BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

NAME

Jian Xu, Ph.D.

POSITION TITLE

Associate Professor in Children's Research Institute (CRI)
Associate Professor in Pediatrics, Division of Hematology and Oncology
UT Southwestern Medical Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Los Angeles (UCLA)	Ph.D.	2008	Molecular Biology, Stem Cell Biology
Boston Children's Hospital, HHMI, Harvard Medical School	Postdoctoral Associate	2008-2012	Developmental Biology, Hematology/Oncology

A. Personal Statement

My lab studies the gene regulatory processes that control stem cell development and cancers, particularly the mechanisms that control non-coding genomic elements (e.g. transcriptional enhancers), epigenetic gene regulation and cellular metabolism. I also oversee the Sequencing Core Facility at Children's Research Institute at UT Southwestern, which uses next-generation sequencing technologies to study cancer genetics and genomics. I received my Ph.D. from UCLA with Dr. Stephen Smale, where I studied transcriptional regulation of stem cell pluripotency. I then joined Dr. Stuart Orkin's laboratory at Boston Children's as a Helen Hay Whitney-HHMI postdoctoral fellow, and studied the role of BCL11A in controlling fetal-to-adult hemoglobin switching [1] and epigenetic control of hematopoiesis. My studies with Dr. Orkin provide the first *in vivo* evidence that genetic inactivation of BCL11A is sufficient to ameliorate sickle cell disease (SCD) in preclinical models, and lay the groundwork for ongoing development of gene therapies to target BCL11A for treating patients with inherited hemoglobin disorders. As an independent faculty, my research focuses on elucidating novel mechanisms controlling disease-associated genes and genetic regulatory elements in hematopoiesis, erythroid biology, and hematologic malignancies. We use multidisciplinary and quantitative approaches including (epi)genomics, proteomics, metabolomics, mouse genetics, and genome editing to characterize the structure-function of enhancers [2], the post-transcriptional mechanisms controlling mitochondria biogenesis [3], the interplay between epigenetic gene regulation and intracellular metabolism in leukemia development [4], and the role of pathogenic non-coding variants in hematologic malignancies [5]. Along with these studies, we also developed new CRISPR/Cas9-based 'CAPTURE' technologies to identify locus-specific chromatin interactions that regulate non-coding regulatory genome [2], and enhanced CRISPR epigenetic editing systems for *in situ* and *in vivo* interrogation of enhancer function [5]. These methods are widely adopted by other researchers for studying genome structure and function in various model systems. In summary, our research utilizes interdisciplinary approaches to discover novel mechanisms in gene regulation and hematology, with the long-term goal to develop innovative strategies that advance diagnosis, prognosis and treatment of blood disorders.

Recent Publications: (#corresponding author)

1. **Xu J**, Peng C, Sankaran VG, Shao Z, Esrick EB, Chong BG, Ippolito GC, Fujiwara Y, Ebert BL, Tucker PW, Orkin SH#. (2011). Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. ***Science***, 334(6058):993-996. PMCID: PMC3746545
2. Liu X, Zhang Y, Chen Y, Li M, Zhou F#, Li K, Cao H, Ni M, Liu Y, Gu Z, Dickerson KE, Xie S, Hon GC, Xuan Z, Zhang MQ, Shao Z, **Xu J#**. (2017) *In situ* capture of chromatin interactions by biotinylated dCas9. ***Cell***, 170:1028-1043. PMCID: PMC6857456.
3. Liu X, Zhang Y, Ni M, Cao H, Signer RAJ, Li D, Li M, Gu Z, Hu Z, Dickerson KE, Weinberg SE, Chandel NS, DeBerardinis RJ, Zhou F#, Shao Z#, **Xu J#**. (2017) Regulation of mitochondrial biogenesis in erythropoiesis by mTORC1-mediated protein translation. ***Nature Cell Biology***, 19:626-638. PMCID: PMC5771482.

4. Gu Z, Liu Y, Cai F, Patrick M, Zmajkovic J, Cao H, Zhang Y, Tasdogan A, Chen M, Qi L, Liu X, Li K, Lyu J, Dickerson KE, Chen W, Ni M, Merritt ME, Morrison SJ, Skoda RC, DeBerardinis RJ, **Xu J**[#]. (2019) Loss of EZH2 reprograms BCAA metabolism to drive leukemic transformation. ***Cancer Discovery*** 9:1228-1247. PMCID: 28841410.
5. Li K, Zhang Y, Liu X, Liu Y, Gu Z, Cao H, Dickerson KE, Chen M, Chen W, Shao Z, Ni M, **Xu J**[#]. (2020) Non-coding variants connect enhancer dysregulation with nuclear receptor signaling in hematopoietic malignancies. ***Cancer Discovery***, 10:724-745. PMCID: PMC7196497.

B. Positions and Honors

Positions and Employment

2003 - 2008 Graduate Student (Ph.D.) in the laboratory of Dr. Stephen T. Smale, HHMI, UCLA
2008 - 2012 Helen Hay Whitney-HHMI Postdoc Fellow in the laboratory of Dr. Stuart H. Orkin, HHMI, Boston Children's Hospital, Harvard Medical School
2012 - 2014 Instructor in Pediatric Hematology-Oncology, Harvard Medical School
2014 - 2020 Assistant Professor in Children's Research Institute, CPRIT Scholar in Cancer Research, University of Texas Southwestern Medical Center
2020 - Associate Professor in Children's Research Institute, CPRIT Scholar in Cancer Research, University of Texas Southwestern Medical Center

Honors and Awards

2007 Miyada Special Merit Award, UCLA
2007 - 2008 CIRM (California Institute for Regenerative Medicine) Pre-Doctoral Fellowship
2009 Speaker of 'Plenary Scientific Session'' during 51st ASH Annual Meeting
2009 ASH Merit Award, American Society of Hematology
2009 - 2012 Helen Hay Whitney Foundation-HHMI Post-Doctoral Fellowship
2010 ASH Merit Award, American Society of Hematology
2011 - 2013 ASH Abstract Achievement Award, American Society of Hematology
2012 Harvard Chinese Life Science Annual Distinguished Research Award
2011 - 2016 NIH/NIDDK Career Development Award (K01)
2014 - 2018 CPRIT Scholar in Cancer Research
2015 - 2018 American Society of Hematology (ASH) Scholar Award
2018 Outstanding Mentor Award, UT Southwestern Center for Translational Medicine
2019 Leukemia and Lymphoma Society (LLS) Scholar Award

Memberships and Professional Activities

2008 - Member, American Society of Hematology (ASH)
2014 - Member, International Society for Stem Cell Research (ISSCR)
2015 - Member, American Association for Cancer Research (AACR)
2016 - Lifetime Member, Society of Chinese Bioscientists in America (SCBA)
2017 - Member, International Society of Experimental Hematology (ISEH)
2017 - 2019 Ad hoc Reviewer, DOD Study Session (CDMRP)
2017 - 2019 Ad hoc Reviewer, NIH Study Session (MCH)
2018 Reviewer, Medical Research Council (MRC), UK
2018 - 2019 Ad hoc Reviewer, DOD Study Session (PRCRP)
2018 - 2020 Reviewer, NIH/NIDDK CCEH Pilot & Feasibility Program
2020 - Scientific Advisory Board, Forma Therapeutics
2020 - 2021 Standing Member, NIH Study Session (MCH)
2021 - 2024 Standing Member, NIH Study Session (BBHV)

C. Contribution to Science

1. **Molecular Analysis of Transcriptional Enhancers.** One of the fundamental questions in biology is how gene expression programs are established and maintained to preserve or alter cell identity. This question is intimately related to how transcription factors interact with the appropriate gene-specific *cis*-regulatory elements within chromatin. Enhancers are *cis*-acting DNA sequences that determine cell identity by directing spatiotemporal gene expression, yet the regulatory components controlling the structure and

function of enhancers during lineage development and disease pathogenesis remain largely unknown. We recently developed a new system ('CAPTURE') to unbiasedly identify chromatin interactions that regulate non-coding genomic sequences including enhancers. Using deactivated Cas9 protein and programmable sgRNAs, we were able to selectively isolate the native genomic locus-associated protein complexes and 3D chromatin structures (Liu *et al.*, 2017, 2020). The CAPTURE system provides a 'first-in-kind' approach to simultaneously identify *cis*-element-regulating proteins and DNA structures, and to compare the results to establish the causality of gene expression during hematopoietic development and disorders. We also developed enhancer-targeting dCas9-based epigenetic perturbation systems for high throughput analyses of enhancer function in lineage differentiation and cancer pathogenesis (Li *et al.*, 2020). Building on these discoveries, it is our long-term goal to demystify the *cis*-regulatory logics as fundamental principles that control stem cell development and disorders.

a. Liu X, Zhang Y, Chen Y, Li M, Zhou F[#], Li K, Cao H, Ni M, Liu Y, Gu Z, Dickerson KE, Xie S, Hon GC, Xuan Z, Zhang MQ, Shao Z, **Xu J**[#]. (2017) *In situ* capture of chromatin interactions by biotinylated dCas9. ***Cell***, 170:1028-1043. PMCID: PMC6857456.
b. Li K, Zhang Y, Liu X, Liu Y, Gu Z, Cao H, Dickerson KE, Chen M, Chen W, Shao Z, Ni M, **Xu J**[#]. (2020) Non-coding variants connect enhancer dysregulation with nuclear receptor signaling in hematopoietic malignancies. ***Cancer Discovery***, 10:724-745. PMCID: PMC7196497.
c. Li K, Liu Y, Cao H, Zhang Y, Gu Z, Liu X, Yu A, Kaphle P, Dickerson KE, Ni M, **Xu J**[#]. (2020) Interrogation of enhancer function by enhancer-targeting CRISPR epigenetic editing. ***Nature Communications*** 11,485. PMCID: PMC6981169.
d. Liu X, Chen Y, Zhang Y, Liu Y, Liu N, Botten GA, Cao H, Orkin SH, Zhang MQ, **Xu J**[#]. (2020) Multiplexed capture of spatial configuration and temporal dynamics of locus-specific 3D chromatin by biotinylated dCas9. ***Genome Biology***, 21:59. PMCID: PMC7059722.
e. Huang J, Liu X, Li D, Shao Z, Cao H, Zhang Y, Trompouki E, Bowman TV, Zon LI, Yuan GC, Orkin SH[#], and **Xu J**[#]. (2016) Dynamic control of enhancer repertoires drives lineage and stage-specific transcription during hematopoiesis. ***Developmental Cell***, 36(1):9-23. PMCID: PMC4714361.

2. **Epigenetic and Metabolic Control of Hematopoiesis and Leukemia.** How epigenetics and metabolism cooperate to control development and disease processes is a fundamentally important question with significant clinical implication. Many epigenetic enzymes catalyzing DNA or histone modifications are susceptible to changes in co-substrates of cellular metabolism, but little is known about whether and how altered epigenetics influences metabolism during cancer progression. We recently described that inactivation of the histone methyltransferase EZH2 promotes leukemic transformation by aberrant activation of branched-chain amino acid (BCAA) metabolism in leukemia-initiating cells, establishing a new molecular link between altered epigenetics and metabolism in cancer progression (Gu *et al.*, 2019). This study was among the first to show that epigenetic alterations rewire intracellular metabolism during leukemic transformation, causing epigenetic and metabolic vulnerabilities in cancer-initiating cells. In other studies, we compared the proteomic and transcriptomic changes in human primary HSPCs and erythroid cells, and uncovered pathways related to mitochondrial biogenesis enhanced through protein translation, establishing a new mechanism for post-transcriptional control of mitochondria related to hematologic defects in mitochondrial diseases and aging (Liu *et al.*, 2017). We are examining the epigenetic and metabolic liabilities of blood stem cells in development and pathological conditions.

a. Gu Z, Liu Y, Cai F, Patrick M, Zmajkovic J, Cao H, Zhang Y, Tasdogan A, Chen M, Qi L, Liu X, Li K, Lyu J, Dickerson KE, Chen W, Ni M, Merritt ME, Morrison SJ, Skoda RC, DeBerardinis RJ, **Xu J**[#]. (2019) Loss of EZH2 reprograms BCAA metabolism to drive leukemic transformation. ***Cancer Discovery*** 9:1228-1247. PMCID: 28841410.
b. Liu X, Zhang Y, Ni M, Cao H, Signer RAJ, Li D, Li M, Gu Z, Hu Z, Dickerson KE, Weinberg SE, Chandel NS, DeBerardinis RJ, Zhou F[#], Shao Z[#], **Xu J**[#]. (2017) Regulation of mitochondrial biogenesis in erythropoiesis by mTORC1-mediated protein translation. ***Nature Cell Biology***, 19:626-638. PMCID: PMC5771482.
c. Vo LT, Kinney MA, Liu X, Zhang Y, Barrangan J, Sousa PM, Jha DK, Han A, Cesana M, Shao Z, North TE, Orkin SH, Doulatov S, **Xu J**, Daley GQ. (2018) Regulation of haematopoietic multipotency by EZH1. ***Nature***, 553:506-510. PMCID: 29342143. PMCID: PMC5785461.

d. **Xu J***, Shao Z*, Li D, Xie H, Kim W, Huang J, Taylor JE, Pinello L, Glass K, Jaffe JD, Yuan GC, and Orkin SH. (2015). Developmental control of Polycomb subunit composition by GATA factors mediates a switch to non-canonical functions. ***Molecular Cell***, 57(2):304-316 (*co-first author). PMCID: PMC4305004.

e. Gu Z, Dickerson KE, **Xu J**. Therapeutic response and outcome explained by leukemia cell of origin. ***Cancer Discovery*** 2020, 10:1445-1447.

3. **Developmental Control of Fetal-to-Adult Hemoglobin Switching.** The developmental switch from fetal to adult hemoglobin is critical to the pathogenesis of sickle cell disease (SCD) and β-thalassemias. As increased fetal hemoglobin (HbF) lessens the severity of these conditions, elucidating the mechanisms to relieve HbF silencing has been a long-sought goal. Our studies provide the first genetic evidence to validate the zinc finger protein and transcriptional repressor, BCL11A, as a major modulator of hemoglobin switching in mouse and human (Sankaran and Xu *et al.*, 2009). To establish the preclinical evidence for BCL11A as a potential therapeutic target, I documented that genetic inactivation of BCL11A in humanized SCD mouse models corrects the hematologic and pathologic defects associated with SCD through HbF reactivation (Xu *et al.*, 2011). These findings represent a milestone in the field of molecular hematology and lay the groundwork for the ongoing clinical development of targeting BCL11A and its erythroid-specific enhancers for treating patients with SCD and β-thalassemias.

   a. Liu N, Hargreaves VV, Zhu Q, Kurland JV, Hong J, Kim W, Sher F, Macias-Trrevino C, Rogers JM, Kurita R, Nakamura Y, Yuan GC, Bauer DE, **Xu J**, Bulyk ML, Orkin SH. Direct promoter repression by BCL11A controls the fetal to adult hemoglobin switch. ***Cell*** 2018, 173:1-13. PMCID: PMC5889339.

   b. Luc S, Huang J, McEldoon JL, Somuncular E, Li D, Rhodes C, Mamoor S, Hou S, **Xu J**[#], Orkin SH[#]. (2016) Bcl11a deficiency leads to hematopoietic stem cell defects with an aging-like phenotype. ***Cell Reports***, 16:3181-94. PMCID: PMC5054719. ([#]corresponding author).

   c. **Xu J**, Peng C, Sankaran VG, Shao Z, Esrick EB, Chong BG, Ippolito GC, Fujiwara Y, Ebert BL, Tucker PW, Orkin SH. (2011). Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. ***Science***, 334(6058):993-996. PMCID: PMC3746545

   d. Sankaran VG*, **Xu J***, Ragoczy T, Ippolito GC, Walkley CR, Maika SD, Fujiwara Y, Ito M, Groudine M, Bender MA, Tucker PW, Orkin SH. (2009). Developmental and species-divergent globin switching are driven by BCL11A. ***Nature*** (Article), 460: 1093-1097. PMCID: PMC3749913 (*co-first author).

4. **Transcriptional Competence of Pluripotency.** My early publications are focused on the transcriptional regulatory processes governing the pluripotency of embryonic (ES and iPS) and hematopoietic stem cells. Specifically, I discovered that chromatin within well-characterized tissue-specific loci contain windows of unmethylated CpG residues and are protected by 'pioneer factor' interactions in stem cells. Importantly, loss of pre-established marks consistently resulted in resistance to transcriptional activation during later differentiation. These findings support a model in which tissue-specific genes are actively marked by a group of 'pioneer factors' in the pluripotent state, and that pluripotency and successful reprogramming may be critically dependent on the transcriptional competence of many tissue-specific genes.

   a. **Xu J**, Pope SD, Jazirehi AR, Attema JL, Papathanasiou P, Watts JA, Zaret KS, Weissman IL, and Smale ST. (2007). Pioneer factor interactions and unmethylated CpG dinucleotides mark silent tissue-specific enhancers in embryonic stem cells. ***PNAS***, 104: 12377-12382. PMCID: PMC1941477

   b. Attema JL, Papathanasiou P, Forsberg EC, **Xu J**, Smale ST, and Weissman IL. (2007). Epigenetic characterization of hematopoietic stem cell differentiation using miniChIP and bisulfite sequencing analysis. ***PNAS***, 104: 12371-12376. PMCID: PMC1924790

   c. **Xu J**, Watts JA, Pope SD, Gadue P, Kamps M, Plath K, Zaret KS, and Smale ST. (2009). Transcriptional competence and the active marking of tissue-specific enhancers by defined transcription factors in embryonic and induced pluripotent stem cells. ***Genes & Development***, 23(24):2824-2838. PMCID: PMC2800090

   d. **Xu J**, Smale ST. (2012). Designing an enhancer landscape. ***Cell***, 151(5):929-931. PMC3732118

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1-Q6j7e3eh3Ae/bibliography/public/