, Kubo N, Jiang S, Hu R, Rooholfada E, **Wu S**, Wang M, Wang W, McVicker G, Mischel PS, Ren B. Systematic discovery and functional dissection of enhancers needed for cancer cell fitness and proliferation. **Cell Rep.** 2022 Nov 8;41(6):111630. PubMed PMID: 36351387.

   b. Zanca C, Villa GR, Benitez JA, Thorne AH, Koga T, D'Antonio M, Ikegami S, Ma J, Boyer AD, Banisadr A, Jameson NM, Parisian AD, Eliseeva OV, Barnabe GF, Liu F, **Wu S**, Yang H, Wykosky J, Frazer KA, Verkhusha VV, Isaguliants MG, Weiss WA, Gahman TC, Shiau AK, Chen CC, Mischel PS, Cavenee WK, Furnari FB. Glioblastoma cellular cross-talk converges on NF-κB to attenuate EGFR inhibitor sensitivity. **Genes Dev.** 2017 Jun 15;31(12):1212-1227. PubMed Central PMCID: PMC5558924.

c. 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 Oncol.** 2015 Dec;17(12):1578-88. PubMed Central PMCID: PMC4633926.

d. **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. PubMed PMID: 22139076.

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. PubMed PMID: 32770142.

   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. **Proc Natl Acad Sci U S A.** 2014 Oct 21;111(42):E4504-12. PubMed Central PMCID: PMC4210284.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/sihan.wu.1/bibliography/public/