## BIOGRAPHICAL SKETCH

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NAME: **Yi Zhang**

eRA COMMONS USER NAME (credential, e.g., agency login): **ZHANGYI2**

POSITION TITLE: **Member, 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)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Tokyo, Japan<br>University of Kanazawa, Japan | MD, PhD | 09/1998 | Immunology and Molecular Medicine |
| Suzhou Medical College, Suzhou, P.R.China | M.S. | 07/1989 | Immunology and Microbiology |
| Zhengjiang Medical College, Zhengjiang, P.R.China | B.S. | 09/1983 | Medicine |

**A. Personal Statement.**

I have long-term interest in understanding of pathophysiology of GVHD, allogeneic hematopoietic stem cell transplantation (allo-HSCT) biology, leukemia immunology and development of novel approaches to improve the safety of allo-HSCT. I am a director member at CDI and also a co-leader of CHI program at Georgetown Lombardi Comprehensive Cancer Center (GLCCC), Georgetown University, Washington DC. Through collaborations between the CDI, John Theurer Cancer Center, and GLCCC, my lab aims at translating this knowledge to novel approaches to improve the efficacy of cancer immunotherapy and therapeutic intervention of alloimmunity. At CDI, we have recently established “Institute for Immunological Intervention (**III**)”. The mission of **III** is to improve the knowledge of T cell development, infection immunity, autoimmune inflammation, tumor immunity and alloimmunity.

My longstanding goal has focused on understanding how transcriptional and epigenetic regulators regulate the severity of GVHD with a particular emphasis on alloreactive T cells. Key findings from our dedicated work in the past two decades include: 1) alloreactive memory T cells are responsible for the persistence of GVHD. We were among the first to introduce the concept of alloantigen-sensitized stem cell memory T cells ($T_{SCM}$) in sustaining alloreactive T cell responses and GVHD (Nat Med 2005). This concept of $T_{SCM}$ stimulates many other groups to develop novel strategies for improving the efficacy of cancer immunotherapy; 2) Ezh2, a histone-modifying enzyme, is essential for alloreactive T cell responses and their induction of GVHD; and 3) Ezh2 controls formation and recall response of memory $CD8^+$ T cells and their antitumor activity. As part of these ongoing studies to identify molecular mechanisms that underlie GVHD T cell responses, we recently uncovered that the role of receptor-interacting protein kinase-1 (RIPK1) and RIPK3 in propagating alloreactive T cell-mediated GVHD in gastrointestinal tract (PMID: 36356302).

Most recently, we discovered the critical role of transcriptional regulator Id3 in sustaining tissue-infiltrating T cell responses in GVHD target tissues locally, including the liver and intestines. Id3 reduces chromatin accessibility for multiple transcription factors to repress PD-1 transcription, T cells differentiation and dysfunction (PMID: 37871574). We also have long-term interest in the development of living cell therapy for preventing GVHD, which offers many advantages compared to systemic drug interventions.

**Ongoing projects relevant to allo-HSCT biology and epigenetic regulation of T cells and dendritic cells:**

1R01CA290808-01, NIH/NCI(PI: Zhang). 04/30/2024 - 04/30/2029
Title: ID3 regulation of tissue-infiltrating T cells mediating graft-versus-host disease and leukemia rejection

1R01HL154757-01A1, NIH/NHLBI (PI: Zhang). 04/2021 – 03/2025
Title: Dot1l, Plasmacytoid Dendritic Cells and Alloimmunity

1 P50 CA254897-01, The SPORE (NIH), Project-1: Epigenetic Therapy
Co-leader of projet-1. 06/2021 – 05/2026
Title: Cyclin Dependent Kinases as Epigenetic Therapy Targets

5R01-AI121080-06, NIH/NIAID Zhang (Co-investigator). 10/2022 – 9/2027
Title: CTCF in CD8 T cell homeostasis and anti-viral/tumor immunity

**Key publications relevant to this proposal demonstrating our experience in characterizing alloreactive T cell responses using multiomics and immune-profiling approaches:**

a. Ying Wang, Shan He, Gennaro Calendo, Tien Bui, Yuanyuan Tian, Che Young Lee, Uan Zhou, Xin Zhao, Ciril Abraham, Wenbin Mo, Mimi Chen, Ruqayyah Sanders-Braggs, Jozef Madzo, Jean-Pierre Issa, Elizabeth O Hexner, David Wiest, Ran Reshef, Hai-Hui Xue, Yi Zhang (Correspondence). Tissue-infiltrating alloreactive T cells require Id3 to deflect PD-1-mediated immune suppression during GVHD. Blood 2024, 143:166-177. PMID: 37871574, PMCID: PMC 10797551.
b. Xiaoliang Yu, Haikuo Ma, Bohan Li , Yuting Ji , Yayun Du , Siying Liu , Zhanhai Li , Yongjin Hao , Sheng Tian, Cong Zhao, Qian Du, Zhongqin Jin, Xueming Zhu, Yuanyuan Tian, Xin Chen , Xue Sun , Chengkui Yang, Fang Zhu, Jie Ju, Yunjing Zheng, Wei Zhang, Jingrui Wang, Tao Yang , Xinhui Wang, Jingjing Li, Xiangping Xu, Shujing Du, Haohao Lu, Feng Ma, Haibing Zhang, **Yi Zhang** (Co-corespondence), Xiaohu Zhang, Shaoyan Hu, Sudan He. A Novel RIPK1 Inhibitor Reduces GVHD in Mice via a Non-immunosuppressive Mechanism that Restores Intestinal Homeostasis. Blood 2023 Mar 2;141(9):1070-1086. PMID: 36356302.
c. Yuanyuan Tian, Lijun Meng, Ying Wang, Bohan Li, Hongshuang Yu, Yan Zhou, Tien Bui, Alicia Li, Yongping Zhang, Jian Wang, Shin Mineishi, Hong Zheng, Stefania Gallucci, Yanyun Zhang, Shaoyan Hu and **Yi Zhang** (Correspondence author). GVHD Depletes Plasmacytoid Dendritic Cell Progenitors to Impair Tolerance Induction. JCI, 2021, 131(1):e136774, PMID: 33090973.
d. Shan He, Yongnian Liu, Lijun Meng, Hongxing Sun, Janaki Purushe, Pan Chen, Changhong Li, Jozef Madzo, Jean-Pierre Issa, Jonathan Soboloff, Bethany B Moore, Luca Gattinoni and **Yi Zhang** (Correspondence author), Ezh2 Phosphorylation State Determines its Capacity to Maintain $CD8^+$ Memory T Cells for Antitumor Immunity. Nature Communications, 2017, 8(1):2125. PMID:29242551.

**B. Positions and Honors**

**Positions and Employment**

| | |
|---|---|
| 2021 – | Director member/Professor, Center for Discovery and Innovation, Hackensack University Medical Center, Nutley, NJ. |
| 2021 – | Co-leader, Cancer-Host Interaction (CHI) program, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC, USA |
| 2017 – 2021 | Professor (with tenured), Fels Institute, Department of Microbiology & Immunology, Temple University, Philadelphia, USA |
| 2014 – 2017 | Associate Professor, Fels Institute, Department of Microbiology & Immunology, Temple University, Philadelphia, USA |
| 2007 – 2014 | Assistant Professor, University of Michigan, Ann Arbor, MI, USA |
| 2003 – 2007 | Research Assistant Professor, University of Pennsylvania, Philadelphia, PA. USA |
| 2000 – 2003 | Research Associate, University of Pennsylvania, Philadelphia, PA. USA |
| 1998 – 2000 | Postdoctoral Fellow, University of Pennsylvania, Philadelphia, PA, USA |
| 1996 – 1998 | Associate Professor of Immunology, Suzhou Medical College, P.R. China |
| 1989 – 1995 | Assistant Professor of Immunology, Suzhou Medical College, P.R. China |
| 1983 – 1986 | Residency, No.2 People's Hospital of Suzhou, P.R. China |

**Other Experience and Professional Memberships**

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|---|---|
| 2002 - | Member, American Society of Hematology |
| 2003 - | Member, Center for International Blood and Marrow Transplant Research (CIBMTR) |

2009 - Member, American Society of Immunology

**Scientific Review Panels**

**2014**, Ad Hoc reviewer, CMIA, NIH; **2015**, Ad Hoc reviewer, ZRG1 F07 S 20 L, IMM, NIH; **2016**, Ad Hoc reviewer, TTT, NIH, Ad Hoc reviewer, Ad hocZRG1 IMM-K 51, NIH; **2017**, Ad Hoc reviewer, CII, NIH, Ad Hoc reviewer, TTT, NIH; **2018**, Ad Hoc reviewer, CII, NIH; Ad Hoc ZRG1 F07-U20, **2018**; Ad HocZRG1 F09C-Q (20)-March, 2019; Ad Hoc ZRG1 F09C-Q 20-June, **2019**. Regular member, TTT, NIH, July-2019~June 2023.

**Honors and Awards**

01/1995 Prize for academic achievements (National Education Ministry of China); 12/1999 Prize for the Most Excellent Young Teacher (Education Committee of Jiangsu Province, China); 05/1998 Prize for Extraordinary Academic Achievements (State Council of P.R. China); 01/2009 Damon Runyon Rachleff Innovation Award; 07/2010 Research Scholar Grants, American Cancer Society, USA; 09/2011 New Investigator Awards, Department of Defense, USA; 01/2012 Bai Yu Lan Prize for Research Scholar, Shanghai, China; 01/2015 Leukemia Spore Developmental Research Award, USA

**Presentations ( recent 5 years):** Invited Speaker, The Stanley S. Scott Cancer Center, Louisiana State University, 2023; Georgetown University, Lombardi Comprehensive Cancer Center, 2021; Medical University of South Carolina, South Carolina, 2021; University of Miami, 2020; University of Maryland 2019; Invited speaker-Fox Chase Cancer Center, 2018; University of Iowa, 2018; Medical College of Wisconsin, WI 2017; Jiao-Tong University Xinghau Hospital, Shanghai, China 2017; Shanghai Personalized Medicine Summit, Shanghai, China 2017; Fox Chase Cancer Center, PA, 09/2016; Stand-up-to-Cancer (SU2C), PA, 07/2016; Pennsylvania State University, PA, 10/2015; Temple University, PA, 10/2015; Temple University, 05/2014; The Fox Chase Cancer Center, PA, 03/2014; The Fox Chase Cancer Center, PA, 02/2014;Temple University, 01/2014.

**C. Contribution to Science (All publications listed below heavily rely on FACS instrument)**

**1. Epigenetic regulation of T cell immunity:** My laboratory has made a continuous stream of novel fundamental contributions in GVHD. They include the identification of the histone methyltransferase Ezh2 in regulating T cell responses and GVHD. Specifically, we identify that Ezh2, which catalyzes histone H3 lysine 27 trimethylation, plays a central role of Ezh2 in regulating allogeneic T cells. Inhibition of Ezh2 in donor T cells inhibited GVHD in mice after allogeneic BM transplantation. Further studies revealed that Ezh2 was required to prevent proteasome-mediated degradation of T-bet protein in Th1 cells, thereby promoting Th1 differentiation. Most recently, we identified that Ezh2 is crucially involved in the regulation of DNA damage responses in proliferating T cells through interacting DN-PKc. We also discovered the crucial role of Ezh2 in regulating memory T cell formation and how intermediate signaling such as the AKT pathway modified T cell Ezh2 function. All these findings have established a novel function of Ezh2 in T cells, and that Ezh2 can serve as a therapeutic strategy for the treatment of GVHD, tumor immunotherapy and other T cell-mediated inflammatory disorders.

a. Yun Ji, Yun Ji, Wei Zhu, Hongjun Wang, Tuoqi Wu, Jinhui Hu, Jessica Fioravanti, Neal Lacey, Sanjivan Gautam, John Le Gall, Xia Yang, James Hocker, Thelma Escobar, Shan He, Stefania Dell'Orso, Nga Hawk, Veena Kapoor, William Telford, Luciano Di Croce, Stefan Muljo, **Yi Zhang**, Vittorio Sartorelli, and Luca Gattinoni. miR-155 harnesses Phf19 to potentiate cancer immunotherapy through epigenetic reprogramming of $CD8^+$ T cell fate. Nature Communications 2019, 14;10(1):2157. PMID: 31089138
b. Shan He, Yongnian Liu, Lijun Meng, Hongxing Sun, Janaki Purushe, Pan Chen, Changhong Li, Jozef Madzo, Jean-Pierre Issa, Jonathan Soboloff, Bethany B Moore, Luca Gattinoni and **Yi Zhang** (Correspondence author), Ezh2 Phosphorylation State Determines its Capacity to Maintain $CD8^+$ Memory T Cells for Antitumor Immunity. Nature Communications, 2017, 8(1):2125. PMID:29242551.
c. Qingrong Huang, Shan He, Yuanyuan Tian, Yuting Gu, Pan Chen, Changhong Li, Jiefang Huang, Yongnian Liu, Min Jin, Shaoyan Hu, Qing Tong, Anqi Ma, Jian Jin, Elizabeth Hexner, Henry Fung, Ran Reshef, **Yi Zhang** (Correspondence author) and Yanyun Zhang. Hsp90 inhibition destabilizes Ezh2 protein in alloreactive T cells and reduces graft-versus-host disease in mice. Blood 2017: 18;129(20):2737-2748 (Cover story). PMID: 28246193.
d. Tong Q, He S, Xie F, Mochizuki K, Liu Y, Mochizuki I, Meng L, Sun H, Zhang YY, Guo Y, Hexner E, and **Zhang Y** (Correspondence author). Ezh2 regulates transcriptional and post-translational expression of T-bet and promotes Th1 cell responses mediating aplastic anemia in mice. J Immunol 2014,

192(11) 5012-5022, PMID:24760151.

**2. Antigen-presenting cells and alloimmuniy:** I have made two major contributions to understanding of how APCs regulate alloimmunity after HSCT, including: **1)** discovering the role of host APCs in regulating allogeneic T cell responses and GVHD; and **2)** identifying APC-derived signals crucial for activating Notch signaling in allogeneic T cells to mediate GVHD. We discovered previously uncharacterized inflammatory DLL4$^{+}$ DCs. These DLL4$^{+}$ DCs have greater ability than conventional DCs to induce Th1 and Th17 cell responses during GVHD. We also discovered human DLL4$^{+}$ DCs and their critical role in T cells.

e. Yuanyuan Tian, Lijun Meng, Ying Wang, Bohan Li, Hongshuang Yu, Yan Zhou, Tien Bui, Alicia Li, Yongping Zhang, Jian Wang, Shin Mineishi, Hong Zheng, Stefania Gallucci, Yanyun Zhang, Shaoyan Hu and **Yi Zhang**(Correspondence author). GVHD Depletes Plasmacytoid Dendritic Cell Progenitors to Impair Tolerance Induction. JCI, 2021, 131(1):e136774, PMID: 33090973.
f. Mochizuki K, Meng L, Mochizuki I, Tong Q, He S, Liu Y, Purushe J, Sun H, Fung H, Zaidi MR, Reshef R, Blazar BR, Yagita H, Mineishi S, and **Zhang Y** (Correspondence author). Programming of Donor T Cells Using Allogeneic Delta-like ligand 4-positive Dendritic Cells to Reduce GVHD but Retain GVL activity. Blood (DOI 10.1182/blood-2015-05-644476), Blood 2016, 127:3270-328.
g. Meng L, Bai ZJ, He S, Mochizuki K, Liu YN, Purushe J, Sun HX, Wang J, Yagita H, Mineishi S, Fung H, Yanik GA, Caricchio R, Fan X, Crisalli LM, Reshef R, Zhang YY, and **Zhang Y**. The Notch ligand DLL4 derived from human dendritic cells is critical for promoting T helper (Th)1 and Th17 cell differentiation. J Immunol. 2016 Feb 1;196(3):1070-80. PMID: 26712946; PMCID: PMC4930627
h. Mochizuki K, Xie F, He S, Tong Q, Liu Y, Guo YJ, Kato K, Yagita H, Mineishi S, and **Zhang Y** (Correspondence author). Delta-like Ligand 4 Identifies a Previously Uncharacterized Population of Inflammatory Dendritic Cells That Plays Important Roles in Eliciting Allogeneic T-cell Responses in Mice. *Journal of Immunology* 2013. 190(7):3772-82. PMID:23440416; PMCID:PMC3608722

**3. Novel and clinically relevant approaches to control GVHD but retain anti-leukemia effects:** We have recently established a culture system to produce large number of DLL4$^{+}$DCs and DLL4$^{-}$DCs from cultured BM cells. Using these DLL4$^{+}$DCs, we developed a clinically relevant strategy to program donor T cells that preserved potent anti-leukemia activity without causing severe GVHD in preclinical models. Our work has been instrumental in defining the critical role of DCs and Notch ligands in the regulation of alloimmunity. In addition, we have recently established a new approach of destabilizing T cell Ezh2 protein using the Hsp90 specific inhibitor UY922. *In vivo* administration of AUY922 selectively induced apoptosis of activated T cells and decreased the production of effector cells, similar to genetic deletion of Ezh2. Importantly, pharmacological inhibition of Hsp90 preserved anti-leukemia activity of donor T cells, leading to improved overall survival of recipient mice after allogeneic HSCT. Since the Hsp90 inhibitor is in clinical trials for cancer treatment, we expect that these Hsp90 inhibitors may find new applications for the treatment of T-cell inflammatory disorders such as GVHD.

a. Xiaoliang Yu, Haikuo Ma, Bohan Li , Yuting Ji , Yayun Du , Siying Liu , Zhanhai Li , Yongjin Hao , Sheng Tian, Cong Zhao, Qian Du, Zhongqin Jin, Xueming Zhu, Yuanyuan Tian, Xin Chen , Xue Sun , Chengkui Yang, Fang Zhu, Jie Ju, Yunjing Zheng, Wei Zhang, Jingrui Wang, Tao Yang , Xinhui Wang, Jingjing Li, Xiangping Xu, Shujing Du, Haohao Lu, Feng Ma, Haibing Zhang, **Yi Zhang** (Co-correspondence), Xiaohu Zhang, Shaoyan Hu, Sudan He. A Novel RIPK1 Inhibitor Reduces GVHD in Mice via a Non-immunosuppressive Mechanism that Restores Intestinal Homeostasis. Blood 2022, doi: 10.1182/blood.2022017262.
b. Yuanyuan Tian, Lijun Meng, Ying Wang, Bohan Li, Hongshuang Yu, Yan Zhou, Tien Bui, Alicia Li, Yongping Zhang, Jian Wang, Shin Mineishi, Hong Zheng, Stefania Gallucci, Yanyun Zhang, Shaoyan Hu, **Yi Zhang** (Correspondence author). GVHD depletes plasmacytoid dendritic cell progenitors to impair tolerance induction, JCI, 2021, 131(1):e136774, PMID: 33090973.
c. Qingrong Huang, Shan He, Yuanyuan Tian, Yuting Gu, Pan Chen, Changhong Li, Jiefang Huang, Yongnian Liu, Min Jin, Shaoyan Hu, Qing Tong, Anqi Ma, Jian Jin, Elizabeth Hexner, Henry Fung, Ran Reshef, **Yi Zhang** (Co-correspondence author) and Yanyun Zhang. Hsp90 inhibition destabilizes Ezh2 protein in alloreactive T cells and reduces graft-versus-host disease in mice. Blood 2017: 18;129(20):2737-2748 (Cover story). PMID: 28246193.
d. Mochizuki K, Meng L, Mochizuki I, Tong Q, He S, Liu Y, Purushe J, Sun H, Fung H, Zaidi MR, Reshef R, Blazar BR, Yagita H, Mineishi S, and **Zhang Y(**Co-correspondence author). Programming of Donor T

Cells Using Allogeneic Delta-like ligand 4-positive Dendritic Cells to Reduce GVHD but Retain GVL activity. Blood 2016, 127:3270-328. PMID: 27143255.

**4. Epigenetic therapy to sensitize tumor to immunotherapy:** Significant progress has been made for cancer immunotherapy over the past two decades. However, clinical studies with adoptive T cell immunotherapy, such as anti-CD19 CAR T cells, have shown that cancer resistance to tumor-reactive T cells is a significant barrier to efficacy in the treatment of malignancies. Our recent studies have demonstrated that inhibiting epigenetic regulators in tumor cells, such as EZH2, CDK9 and DNA methyltransferases, can enhance the sensitivity of these tumor cells to T cell-mediated killing. Thus, understanding the epigenetic mechanisms by which tumor cells acquire the capacity to resist CAR-T cell killing may lead to novel strategies to improve the efficacy of T cell immunotherapy.

a. He-Zhou Guo, Zi-Hua Guo, Shan-He Yu, Li-Ting Niu, Wan-Ting Qiang, Meng-Meng Huang, Yuan-Yuan Tian, Juan Chen, Hui Yang, Xiang-Qin Weng, **Yi Zhang**, Wu Zhang, Shao-Yan Hu, Jun Shi and Jiang Zhu. Leukemic progenitor cells enable immunosuppression and post-chemotherapy 3 relapse via IL-36-inflammatory monocyte axis. Science Advances, 2021, 7(41), eabg 4167. PMID: 34623912
b. Kazuhiro Mochizuki, Shogo Kobayashi, Nobuhisa Takahashi, Kotaro Sugimoto, Hideki Sano, Yoshihiro Ohara, Shin Mineishi, **Yi Zhang**, and Atsushi Kikuta. Alloantigen-activated (AAA) $CD4^+$ T cells reinvigorate host endogenous T cell immunity to eliminate pre-established tumors in mice. Journal of Experimental and Clinical Cancer Research. 2021, 40(1), 1-18. PMID: 34625113
c. Jayati Mookerjee Basu, Robert Hooper, Scott Gross, Bryant Schultz, Christina Go, Elsie Samakai, Jonathan Ladner, Emmanuelle Nicolas, Yuanyuan Tian, Bo Zhou, M. Raza Zaidi, Warren Tourtellotte, Shan He, **Yi Zhang**, Dietmar Kappes, and Jonathan Soboloff. Suppression of Ca2+ Signals by EGR4 controls Th1 differentiation and anti-cancer immunity in vivo. EMBO Rep. 2020 May 6;21(5):e48904. PMID: 32212315**.**
d. Hanghang Zhang, Somnath Pandey, Meghan Travers, Hongxing Sun, George Morton, Jozef Madzo, Woonbok Chung, Jittasak Khowsathit, Oscar Perez-Leal, Carlos A. Barrero, Carmen Merali, Yasuyuki Okamoto, Takahiro Sato, Josh Pan, Judit Garriga, Natarajan V. Bhanu, Johayra Simithy, Bela Patel, Jian Huang, Noël J.-M. Raynal, Benjamin A. Garcia, Marlene A. Jacobson, Cigall Kadoch, Salim Merali, **Yi Zhang**, Wayne Childers, Magid Abou-Gharbia, John Karanicolas, Stephen B. Baylin, Cynthia A. Zahnow, Jaroslav Jelinek, Xavier Graña and Jean-Pierre J. Issa. Targeting CDK9 Reactivates Epigenetically Silenced Genes in Cancer. Cell 2018, 175(5):1244-1258. PMID: 3045464

**Complete list of publications**

**https://www.ncbi.nlm.nih.gov/myncbi/yi.zhang.7/bibliography/public/**