BIOGRAPHICAL SKETCH

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NAME: **Hao Zhu, M.D.**

POSITION TITLE: Kern Wildenthal, M.D., Ph.D. Distinguished Professorship in Pediatric Research
Professor in Children's Research Institute
Associate Professor in Pediatrics and Internal Medicine
Divisions of Hematology and Oncology

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
Duke University	B.S.	05/1999	Biology
Harvard Medical School and MIT	M.D.	06/2005	Medicine
University of California, San Francisco	Residency	06/2007	Internal Medicine
Dana-Farber/Brigham and Women's Hospital/ Massachusetts General Hospital	Fellowship	06/2011	Hematology/Oncology

A. Personal Statement

Dr. Zhu's lab is focused on understanding the connections between tissue injury, regeneration, and cancer. It is well known that chronic tissue damage increases the risk of cancer in multiple tissues, but the underlying mechanisms are poorly understood. The liver is an ideal setting to address this question because cirrhosis and hepatocellular carcinoma (HCC) are frequent and devastating outcomes of chronic liver damage. We are interested in functionally dissecting cell type heterogeneity in the liver in order to understand the cellular origins of HCCs, and how these origins impact cancer biology. We are also interested in identifying genes that can increase or decrease regenerative and malignant capacity within important cell types. Over the last several years, we have shown that important chromatin remodeling mechanisms such as SWI/SNF can modulate cancer and regeneration in the liver. Our findings indicate that regenerative capacity can be dissociated from cancer risk and we seek to translate these findings into clinical use. Part of my time is spent caring for liver cancer patients at the Parkland Memorial Hospital Multidisciplinary HCC Clinic, work that fuels translational aspects of my research.

Key publications from my lab:

a. Sun X, Chuang J, Kanchwala M, Wu L, Celen C, Li L, Liang H, Zhang S, Maples T, Nguyen L, Wang S, Signer R, Sorouri M, Nassour I, Liu X, Xu J, Wu, M, Zhao Y, Kuo Y, Wang Z, Xing C, and Zhu H. Suppression of the SWI/SNF component Arid1a promotes mammalian regeneration. ***Cell Stem Cell***. 2016 Apr 7;18(4):456-66. PMID: 27044474.

b. Sun X*, Wang SC*, Luo X, Jia Y, Gopal P, Zhu M, Li L, Nassour I, Chuang JC, Maples T, Celen C, Nguyen LH, Wu L, Fu S, Li W, Hui L, Tian F, Ji Y, Zhang S, Sorouri M, Hwang TH, Letzig L, James L, Yopp A, Singal A, Zhu H. *Equal contributors. *Arid1a* has context-dependent oncogenic and tumor suppressor functions in liver cancer. ***Cancer Cell***. 2017. Nov 13;32(5):574-589.e6. PMID: 29136504.

c. Zhang S, Zhou K, Luo X, Li L, Nguyen LH, Zhang Y, Tarlow B, Siegwart DJ, and Zhu H. The polyploid state plays a tumor suppressive role in the liver. ***Developmental Cell***. 2018 Feb 26;44(4):447-459.e5. PMID: 29429824.

d. Zhu M*, Lu T*, Jia Y*, Luo X*, Gopal P, Li L, Odewole M, Renteria V, Singal AG, Jang Y, Ge K, Wang SC, Sorouri M, Parekh JR, MacConmara MP, Yopp AC, Wang T†, Zhu H†. *Equal contributors. †Co-corresponding authors. Somatic mutations increase hepatic clonal fitness and regeneration in chronic liver disease. ***Cell.*** 2019. Apr 2. pii: S0092-8674(19)30288-0. PMID: 30955891.

B. Positions and Honors

1998-99	Undergraduate Research Student, Lab of Daniel Kiehart, Duke Medical Center, Durham, NC
1999-00	Research Technician, Lab of Ron Vale, University of California at San Francisco, CA
2001-04	Medical Student, Lab of Leonard Zon, Division of Hematology/Oncology, Children's Hospital Boston, Harvard Medical School, Boston, MA
2005-07	Categorical Internal Medicine Residency, University of California at San Francisco, CA.
2005-07	Molecular Medicine Program Fellow, University of California at San Francisco, CA.
2007-	Hematology/Oncology Fellowship, Dana-Farber Cancer Institute/Mass General Hospital.
2008-	Research fellow, Lab of George Daley. Division of Hematology/Oncology, Children's Hospital Boston, Harvard Medical School, Boston, MA
2011-12	Instructor in Medicine, Harvard Medical School.
2012-	Assistant Professor in Children's Research Institute and Assistant Professor in Pediatrics and Internal Medicine, Divisions of Hematology-Oncology, UT Southwestern Medical Center, Dallas, TX.
2015-	CRI Mouse Genome Engineering Core Director, UT Southwestern Medical Center, Dallas, TX.
2018-	Associate Professor in Children's Research Institute and Associate Professor in Pediatrics and Internal Medicine, Divisions of Hematology-Oncology, UT Southwestern Medical Center, Dallas, TX.
2019-	Kern Wildenthal, M.D., Ph.D. Distinguished Professorship in Pediatric Research

Board Certification/Professional Memberships

2008	Member, Massachusetts Medical Society
2008-	Associate Member, International Society for Stem Cell Research
2008-	Board Certified, Internal Medicine
2008-12	Massachusetts License #230861
2012-	Texas Medical License #P4841
2013-	Board Certified, Adult Medical Oncology
2015-	Active Member, American Association for Cancer Research
2018	NIH Hepatobiliary pathophysiology (HBPP) Study Section, ad hoc reviewer
2018-21	Associate Editor, Gastroenterology
2019-	Board of Reviewing Editors, eLIFE

Honors

1999	Barry M. Goldwater Undergraduate Science Scholarship
1999	Duke University Faculty Scholar Award, Honorable Mention
1999	University Graduation with Distinction, Summa Cum Laude, Phi Beta Kappa
2002	American Society of Hematology Medical Student Award
2003	Howard Hughes Medical Student Research Fellowship
2003	Best Poster Award, ASCI/AAP Joint Meeting
2005	Graduated with MD honors, Magna Cum Laude
2005	James Tolbert Shipley Prize for excellence in medical research for MD Honors Thesis
2009	National Institutes of Health Pediatric Loan Repayment Program Grant
2010	Burroughs Wellcome Fund Travel Grant
2010	8th Annual ISSCR Meeting, Travel Award for Oral Presentation
2010	American Cancer Society Postdoctoral Fellowship Award
2011	9th Annual ISSCR Meeting, Poster Award
2012	CPRIT Scholar in Cancer Research
2012	Burroughs Wellcome Fund Career Award for Medical Scientists
2012	Forbeck Scholar Award
2015	ASCI Young Physician-Scientist Award, Best Poster Award
2016	Stand Up 2 Cancer Innovative Research Grant
2018	Member, American Society of Clinical Investigation
2019	Kern Wildenthal, M.D., Ph.D. Distinguished Professorship in Pediatric Research

C. Contributions to Science

The *Lin28/let-7* pathway in development, physiology, and disease. My lab has explored the mechanistic interplay between cancer, stem cells, and microRNAs. One focus of the lab has been on understanding the physiologic impact of the Lin28-let-7 microRNA pathway.

a. Zhu H, Shah S, Shyh-Chang N, Shinoda G, Einhorn WS, Viswanathan SR, Takeuchi A, Grasemann C, Rinn JL, Lopez MF, Hirschhorn JN, Palmert MR, Daley GQ. Lin28a transgenic mice manifest size and puberty phenotypes identified in human genetic association studies. ***Nature Genetics***. 2010 Jul; 42(7):626-30. PMID: 20512147.
b. Zhu H*, Shyh-Chang N*, Segrè AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, Urbach A, Thornton JE, Triboulet R, Gregory RI; DIAGRAM Consortium; MAGIC Investigators, Altshuler D, Daley GQ. *Equal contributors. The Lin28/let-7 axis regulates glucose metabolism. ***Cell***. 2011 Sep 30; 147(1):81-94. PMID: 21962509.
c. Nguyen LH*, Robinton DA*, Seligson MT*, Wu L, Li L, Rakheja D, Comerford SA, Ramezani S, Sun X, Parikh MS, Yang EH, Powers JT, Shinoda G, Shah SP, Hammer RE, Daley GQ† and Zhu H†. *Equal contributors. †Co-corresponding authors. Lin28b is sufficient to drive liver cancer and necessary for its maintenance in murine models. ***Cancer Cell***. 2014 Aug 11; 26(2):248-61. PMID: 25117712.
d. Wu L*, Nguyen LH*, Zhou K, Soysa TY, Li L, Miller JB, Tian J, Locker J, Zhang S, Shinoda G, Seligson MT, Zeitels LR, Acharya A, Wang SC, Mendell JT, He X, Nishino J, Morrison SJ, Siegwart DJ, Daley GQ, Shyh-Chang N, and Zhu H. *Equal contributors. Precise *Let-7* expression levels balance organ regeneration against tumor suppression. ***eLife***. 2015 Oct 7;4:e09431. PMID: 26445246.

Understanding mechanisms of mammalian organ regeneration and how they relate to cancer. My lab has identified new mechanisms that regulate regeneration. Re-expression of the embryonic RNA-binding protein *Lin28a* in adult tissues accelerated regeneration, but this came at the cost of liver cancer development. Deletion of *Arid1a* promoted regeneration but suppressed tumor initiation in the liver, indicating that other mechanisms can promote regeneration while inhibiting cancer development. We also discovered that increasing hepatocyte polyploidy reduced tumorigenesis without compromising regeneration. Our findings indicate that regenerative capacity can be dissociated from cancer predisposition.

a. Shyh-Chang N*, Zhu H*, de Soysa NT, Shinoda G, Seligson MT, Tsanov K, Nguyen L, Asara JM, Cantley LC and Daley GQ. *Equal contributors. Lin28 enhances tissue repair by reprogramming cellular metabolism. ***Cell***. 2013 Nov 7; 155(4):778-92. PMID: 24209617.
b. Sun X, Chuang J, Kanchwala M, Wu L, Celen C, Li L, Liang H, Zhang S, Maples T, Nguyen L, Wang S, Signer R, Sorouri M, Nassour I, Liu X, Xu J, Wu, M, Zhao Y, Kuo Y, Wang Z, Xing C, and Zhu H. Suppression of the SWI/SNF component Arid1a promotes mammalian regeneration. ***Cell Stem Cell***. 2016 Apr 7;18(4):456-66. PMID: 27044474.
c. Sun X*, Wang SC*, Luo X, Jia Y, Gopal P, Zhu M, Li L, Nassour I, Chuang JC, Maples T, Celen C, Nguyen LH, Wu L, Fu S, Li W, Hui L, Tian F, Ji Y, Zhang S, Sorouri M, Hwang TH, Letzig L, James L, Yopp A, Singal A, Zhu H. *Equal contributors. *Arid1a* has context-dependent oncogenic and tumor suppressor functions in liver cancer. ***Cancer Cell***. 2017. Nov 13;32(5):574-589.e6. PMID: 29136504.
d. Zhu M*, Lu T*, Jia Y*, Luo X*, Gopal P, Li L, Odewole M, Renteria V, Singal AG, Jang Y, Ge K, Wang SC, Sorouri M, Parekh JR, MacConmara MP, Yopp AC, Wang T†, Zhu H†. *Equal contributors. †Co-corresponding authors. Somatic mutations increase hepatic clonal fitness and regeneration in chronic liver disease. ***Cell.*** 2019. Apr 2. pii: S0092-8674(19)30288-0. PMID: 30955891.

Discovered a functional role for hepatocyte polyploidy. Polyploid cells and organisms contain more than two homologous sets of chromosomes. Up to 90% of rodent and 40% of human hepatocytes are polyploid, making this an extraordinary property of the liver whose significance was not known. We were the first to discover a functional impact for polyploid liver cells. These cells prevent tumorigenesis in the context of acute mutagenic insults as well as during chronic injury. This suggests innovative ways to prevent liver cancer development, and the lab is current pursing an siRNA approach to increase polyploidy in cirrhotic patients with a high risk for cancer development.

a. Zhang S, Zhou K, Luo X, Li L, Nguyen LH, Zhang Y, Tarlow B, Siegwart DJ, and Zhu H. The polyploid state plays a tumor suppressive role in the liver. ***Developmental Cell***. 2018 Feb 26;44(4):447-459.e5. PMID: 29429824.
b. Zhang S, Nguyen LH, Zhou K, Tu HC, Sehgal A, Nassour I, Li L, Gopal P, Goodman J, Singal AG, Yopp A, Zhang Y, Siegwart DJ, and Zhu H. Knockdown of Anillin Actin Binding Protein Blocks Cytokinesis in Hepatocytes and Reduces Liver Tumor Development in Mice without Affecting Regeneration. ***Gastroenterology***. 2017. Dec 20. pii: S0016-5085(17)36717-3. PMID: 29274368.
c. Lin YH, Zhang S, Zhu M, Lu T, Chen K, Wen Z, Wang S, Xiao GH, Luo D, Li L, MacConmara M, Hoshida Y, Singal A, Yopp A, Wang T, and Zhu H. Polyploid hepatocytes are protected from cancer but maintain regenerative capacity in chronic liver disease. ***Gastroenterology***. 2020. doi:10.1053/j.gastro.2020.01.026. PMID: 31972235.

Understanding the role of SWI/SNF chromatin remodeling components in human disease. Many human diseases involve germline or somatic mutations in SWI/SNF components, but it is unknown how these mutations manifest phenotypically and if there are therapeutic opportunities. We have contributed to understanding the mechanistic basis of these disorders.

a. Celen C*, Chuang JC*, Luo X, Nijem N, Walker AK, Chen F, Zhang S, Chung AS, Nguyen LH, Nassour I, Budhipramono A, Sun X, Bok LA, McEntagart M, Gevers EF, Birnbaum SG, Eisch AJ, Powell CM, Ge WP, Santen GW, Chahrour M, Zhu H. *Equal contributors. *Arid1b* haploinsufficient mice reveal neuropsychiatric phenotypes and reversible causes of growth impairment. ***eLIFE***. 2017 Jul 11;6. pii: e25730.
b. Wang SC, Nassour I, Xiao S, Zhang S, Luo X, Lee J, Li L, Sun X, Nguyen LH, Chuang JC, Peng L, Daigle S, Shen J, Zhu H. SWI/SNF component ARID1A restrains pancreatic neoplasia formation. ***Gut***. 2018 Oct 12. pii: gutjnl-2017-315490.
c. Moore A, Wu L, Chuang JC, Sun X, Luo X, Gopal P, Li L, Celen C, Zimmer M, and Zhu H. Arid1a loss drives non-alcoholic steatohepatitis in mice via epigenetic dysregulation of hepatic lipogenesis and fatty acid oxidation. ***Hepatology.*** 2018. Dec 25. doi: 10.1002/hep.30487.

Mouse modeling of liver cancer. My lab studies the mechanisms that regulate liver injury and regeneration, and how these mechanisms influence hepatocellular carcinoma (HCC) development. Our goal is to understand how growth and regeneration capacity is controlled on the genetic and cellular levels, and to apply this towards understanding how cancer evolves and progresses in the context of chronic injury.

a. Zhang S*, Li L*, Kendrick SL, Gerard RD, Zhu H. *Equal contributors. TALEN-mediated somatic mutagenesis in murine models of cancer. ***Cancer Research***. 2014 Sep 15;74(18):5311-21. PMID: 25070752.
b. Zhou K*, Nguyen LH*, Miller JB, Yan Y, Kos P, Xiong H, Li L, Minnig JT, Zhu H**,** Siegwart DJ**.** *Equal contributors. Modular degradable dendrimers enable small RNAs to extend survival in an aggressive liver cancer model. ***PNAS***. 2016 Jan 19; 113(3):520-5. PMID: 26729861.
c. Zhu M, Li L, Lu T, Yoo H, Zhu J, Gopal P, Wang SC, Porempka MR, Rich NE, Kagan S, Odewole M, Renteria V, Waljee AK, Wang T, Singal AG, Yopp AC, Zhu H. Uncovering biological factors that regulate hepatocellular carcinoma growth using patient derived xenograft assays. ***Hepatology***. 2020 Jan 03. doi:10.1002/hep.31096. PMID: 31899548.

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