BIOGRAPHICAL SKETCH

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NAME: ZHOU, XU

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POSITION TITLE: Assistant Professor of Pediatrics

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
Peking University, Beijing	BS	06/2006	Biological Sciences
Harvard University, Cambridge, MA	PHD	06/2013	Gene regulation/Systems biology
Yale School of Medicine, New Haven, CT	Postdoctoral Fellow	12/2020	Immunology/Tissue biology

A. Personal Statement

I am a junior faculty in the Division of Gastroenterology, Hepatology and Nutrition, in the Department of Pediatrics at Boston Children's Hospital and Harvard Medical School. I am interested in deciphering the molecular and cellular mechanisms that govern the transition from tissue homeostasis to disease and to developing innovative therapeutic strategies to restore balance and treat inflammation-related diseases**.** My lab has a broad background in immunology, systems biology, molecular and cellular biology, with specific expertise in immune profiling, imaging, transcriptomic and genomic analyses, and animal disease models. This experience equipped us with interdisciplinary approaches to probe the complex disease mechanisms.

During my early scientific career studying mechanisms of gene regulation, I established a novel systems approach that combines genomic, transcriptomic and mathematical methods to understand how specific transcriptional regulation is achieved across the whole genome (Contribution 1). I also developed a new analytic approach to characterize the epigenetic features at an unprecedented accuracy and precision (Contribution 2).

During my postdoc training and in my independent laboratory, we have pioneered a bottom-up systems approach to unravel the dynamic interplay between macrophages and fibroblasts-two pivotal cell types in tissue regulation. (Contribution 3) We discovered a novel growth factor-mediated crosstalk, whereby fibroblasts maintain a stable macrophage population at homeostasis (REF 3) and enable their rapid expansion in response to microenvironmental cues (REF 4). These works have helped redefine our understanding of immune-stromal interactions, unveiling a critical link between the spatial organization of cells and their immunological functions.

Expanding our research program, my lab is now investigating how environmental pH sensing regulates inflammatory and oncogenic responses. Our recent work uncovered a novel intracellular pH-sensing mechanism in macrophages and other immune cell types mediated by the epigenetic regulator BRD4 (Contribution 4; REF 2). We demonstrated that BRD4 functions as an intracellular pH sensor within the physiologically relevant range (pH 6.5–7.0), where acidic conditions modulate gene-specific inflammatory responses by altering BRD4-mediated transcriptional condensates. This finding links pH fluctuations to precise transcriptional control of inflammation. Since 2024, we started collaboration with the Zang lab to combine computational and experimental expertise to understand logics of transcriptional control by transcriptional condensates and super enhancers (REF 1). Our preliminary data further suggest that pH-dependent transcriptional mechanisms are common in cancer cells, and that different tumor types possess intrinsic capabilities to resist extracellular acidification—an established hallmark of solid tumors. Together, these observations suggest a previously unrecognized intersection between pH sensing, epigenetic regulation, and oncogenic transcriptional programs.

1. Wang S, Wu Z, Zhong Z, Zhou X, Zang C. Transcriptional condensates at super-enhancers mediate pH-dependent transcriptional control in innate immunity. bioRxiv. 2025 Oct 30; PubMed Central PMCID: PMC12636582.
2. Wu Z, Pope SD, Ahmed NS, Leung DL, Hong Y, Hajjar S, Krabak C, Zhong Z, Raghunathan K, Yue Q, Anand DM, Kopp EB, Okin D, Ma W, Zanoni I, Kagan JC, Thiagarajah JR, Hargreaves DC, Medzhitov R, Zhou X. Regulation of inflammatory responses by pH-dependent transcriptional condensates. Cell. 2025 Oct 2;188(20):5632-5652.e25. PubMed Central PMCID: PMC12313145.
3. Zhou X, Franklin RA, Adler M, Carter TS, Condiff E, Adams TS, Pope SD, Philip NH, Meizlish ML, Kaminski N, Medzhitov R. Microenvironmental sensing by fibroblasts controls macrophage population size. Proc Natl Acad Sci U S A. 2022 Aug 9;119(32):e2205360119. PubMed Central PMCID: PMC9371703.
4. Zhou X, Franklin RA, Adler M, Jacox JB, Bailis W, Shyer JA, Flavell RA, Mayo A, Alon U, Medzhitov R. Circuit Design Features of a Stable Two-Cell System. Cell. 2018 Feb 8;172(4):744-757.e17. PubMed Central PMCID: PMC7377352.

Ongoing and recently completed projects that I would like to highlight include:

R35GM151000, NIH/NIGMS
Zhou (PI), 8/2023-5/2028
Understanding Immune-Stromal Interactions in Tissue Homeostasis and Inflammation

R01CA269898, NIH/NCI
Zhou (Co-I), 3/2023-2/2028
Elucidating the Immune Suppressive Mechanism of SIGLEC-15 in the Tumor Microenvironment

Israeli Science Foundation, Research Grant
Zhou (Co-PI), 10/2024-09/2027
Principles of functional coordination between stromal and immune cells at tissue homeostasis and inflammation

Cystic Fibrosis Foundation
Zhou (PI), 11/2025-10/2027
Immune-mediated pH-sensing in Modulating Inflammatory Risk in Cystic Fibrosis

Smith Family Foundation, Odyssey award
Zhou (PI), 11/2025-10/2027
Intracellular Environment Engineering in Immune Modulation

The G. Harold and Leila Y. Mathers Foundation, Research Grant
Zhou (Co-PI), 05/2022 - 04/2025
Programming Stromal Compartment Size and Inflammatory State in Development.

Kenneth Rainin Foundation, Innovator Award
Zhou (PI), 06/2022 – 05/2025
Defining immune organization in intestinal inflammation

Charles H. Hood Foundation, Child Health Research Awards Program
Zhou (PI), 09/2022 – 08/2024
Mechanisms Of Contact-Dependent Immune-Stromal Interactions.

Pilot and feasibility grant, Harvard Digestive Disease Center/NIDDK P30DK034854
Zhou (PI), 7/2022-6/2024
Dissecting the Role of pH Sensing in Immunity and Inflammation

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 -	Co-Chair, Strategic committee for Pilot Research and Education, Boston Children's Hospital, Boston, MA
2024 -	Admission committee, Master of Medical Sciences in Immunology, Harvard Medical School, Boston, MA
2022 -	Associate Member, Broad Institute of MIT and Harvard, Cambridge, MA
2022 -	Graduate admission committee, PhD Program in Immunology, Harvard Medical School, Boston, MA
2021 -	Assistant Professor, Harvard Medical School, Department of Pediatrics, Boston, MA
2021 -	Member, Program in Immunology, Harvard Medical School, Boston, MA
2021 -	Affiliate member, Harvard Digestive Disease Center, Boston, MA
2021 -	Principal Investigator, Boston Children's Hospital, Division of Gastroenterology, Hepatology and Nutrition, Boston, MA
2013 - 2020	Postdoc fellow, Yale School of Medicine, Department of Immunobiology, New Haven, CT
2007 - 2013	Graduate Research Assistant, Harvard University and HHMI, Department of Molecular and Cellular Biology, Cambridge, MA
2004 - 2007	Undergraduate Research Assistant, Peking University, College of Life Sciences, Beijing

Honors

2025 - 2027	Odyssey Award, Richard and Susan Smith Family Foundation
2022 - 2025	Innovator Award, Kenneth Rainin Foundation
2021 - 2021	Early career faculty grant, Oakland, CA 2021 Early career faculty grant, American
2018 - 2018	Poster award, 6th ISF-Broad symposium, Broad Institute
2018 - 2018	Cell Symposium travel fellowship, NextGen Immunology meeting
2014 - 2017	Postdoctoral fellows, Jane Coffin Childs Memorial Fund
2009 - 2009	Cabot fellow, Harvard University

C. Contribution to Science

1. **The mechanisms of how specific gene expression program is controlled at genomic level by transcription factors.** Environmental signals can drive cellular decisions through specific transcription programs, from unicellular organisms to mammalian cells. However, it was unclear how transcription factors selectively identify and regulate a set of genes when thousands of other genes carry the same regulatory sequences. As a graduate student at Harvard University, I worked with Dr. Erin O'Shea to use genomic and computational approaches to present a holistic view of the mechanisms determining specificity in transcriptional regulation (Zhou, 2011), and uncovered that rewiring epigenetic mechanisms markedly altered the spectrum of a cellular response (He, 2017). In these work, we developed Biotin-ChIP-seq to improve specificity of conventional ChIP-seq. We were among the first labs applying MNase-seq to study chromatin landscapes. We also developed computational deconvolution algorithms to quantify the regulatory interactions between multiple transcription factors (Zhou, 2011). These findings and tools added to our mechanistic understanding of transcriptional regulation at the whole-genome level.

    a. Snyder LF, O'Brien EM, Zhao J, Liang J, Bruce BJ, Zhang Y, Zhu W, Cassier TH, Schnicker NJ, Zhou X, Gordân R, He BZ. Divergence in a eukaryotic transcription factor's co-TF dependence involves multiple intrinsically disordered regions. Nat Commun. 2025 Jun 18;16(1):5340. PubMed Central PMCID: PMC12177071.

    b. He BZ, Zhou X, O'Shea EK. Evolution of reduced co-activator dependence led to target expansion of a starvation response pathway. Elife. 2017 May 9;6 PubMed Central PMCID: PMC5446240.

c. Zhou X, O'Shea EK. Integrated approaches reveal determinants of genome-wide binding and function of the transcription factor Pho4. Mol Cell. 2011 Jun 24;42(6):826-36. PubMed Central PMCID: PMC3127084.

2. **A novel method to identify the genomic locations of nucleosomes with unprecedented resolution.** Nucleosome is the very basic structural unit of eukaryotic chromatin. Nevertheless, determining the position of nucleosomes accurately requires a combination of sophisticated genetic, chemical and sequencing techniques. With Dr. Alex Blocker and Dr. Edo Airoldi, two statisticians at Harvard University, we developed a novel computational approach that identified nucleosome positions precisely to single base-pair resolution with traditional Nucleosome-sequencing. This method revealed that chromatin landscape is extremely heterogeneous. For example, a given nucleosome is found at slightly different positions in different cells in more than half of the yeast genome, and the nucleosomes that are positioned near the beginning of a gene mark heterogenous states for transcriptional machinery.

   a. Zhou X, Blocker AW, Airoldi EM, O'Shea EK. A computational approach to map nucleosome positions and alternative chromatin states with base pair resolution. Elife. 2016 Sep 13;5 PubMed Central PMCID: PMC5094857.

3. **Mechanisms for maintaining homeostasis of multicellular mammalian systems.** Appropriate numbers and ratios of different cell types are ensured throughout tissue development. As a postdoc with Dr. Ruslan Medzhitov at Yale School of Medicine, I led a collaborative project using macrophages and fibroblasts to reconstruct a two-cell-type system, where the relative ratio of each cell type reaches stability even after transient perturbations. This reduction approach established the first in vitro platform to study properties of tissue homeostasis and demonstrated that reciprocal communication of growth factors and their feedback provide a mechanism for maintaining population homeostasis (Zhou, 2018). In a collaboration with Dr. Uri Alon at Weizmann Institute of Science, we further applied mathematical modeling to uncover general features a stable two-cell system (Alder, 2018). An unexpected discovery was that contact-dependent interaction between the two cell types is critical to maintaining their homeostasis (Zhou, 2018). Recently, we identified cell-type specific growth strategies for macrophages and fibroblasts, and unveiled cellular mechanisms underlying their numeric control within tissues (Zhou, 2022). The findings led us to propose the concept of cell circuit in maintaining tissue homeostasis. Stemmed from these work, we presented a perspective on functional organization of tissues allows for the maintenance of both tissue and organismal homeostasis (Meizlish, 2021).

   a. Zhou X, Franklin RA, Adler M, Carter TS, Condiff E, Adams TS, Pope SD, Philip NH, Meizlish ML, Kaminski N, Medzhitov R. Microenvironmental sensing by fibroblasts controls macrophage population size. Proc Natl Acad Sci U S A. 2022 Aug 9;119(32):e2205360119. PubMed Central PMCID: PMC9371703.
   b. Meizlish ML, Franklin RA, Zhou X, Medzhitov R. Tissue Homeostasis and Inflammation. Annu Rev Immunol. 2021 Apr 26;39:557-581. PubMed PMID: 33651964.
   c. Adler M, Mayo A, Zhou X, Franklin RA, Jacox JB, Medzhitov R, Alon U. Endocytosis as a stabilizing mechanism for tissue homeostasis. Proc Natl Acad Sci U S A. 2018 Feb 20;115(8):E1926-E1935. PubMed Central PMCID: PMC5828590.
   d. Zhou X, Franklin RA, Adler M, Jacox JB, Bailis W, Shyer JA, Flavell RA, Mayo A, Alon U, Medzhitov R. Circuit Design Features of a Stable Two-Cell System. Cell. 2018 Feb 8;172(4):744-757.e17. PubMed Central PMCID: PMC7377352.

4. **Immune sensing of pH in tissue homeostasis and inflammation.** The balance of pH is critical at cellular, tissue, and systemic levels, with deviations, particularly acidification, strongly associated with both physiological and pathological inflammation. However, the mechanisms by which tissues sense and regulate pH remain poorly understood. We hypothesize that the immune system integrates information on tissue and cellular states through extracellular and intracellular pH-sensing mechanisms to regulate homeostatic and inflammatory programs (Hajjar, 2023). Extracellularly, we focus on GPR65, a proton-sensing G-protein-coupled receptor strongly associated with ulcerative colitis, Crohn’s disease, multiple

sclerosis, and other inflammatory disorders. Using whole-body and conditional knockout mouse models, we are dissecting the role of GPR65 in orchestrating tissue and systemic inflammatory responses. Intracellularly, we recently identified a novel pH-sensing pathway critical for macrophage-mediated inflammation (Wu, 2024). Acidic intracellular pH specifically modulates BRD4-dependent transcriptional condensates, essential for initiating antiviral inflammatory programs. PH shifts within macrophages disrupts BRD4 function and suppressing inflammatory pathways both in vitro and in vivo. As an essential and broadly expressed epigenetic regulator, BRD4 functions as an intracellular pH sensor through its histidine-rich intrinsically disordered regions, revealing a new paradigm of intracellular pH sensing that may have transformative implications for tissue repair, inflammatory disorders, and tumor-immune interactions (Wu, 2025). Combining with new computational methods, we further revealed transcriptional factors that integrate into condensate dependent regulation of inflammatory response (Wang, 2025).

a. Wang S, Wu Z, Zhong Z, Zhou X, Zang C. Transcriptional condensates at super-enhancers mediate pH-dependent transcriptional control in innate immunity. bioRxiv. 2025 Oct 30; PubMed Central PMCID: PMC12636582.
b. Wu Z, Pope SD, Ahmed NS, Leung DL, Hong Y, Hajjar S, Krabak C, Zhong Z, Raghunathan K, Yue Q, Anand DM, Kopp EB, Okin D, Ma W, Zanoni I, Kagan JC, Thiagarajah JR, Hargreaves DC, Medzhitov R, Zhou X. Regulation of inflammatory responses by pH-dependent transcriptional condensates. Cell. 2025 Jul 17; PubMed Central PMCID: PMC12313145.
c. Hajjar S, Zhou X. pH sensing at the intersection of tissue homeostasis and inflammation. Trends Immunol. 2023 Oct;44(10):807-825. PubMed Central PMCID: PMC10543622.

5. **Collaborative Science.** In collaboration with Dr. Kristopher Kahle at Department of Pediatrics at Yale School of Medicine, I used gene expression analysis to identify the Toll-like receptor 4 dependent inflammatory response in choroid plexus epithelium, triggered by intraventricular hemorrhage (Karimy, 2017). In collaboration with Dr. Lieping Chen at Yale School of Medicine, I discovered that Siglec15, a novel immune suppressor and potential target of immunotherapy, is expressed predominately in myeloid compartment (Wang, 2019). In collaboration with Dr. Peng Wu at Scripps Institute, I contributed to the discovery of a new way of how Siglec molecules suppress T cell activation in cancer immunology (Wang, 2024). In collaboration with Dr. Ivan Zanoni at Boston Children's Hospital, my lab contributed to the identification of EZH2 as a novel epigenetic regulator of IL10 expression (Di Gioia, 2025).

a. Di Gioia M, Poli V, Tan PJ, Spreafico R, Chu A, Cuenca AG, Wu Z, Benamar M, Pandolfi L, Meloni F, Askarian F, Hsiao J, Borroum E, Nizet V, Gordts PLSM, Witztum JL, Chatila TA, Chou J, Zhou X, Springstead JR, Zanoni I. Epigenetic silencing of interleukin-10 by host-derived oxidized phospholipids supports a lethal inflammatory response to infections. Immunity. 2025 Sep 9;58(9):2190-2207.e13. PubMed Central PMCID: PMC12313134.
b. Wang C, Hou Y, Zak J, Zheng Q, McCord KA, Wu M, Zhang D, Chung S, Shi Y, Ye J, Zhao Y, Hajjar S, Wilson IA, Paulson JC, Teijaro JR, Zhou X, Sharpless KB, Macauley MS, Wu P. Reshaping the tumor microenvironment by degrading glycoimmune checkpoints Siglec-7 and -9. bioRxiv. 2024 Oct 12; PubMed Central PMCID: PMC11483058.
c. Wang J, Sun J, Liu LN, Flies DB, Nie X, Toki M, Zhang J, Song C, Zarr M, Zhou X, Han X, Archer KA, O'Neill T, Herbst RS, Boto AN, Sanmamed MF, Langermann S, Rimm DL, Chen L. Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy. Nat Med. 2019 Apr;25(4):656-666. PubMed Central PMCID: PMC7175920.
d. Karimy JK, Zhang J, Kurland DB, Theriault BC, Duran D, Stokum JA, Furey CG, Zhou X, Mansuri MS, Montejo J, Vera A, DiLuna ML, Delpire E, Alper SL, Gunel M, Gerzanich V, Medzhitov R, Simard JM, Kahle KT. Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nat Med. 2017 Aug;23(8):997-1003. PubMed PMID: 28692063.

Complete List of Published Work in MyBibliography
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