BIOGRAPHICAL SKETCH

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NAME: Hao Zhu

eRA COMMONS USER NAME (credential, e.g., agency login): HAOZHU1
POSITION TITLE:

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.	05/99	Biology
Harvard Medical School and MIT	M.D.	06/05	Medicine
University of California, San Francisco		2005-2007	Internal Medicine Residency
Dana-Farber/Brigham and Women's Hospital/ Massachusetts General Hospital		2007-2011	Hematology/Oncology Fellowship

A. Personal Statement

I am a physician-scientist with a lab focused on the basic biology of liver regeneration and cancer. We want to determine the genetic and cellular mechanisms of organ regeneration and to understand how these mechanisms contribute to cancer. One approach we use is to develop mice that possess enhanced organ regeneration in order to understand how regeneration works and to understand the upper limits of mammalian tissue repair. Given the liver's strong self-renewal ability in the face of injury, we expect that regenerative capacity will have strong and potentially targetable influences on carcinogenesis. In particular, we study mouse models of hepatocellular carcinoma (HCC) and cholangiocarcinoma. I also direct the Children's Research Institute Mouse Genome Engineering Core, which uses Crispr technology to generate genetically engineered mouse models. 10% of my time is also devoted to taking care of liver cancer patients at the Parkland Memorial Hospital Multidisciplinary HCC Clinic, work that fuels translational aspects of my research.

a. 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. 2011. The Lin28/let-7 Axis Regulates Glucose Metabolism. **Cell** 147(1):81-94. PMCID: PMC3353524.

b. 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. 2013. Lin28 enhances tissue repair by reprogramming cellular metabolism. **Cell** 155(4):778-92. PMCID: PMC3917449.

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. 2014. *Lin28b* is sufficient to drive liver cancer and necessary for its maintenance in murine models. **Cancer Cell** Aug 11;26(2):248-61. PMCID: PMC4145706.

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. 2015. Precise *Let-7* expression levels balance organ regeneration against tumor suppression. **eLife.** Oct 7;4. pii: e09431. PMID: 26445246.

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, Children's Research Institute Mouse Genome Engineering Core Director, UT Southwestern Medical Center, Dallas, TX.

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

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

C. Contributions to Science

Stem cell biology in zebrafish. I have had a longstanding interest in the functions of oncogenes and tumor suppressors during development, and how these genes can reactivate embryonic growth programs in disease. I performed MD thesis research on hematopoietic stem cell (HSC) biology in Leonard Zon's group at Children's Hospital Boston. I was interested in the developmental and genetic origins of HSCs, so I engineered transgenic zebrafish with HSCs expressing fluorescent proteins under the control of the *lmo2* stem cell promoter. Embryonic blood transplant experiments using these reagents helped to define the fates of the first HSCs and endothelial cells in zebrafish. Analysis of the *lmo2* promoter revealed roles for ETS factors in the transcriptional regulation of blood ontogeny.

a. Zhu H, Traver D, Davidson AJ, Dibiase A, Thisse C, Thisse B, Nimer S, Zon LI. 2005. Regulation of the lmo2 promoter during hematopoietic and vascular development in zebrafish. **Developmental Biology** 281(2):256-269. PMID: 15893977.
b. Gupta S, Zhu H, Zon LI, Evans T. 2006. BMP signaling restricts hemato-vascular development from lateral mesoderm during somitogenesis. **Development** 133(11):2177-87. PMID: 16672337.
c. Brownlie A, Hersey C, Oates AC, Paw BH, Falick AM, Witkowska HE, Flint J, Higgs D, Jessen J, Bahary N, Zhu H, Lin S, Zon L. 2003. Characterization of embryonic globin genes of the zebrafish. **Developmental Biology** 255(1):48-61. PMID: 12618133.
d. Schonberger J, Wang L, Shin JT, Kim SD, Depreux FF, Zhu H, Zon L, Pizard A, Kim JB, Macrae CA, Mungall AJ, Seidman JG, Seidman CE. 2005. Mutation in the transcriptional coactivator EYA4 causes dilated cardiomyopathy and sensorineural hearing loss. **Nature Genetics** 37(4):418-22. PMID: 15735644.

The *Lin28/let-7* stem cell pathway in development and physiology. As post-doctoral fellow in George Daley's lab, I explored the mechanistic interplay between cancer, stem cells, and microRNAs. The Daley lab had just discovered that the Lin28 RNA-binding proteins selectively and potently suppress *let-7* microRNA maturation in ESCs and cancer, which suggested a powerful new mechanism of RNA-mediated oncogenesis. I developed mouse models to study the *Lin28/let-7* microRNA pathway in mammalian physiology. I showed that *Lin28a* hyperfunction in mice led to increased body size, weight, height, and time to puberty, demonstrating a conserved role in developmental timing from worm to mouse to human. Some of these transgenic mice developed soft tissues tumors, indicating *Lin28a's* oncogenic potential *in vivo*. I also showed that the *Lin28/let-7* pathway is a central regulator of mammalian glucose metabolism, lending support to human genetic data connecting the *let-7* pathway to diabetes and growth aberrations.

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. 2010. Lin28a transgenic mice manifest size and puberty phenotypes identified in human genetic association studies. **Nature Genetics** 42(7):626-30. PMCID: PMC3069638.
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. 2011. The Lin28/let-7 Axis Regulates Glucose Metabolism. **Cell** 147(1):81-94. PMCID: PMC3353524.
c. West JA, Viswanathan SR, Yabuuchi A, Cunniff K, Takeuchi A, Park IH, Sero JE, Zhu H, Perez-Atayde A, Frazier AL, Surani MA, Daley GQ. 2009. A role for Lin28 in primordial germ-cell development and germ-cell malignancy. **Nature** 460(7257):909-13. PMCID: PMC2729657.
d. Shinoda G, Shyh-Chang N, de Soysa NT, Zhu H, Seligson MT, Shah SP, Abo-Sido N, Yabuuchi A, Hagan JP, Gregory RI, Asara JM, Cantley LC, Moss EG, Daley GQ. 2013. Fetal Deficiency of Lin28 Programs Life-Long Aberrations in Growth and Glucose Metabolism. **Stem Cells** 31(8):1563-73. PMCID: PMC3775935.

Examining fundamental mechanisms of mammalian organ regeneration. *Lin28* and *let-7* are dynamically opposed in the context of development and cancer to control growth pathways, and that engineered imbalances in either direction could shift regenerative capacity. This body of work indicated that modulation of tumor promoting pathways can significantly influence organ regeneration, and fueled the possibility of genetically enhancing regeneration in mammals. We showed that Lin28a influences tissue repair in adults in multiple contexts including skin, soft tissues, and digits. Mechanistically, Lin28a enhanced tissue repair in some adult tissues by reprogramming cellular bioenergetics, introducing a completely novel way of thinking about regeneration. Other work listed below implicated the pathway in embryonic stem cell metabolism and age related declines in regenerative function.

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. 2013. Lin28 enhances tissue repair by reprogramming bioenergetic metabolism. **Cell** 155(4):778-92. PMID: 24209617.
b. Nishino J, Kim S, Zhu Y, Zhu H, and Morrison SJ. 2013. A network of heterochronic genes including Imp1 regulates temporal changes in stem cell properties. **eLife** 2:e00924. PMCID: PMC3817382.

c. 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. 2015. Precise *Let-7* expression levels balance organ regeneration against tumor suppression. **eLife.** Oct 7;4. pii: e09431. PMID: 26445246.
d. 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. 2016. Loss of SWI/SNF component *Arid1a* enhances mammalian regeneration through chromatin remodeling. **Cell Stem Cell**.

Mouse modeling of cancer, with a focus on pediatric and adult liver cancers. My lab at UTSW studies the mechanisms that regulate liver injury and regeneration, and how these mechanisms influence cancer development. Our work is inspired by the problem of hepatocellular carcinoma (HCC), a malignancy that arises from a highly regenerative organ that experiences recurrent injury, and hepatoblastoma, a pediatric cancer of dysregulated regeneration. To gain mechanistic understanding of malignant liver disease, we have focused on genetic pathways implicated in HCC that also regulate growth and tissue regeneration through 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 in the context of chronic injury. We have also developed gene-editing methods to engineer mouse models of cancer in the liver.

a. Zhang S*, Li L*, Kendrick SL, Gerard RD and Zhu H. *Equal contributors. 2014. TALEN mediated somatic mutagenesis in murine models of cancer. **Cancer Research** Jul 28. pii: canres.0529.2014. PMCID: PMC4167541.
b. 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. 2014. *Lin28b* is sufficient to drive liver cancer and necessary for its maintenance in murine models. **Cancer Cell** Aug 11;26(2):248-61. PMCID: PMC4145706.
c. Urbach A, Yermalovich A, Zhang J, Spina CS, Zhu H, Perez-Atayde AR, Shukrun R, Charlton J, Sebire N, Mifsud W, Dekel B, Pritchard-Jones K, Daley GQ. 2014. *Lin28* sustains early renal progenitors and induces Wilms tumor. **Genes and Development** May 1;28(9):971-82. PMCID: PMC4018495.
d. Tu HC, Schwitalla S, Qian Z, LaPier GS, Yermalovich A, Ku YC, Chen SC, Viswanathan SR, Zhu H, Nishihara R, Inamura K, Kim SA, Morikawa T, Mima K, Sukawa Y, Yang J, Meredith G, Fuchs CS, Ogino S, Daley GQ. 2015. LIN28 cooperates with WNT signaling to drive invasive intestinal and colorectal adenocarcinoma in mice and humans. **Genes & development** May 29(10):1074-86. PMCID: PMC4441054.

Exploration of novel liver cancer therapies. We have also utilized our mouse models of HCC and hepatoblastoma to investigate experimental therapies. In particular, we have investigated lipid nanoparticles in collaboration with Dan Siegwart's Lab and Ian Corbin's Lab at UTSW.

a. Wen X, Reynolds L, Mulik RS, Kim SY, Van Treuren T, Nguyen LH, Zhu H, and Corbin IR. 2016. Hepatic Arterial Infusion of Low-Density Lipoprotein Docosahexaenoic Acid Nanoparticles Selectively Disrupts Redox Balance in Hepatoma Cells and Reduces Growth of Orthotopic Liver Tumors in Rats. **Gastroenterology** Feb; 150(2):488-98. PMID: 26484708.
b. Zhou K*, Nguyen LH*, Miller JB, Yan Y, Kos P, Xiong H, Li L, Minnig JT, Zhu H, and Siegwart DJ. 2016. *Equal contributors. 2016. Modular degradable dendrimers enable small RNAs to extend survival in an aggressive liver cancer model. **PNAS** Jan 19;113(3):520-5. PMID: 26729861.
c. Non-Viral CRISPR/Cas Gene Editing In Vitro and In Vivo Enabled by Synthetic Nanoparticle Co-Delivery of Cas9 mRNA and sgRNA. Miller JB, Zhang S, Kos P, Xiong H, Zhou K, Perelman SS, Zhu H, Siegwart DJ. 2016. **Angew Chem** Int Ed Engl. doi: 10.1002/anie.201610209.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/1ZsOC62p5imbGdoOgdH6gnT5b/?sort=date&direc tion=ascending

D. Additional Information: Research Support and/or Scholastic Performance

ONGOING

CPRIT Early Translation Grant, DP150077 (P.I. Zhu, H.) 12/01/14-11/30/17
Cancer Prevention and Research Institute of Texas
"Targeting SWI/SNF in liver cirrhosis and hepatocellular carcinoma"

BWF Career Awards for Medical Scientists (P.I. Zhu, H.) 09/01/12 – 8/31/2018
Burroughs Wellcome Fund
"Investigating the Lin28/let-7 pathway in mouse models of liver cancer and regeneration"

1 R01 CA190525-01 (P.I., Zhu, H.) 5/01/15 – 4/31/2020
NIH/NCI
"Reactivation of embryonic growth programs in liver cancer"

DOD Team Science Award (Lead P.I., Zhu, H.) 9/30/16 – 9/29/2019
Department of Defense
"Defining hepatocellular carcinoma subtypes and treatment responses in patient derived tumorgrafts"

SU2C Innovative Research Grant (P.I Zhu, H.) 07/01/16 – 6/31/2019
Stand Up 2 Cancer
"Defining the mechanistic connections between injury, regeneration, and cancer"

COMPLETED

(P.I. Zhu, H.) 08/01/13 – 7/31/14 American Cancer Society and UTSW
American Cancer Society Institutional Research Grant
The role of chromosome number in liver cancer development

CPRIT Scholar in Cancer Research, R1209 (P.I. Zhu, H.) 09/01/12 – 8/31/2016
Cancer Prevention and Research Institute of Texas
"Investigating the Lin28-let-7 pathway in hepatoblastoma and hepatocellular carcinoma"

1 K08 CA157727-04 (P.I. Zhu, H.) 07/05/11 – 06/30/16
NIH/NCI
"Metabolic roles for Lin28-let-7 microRNA pathway in sarcoma tumorigenesis"