BIOGRAPHICAL SKETCH

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NAME: Xue, Hai-Hui

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

POSITION TITLE: 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)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
China Medical University, Shenyang, China	M.D.	1985	1991	Medicine
Graduate School, China Medical University, Shenyang, China	Master of Medical Sciences	1991	1994	Biochemistry and Molecular Biology
Graduate School, Hamamatsu University School of Medicine, Hamamatsu, Japan	Ph.D.	1997	2000	Biochemistry and Molecular Biology
National Institutes of Health, Bethesda, MD, US	Postdoctoral training	2000	2006	Molecular Immunology

A. Personal Statement

The major theme of my research is to seek in-depth understanding of transcriptional and epigenetic control during T-cell development in the thymus, T-cell activation and memory formation in the periphery, self-renewal of hematopoietic and leukemic stem cells. For the past twenty years, I have accumulated knowledge in these fields during my postdoctoral training and leading my independent laboratory. Since 2006, my lab has been employing state-of-the-art techniques including mouse genetics, molecular biology, cellular immunology, systems biology approaches to delineate transcriptional and epigenetic regulation of several critical aspects in T cell and stem cell biology.

B. Positions and Honors

Academic Positions and Employment

1994 – 1995	Assistant professor, Dept. of Biochemistry, China Medical University, Shenyang, China.
1995 – 1997	Assistant research scientist, Dept. of Biochemistry, Hamamatsu University School of Medicine, Hamamatsu, Japan. (Supervisor: Dr. Arata Ichiyama, Professor).
2000 – 2006	Research fellow, Laboratory of Molecular Immunology, NHLBI, NIH, Bethesda, MD, US. (Supervisor: Dr. Warren J. Leonard, member of National Academy of Sciences).
2006 – 2012	Assistant professor, Department of Microbiology, The University of Iowa, Iowa City, IA
2012 – 2017	Associate professor with tenure, Department of Microbiology, The University of Iowa, Iowa City, IA
2016 – 2020	VA Research Health Science Specialist, Iowa City Veteran Affairs Medical Center, Iowa City, IA.
2017 – 2020	Professor, Department of Microbiology and Immunology. The University of Iowa, Iowa City, IA.
2020 –	VA Research Health Science Specialist, VA New Jersey Health Care System, East Orange, NJ.
2020 –	Member/Professor, Center for Discovery and Innovation, Hackensack University Medical Center, Nutley, NJ.

Professional Experience and Memberships

1995 – 2000	Japanese Biochemistry Society
2001 –	AAAS (American Association of Advanced Sciences)
2012 –	AAI (American Association of Immunologists)/Membership number: 00228480

2012 –	ASH (American Society of Hematology)/Membership ID number: 1097882
2006 –	Reviewer for research journals: *Nature, Nature Immunology, Nature Reviews Immunology, Immunity, Nature Communications, Cell Reports, Blood, Proc. Natl. Acad. Sci. USA*, *Stem cells, Journal of Immunology, International Immunology, Journal of Leukocyte Biology*, *Oncogene*, *Immunology*, *PLoS One*, *PLoS Biology*, *PLoS Pathogen*, *Cytokine*, *Cellular and Molecular Immunology*, and *Biochimica et Biophysica Acta.*
2012 –	Reviewer, ad-hoc on CMIA study section with Dr. David Winter.
2013 –	Reviewer, ad-hoc on CMIB study section with Dr. Betty Hayden, CMIA SEP with Dr. David Winter, IMM-J02M with Dr. Patrick Lai.
2014, 2015	COBRE II with Dr. Lisa Dunbar.
2015	Small Business Hematology SEP with Dr. Bukhtiar Shah.
2017 –	Standing member, CMIB (with Dr. Betty Hayden).

Awards and Honors

1999	Travel Award for Research Excellence, Japanese Biochemistry Society
2003, 2005	The Fellows Award for Research Excellence, NIH
2005	Lenfant Biochemical Fellow Award, NHLBI, NIH
2011	American Cancer Society Research Scholar
2016	Merit Award, Department of Veterans Affairs.
2017	Donald D. Dorfman Research Award for Outstanding Publication in Leukemia or Lymphoma Research

C. Contribution to Science

1. Delineation of novel roles of Tcf1/Lef1 and their cofactors in T cell development. Tcf1 and Lef1 are known effector transcription factors of the canonical Wnt signaling pathway. A requirement for Tcf1 and Lef1 in T cell development was demonstrated in 1990s and their roles were limited to positive regulation of survival of early thymocytes. Since we directed our research interest to the Wnt-Tcf1/Lef1 pathway in 2008, we have made several novel findings: 1) Tcf1 and Lef1 have cooperative roles in promoting β-selection during early T cell development, 2) Tcf1 acts as tumor suppressor in early thymocytes, and surprisingly, this function is mediated by direct repression of Lef1. This is the first demonstration that Tcf1 and Lef1 have opposing roles in early thymocytes. 3) Tcf1 also actively represses the Notch signaling pathway to prevent malignant transformation of early thymocytes. 4) By conditionally targeting both Tcf1 and Lef1 to bypass their roles in early stages of T cell development, we found that they have unexpected novel roles in promoting $CD4^+$ T cell lineage choice. 5) Although not required for $CD8^+$ T cell fate decision, Tcf1 and Lef1 cooperate with Runx transcription factors to silence the Cd4 gene in mature $CD8^+$ T cells. 6) Most unexpectedly, Tcf1 and Lef1 have intrinsic HDAC activity, which is essential in repressing $CD4^+$ lineage-associated genes in $CD8^+$ T cells and hence establishing $CD8^+$ T cell identity. 7) The Tle/Groucho corepressors act in concert with Tcf1/Lef1 in regulation of $CD8^+$ T cell identity. Our studies substantially advanced the understanding of Wnt-Tcf1/Lef1 pathway in T cell development.

   a. Xing S, Shao P, Li F, Zhao X, Seo W, Wheat JC, Ramasamy S, Wang J, Li X, Peng W, Yu S, Liu C, Taniuchi I, Sweetser DA, Xue HH. Tle corepressors are differentially partitioned to instruct $CD8^+$ T cell lineage choice and identity. **J. Exp. Med**. 2018, 215, 2211-2226 (PMID: 30045946; PMICID: PMC6080905).
   b. Xing S, Li F, Zeng Z, Zhao Y, Yu S, Shan Q, Li Y, Philips FC, Maina PK, Qi HH, Liu C, Zhu J, Pope RM, Musselman CA, Zeng C, Peng W, Xue HH. Tcf1 and Lef1 transcription factors establish $CD8^+$ T cell identity through intrinsic HDAC activity. **Nat. Immunol**. 2016. 17: 695-703. (PMID: 27111144; PMICID: PMC4873337) [**News and Views** by Ng and Littman DR, Tcf1 and Lef1 pack their own HDAC. **Nat Immunol**. 2016, 17: 615-616]
   c. Steinke FC, Yu S, Zhou X, He B, Yang W, Zhou B, Kawamoto H, Zhu J, Tan K, Xue HH. (2014) TCF-1 and LEF-1 act upstream of Th-POK to promote the $CD4^+$ T cell lineage choice and interact with Runx3 to silence *Cd4* in $CD8^+$ T cells. **Nat. Immunol**. 15, 646-656. (PMCID: PMC4064003). [**News and Views** by Mookerjee-Basu J and Kappes DJ. New ingredients for brewing $CD4^+$ T (cells): TCF-1 and LEF-1. **Nat Immunol**. 2014, 15, 593-594.]
   d. Yu S, Zhou X, Steinke FC, Liu C, Chen SC, Zagorodna O, Jing X, Yokota Y, Meyerholz DK, Mullighan CG, Knudson CM, Zhao DM, Xue HH. (2012) The TCF-1 and LEF-1 transcription factors

have cooperative and opposing roles in T-cell development and malignancy. **Immunity**. 37, 813-826. (PMCID: PMC3501598). [**Preview** by Staal and Clevers, Tales of the unexpected: Tcf1 functions as a tumor suppressor for leukemias. **Immunity**. 2012, 37, 761-763]

2. Transcriptional and epigenetic regulation of mature $CD8^+$ T cell responses. Through collaboration with Drs. Harty and Badovinac at the University of Iowa, we broadly contributed to elucidation of pathways and transcriptional programs that control the expansion of $CD8^+$ effector T cells and recall responses by memory $CD8^+$ T cells. Our specific contributions include: 1) systematic mapping of enhancer and super-enhancers, their interactions with target gene promoters during $CD8^+$ T cell responses to infection; 2) dual function of Runx3 in activating the cytotoxic program in $CD8^+$ effector T cells and preventing the diversion to follicular helper lineage; 3) constitutive activation of Wnt pathway favors generation of memory $CD8^+$ T cells; and 4) Tcf1 critically regulate the persistence and maturation of memory $CD8^+$ T cells. We also collaborated with Dr. Rafi Ahmed (Emory) to identify an essential role of Tcf1 in generating a stem cell-like subset of exhausted $CD8^+$ T cells elicited by chronic viral infection and its proliferative capacity to checkpoint blockade therapy.

a. Shan Q, Zeng, Z, Xing, S, Li F, Hartwig S, Gullicksrud JA, Kurup SP, Van Braeckerl-Budimir N, Su Y, Martin MD, Varga SM, Taniuchi I, Harty JT, Peng W, Badovinac VP, Xue HH. The transcription factor Runx3 guards cytotoxic $CD8^+$ effector T cells against deviation toward follicular helper T cell lineage. **Nat. Immunol**. 2017, 18, 931-939. (PMID: 28604718; PMICID: PMC5564218)
b. He B, Xing S, Chen C, Gao P, Teng L, Shan Q, Gullicksrud JA, Martin MD, Yu S, Harty JT, Badovinac VP, Tan K, Xue HH. $CD8^+$ T cells utilize highly dynamic enhancer repertoires and regulatory circuitry in response to infections. **Immunity**, 2016, 45, 1341-1354. (PMID: 27986453; PMICID: PMC5304416)
c. Im SJ, Hashimoto M, Gerner MY, Lee J, Kissick HT, Burger MC, Shan Q, Hale JS, Lee J, Nasti TH, Sharpe AH, Freeman GJ, Germain RN, Nakaya HI, Xue HH, Ahmed R. Defining $CD8^+$ T cells that provide the proliferative burst after PD-1 therapy. **Nature** 2016, 537, 417-421. (PMID: 27501248; PMICID: PMC5297183)
d. Zhou X, Yu S, Zhao DM, Harty JT, Badovinac VP, Xue HH. (2010) Differentiation and persistence of memory CD8 T cells depend on T cell factor 1. **Immunity**. 33, 229-240. (PMCID: PMC2928475) [**Preview** by Paley and Wherry. TCF-1 flips the switch on Eomes. Immunity. 2010, 33: 145-147].

3. Transcriptional and epigenetic regulation of Treg and mature $CD4^+$ T cell responses. With a focus on Tcf1 and Lef1 transcription factors, we have elucidated their roles in mature $CD4^+$ T cells and innate immune cells. Our specific contributions include: 1) Tcf1 and Lef1 act upstream of the master regulator Bcl6, ICOS and IL-6 receptor to promote T_{FH} cell differentiation; 2) In contrast to a conventional role in gene repression, Ezh2, in its Ser21 phosphorylated form, functions as a coactivator of Tcf1 to induce Bcl6 during T_{FH} cell differentiation; 3) Tcf1 short isoforms, without the capacity to interact with β-catenin, are adequate to support Bcl6 transcriptional activation and promoter germinal center T_{FH} maturation; 4) Tcf1 and Lef1, although dubbed as Treg-down signature genes compared with conventional $CD4^+$ T cells, are required for maintaining the immunosuppressive function of Treg cells.

a. Xing S, Gai K, Li X, Shao P, Zeng Z, Zhao X, Zhao X, Chen X, Paradee WJ, Meyerholz DK, Peng W, Xue HH. Tcf1 and Lef1 are required for the immunosuppressive function of regulatory T cells. **J. Exp. Med**. 2019, 216, 847-866. (PMID: 30837262)
b. Li F, Zeng Z, Xing S, Gullicksrud JA, Shan Q, Choi J, Badovinac VP, Crotty S, Peng W, Xue HH. Ezh2 programs Tfh differentiation by integrating phosphorylation-dependent activation of Bcl6 and polycomb-dependent repression of p19Arf. **Nat. Commun**. 2018, 9, 5452 (PMID: 30575739; PMICID: PMC6303346).
c. Choi YS, Gullicksrud JA, Xing S, Zeng Z, Shan Q, Li F, Love PE, Peng W, Xue HH**, Crotty S**. LEF-1 and TCF-1 orchestrate T follicular helper (Tfh) cell differentiation by regulating Tfh differentiation circuits upstream of Bcl6. **Nat. Immunol**. 2015, 16, 980-990 (PMID: 26214741)(**, co-senior authors). [**News and Views** by Kubo M. TCF-1 and LEF-1 help launch the Tfh program. **Nat Immunol**. 2015, 16, 980-990.]

d. Gullickscrud JA, Li F, Xing S, Zeng Z, Peng W, Badovinac VP, Harty JT, Xue HH. Differential requirements for Tcf1 long isoforms in $CD8^+$ and $CD4^+$ T cell responses to acute viral infection. **J. Immunol**. 2017, 199, 911-919. (PMID: 28652395; PMICID: PMC5531591)

4. Transcriptional regulation of self-renewal of hematopoietic and leukemic stem cells. GABP is a broadly expressed Ets family transcription factor that consists of GABPα DNA binding subunit and GABPβ transactivation subunit. In my postdoctoral work in Dr. Warren Leonard's laboratory, I discovered the critical regulatory role of GABP in T and B cell development. In my independent lab, we extended our investigation to self-renewal of hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs) in CML models. Our discoveries include 1) GABP regulates a unique gene regulatory network that controls several aspects of HSC self-renewal, and 2) GABP tetramer are specifically required for self-renewal of CML LSCs. Built on the expertise we acquired during these studies, we recently defined 1) the requirements for Tcf1 and Lef1 transcription factors in the regenerative fitness of HSCs and their indispensable role in CML LSC self-renewal, and 2) identification of prostaglandin E1 and its analogue misoprostol in simulating the effect of genetic ablation of Tcf1 and Lef1, and their synergistic effect with conventional therapy to eradicate CML LSCs.

a. Yu S, Cui K, Jothi R, Zhao DM, Jing X, Zhao K, Xue HH. (2011) GABP controls a critical transcription regulatory module that is essential for maintenance and differentiation of hematopoietic stem/progenitor cells. **Blood**, 117, 2166-2178. (PMCID: PMC3062326).
b. Yu S, Jing X, Colgan JD, Zhao DM, Xue HH. (2012) Targeting tetramer-forming GABPβ isoforms impairs self-renewal of hematopoietic and leukemic stem cells. **Cell Stem Cell**. 11, 207-219. (PMCID: PMC3413094)
c. Yu S, Li F, Xing S, Zhao T, Peng W, Xue HH. Hematopoietic and leukemic stem cells have distinct dependence on Tcf1 and Lef1 transcription factors. **J. Biol. Chem**. 2016, 291:11148-11160. (PMID: 27044748; PMICID: PMC4900264)
d. Li F, He B, Ma X, Yu S, Bhave RR, Lentz SR, Tan K, Guzman ML, Zhao C, Xue HH. Prostaglandin E1 and its analog misoprostol inhibit human CML stem cell self-renewal via EP4 receptor activation and repression of AP-1. **Cell Stem Cell**. 2017, 21, 359-373 (PMID: 28844837; PMICID: PMC5678929).

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1RQTgzkybsBA9/bibliography/41455163/public/?sort=date&direction=descending

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

Ongoing Research Support

1. NIAID, NIH, 7R01-AI121080-05 Xue and Peng (MPI) 6/2016 to 5/2021
Tcf/Lef and β-catenin pathway in follicular helper T cells
Long-term goals: To define the mechanisms by which the Tcf1/Lef1 and β-catenin cofactor orchestrate enhancer organization during in follicular helper T cell differentiation and memory formation.
Role: coPI (contact).

2. NIAID, NIH, 7R01-AI139874-03 Xue and Peng (MPI) 9/2018 to 8/2023
Ezh2 regulates differentiation of follicular helper T cell responses
Long-term goals: To investigate the role of Ezh2, a known epigenetic regulator, in promoting follicular helper T cell responses to viral infection.
Role: coPI (contact).

3. NIAID, NIH, 5R01-AI112579-05 Xue and Zang (MPI) 03/2015 to 04/2025
Tcf1 programs CD8 T cells to enhance viral and cancer immunity.
Research goals: Molecular characterization of Tcf1 transcription factor in preprograming recall response by memory CD8 T cells and reprogramming exhausted CD8 T cells for functional restoration.
Role: coPI (contact).

4. NCI, NIH, Type R01 (CA237006) Zhao (PI) 12/2019 to 11/2024
Heat Shock Transcription Factor 1 specifically regulates AML stem cell self-renewal.
Long-term goals: To investigate the role of HSF1 in regulating AML leukemic stem cells and its potential as a therapeutic target.
Role: co-investigator.

5. BLR&D Merit Review Program, VA, Type I01 (BX002903A)
Xue (PI) 4/2016 to 9/2020
(in no cost extension, A1 competitive renewal to be submitted)
Targeting Tcf/Lef-transcriptional program in leukemic stem cells
Long-term goals: To define the roles of Tcf/Lef transcription factors in self-renewal of leukemic stem cells and characterize small molecules that target Tcf/Lef-dependent transcriptional programs as a novel leukemia therapy.
Role: PI