BIOGRAPHICAL SKETCH

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NAME: **Yi Zhang**

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

POSITION TITLE: **Professor (with tenure)**

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 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. **We have discovered the importance** of dendritic cells (DCs) in the regulation of alloreactive T cells at both priming and effector phase of GVHD. We found that inflammatory DCs expressing the Notch ligand delta-like ligand 4 (Dll4), which are previously uncharacterized DCs, have greater ability than conventional DC to promote Th1 and Th17 cell responses. Inhibition of DLL4 and Notch signaling leads to reduction of GVHD. **We also introduced 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. **Building on these studies**, we have developed a research program to investigate the epigenetic mechanisms that control the generation, maintenance and function of antigen-driven T cells. This includes the identification of the histone methyltransferase Ezh2 in regulating T cell responses and GVHD. Specifically, we identified that inhibition of T cell Ezh2, which catalyzes histone H3 lysine 27 trimethylation, reduces GVHD in mice undergoing allo-HSCT. Most recently, we discovered the crucial role of Ezh2 in regulating memory T cell formation and how intermediate signaling such as the AKT pathway modifies T cell Ezh2 function. My laboratory has made a continuous stream of novel fundamental contributions in GVHD and T cell immunity. **Currently**, we are developing novel and clinically relevant approaches to control GVHD but augment anti-leukemia immunity, including: 1) the establishment a cellular therapy strategy to program donor T cells that preserved potent anti-leukemia activity without causing severe GVHD in preclinical models. For instance, we have discovered that donor-type plasmacytoid DCs have potent immunosuppressive effects on reducing GVHD in mice; 2) development of a new approach of destabilizing T cell Ezh2 protein using pharmacological inhibitors to modulate alloimmunity; and 3) epigenetic therapy to sensitize tumor to CAR-T cell immunotherapy by targeting EZH2, DOT1L andCDK9. The goal of this approach is to discover epigenetic drugs https://scholar.google.com/citations?user=2v7xX3YAAAAJ&hl=enresistance to CAR-T cell therapy to improve the efficacy of immunotherapy for solid tumor.

A link to my complete list of publications can be found here:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44824700/?sort=date&direction=descending

Google scholar:
https://scholar.google.com/citations?user=2v7xX3YAAAAJ&hl=en

B. Positions and Honors

Positions and Employment

1983 – 1986 Residency, No.2 People's Hospital of Suzhou, P.R.China
1989 – 1995 Assistant Professor of Immunology, Suzhou Medical College, P.R.China
1996 – 1998 Associate Professor of Immunology, Suzhou Medical College, P.R.China
1998 – 2000 Postdoctoral Fellow, University of Pennsylvania, Philadelphia, PA, USA
2000 – 2003 Research Associate, University of Pennsylvania, Philadelphia, PA. USA
2003 – 2007 Research Assistant Professor, University of Pennsylvania, Philadelphia, PA. USA
2007 – 2014 Assistant Professor, University of Michigan, Ann Arbor, MI, USA
2014 – 2017 Associate Professor, Fels Institute, Department of Microbiology & Immunology, Temple University, Philadelphia, USA
2017 – present Professor (with tenure), Fels Institute, Department of Microbiology & Immunology, Temple University, Philadelphia, USA

Other Experience and Professional Memberships

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 2024.

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- 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. 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.

a. 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**. GVHD Depletes Plasmacytoid Dendritic Cell Progenitors to Impair Tolerance Induction. JCI, 2021, 131(1):e136774, PMID: 33090973.
b. 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.

c. 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

d. 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

2. 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.

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. Moy RH, Huffman AP, Richman LP, Crisalli L, Wang XK, Hoxie JM, Mick R, Emerson SG, **Zhang Y**, Vonderheide RH, Porter DL and Reshef. Clinical and immunologic impact of CCR5 blockade in graft-versus-host disease prophylaxis. Blood 2017 :blood-2016-08-735076;

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, PMCID: PMC4075972.

e. He S, Xie F, Liu Y, Tong Q, Mochizuki K, Lapinski PE, Mani RS, Reddy P, Mochizuki I, Chinnaiyan AM, Mineishi S, King PD, and **Zhang Y (Correspondence author)**. The histone methyltransferase Ezh2 is a crucial epigenetic regulator of allogeneic T cell responses mediating graft-versus-host disease. *Blood* 2013 Dec 12;122(25):4119-28. PMID:24141370

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. The relevant technology has been filed for patent protection (*DLL4-Expressing Cells and Vaccine, **PCT/US17/29601***). 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. 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 (Co-correspondence author).** GVHD depletes plasmacytoid dendritic cell progenitors to impair tolerance induction, JCI, 2021, 131(1):e136774, PMID: 33090973. doi: 10.1172/JCI136774.
b. 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; PMCID: PMC5437825
c. 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**. 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; PMCID:PMC4920025
d. He S, Wang J, Kato K, Varambally S, Xie F, Kuick R, Mineishi S, Liu Y, Nieves E, Mani R, Chinnaiyan AM, Marquez VE and **Zhang Y (Correspondence author)**, *Inhibition of histone methylation arrests ongoing graft-versus-host diseases in mice by selectively inducing apoptosis of alloreactive effector T cells. Blood*, 2012, 119:1274. PMID:22117046 PMCID:PMC3338164

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 Guo1, 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 (in pressing).
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 (in pressing).
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**, PMCID: PMC7202224.
d. Hongxing Sun, Shan He, Lijun Meng, Ying Wang, Hanghang Zhang, Yongnian Liu, Jian Wang, Min Tao, Stefan K. Barta, Essel Dulaimi, Henry Fung, Jean-Pierre J. Issa, Lei Zhen Zheng, **Yi Zhang**. Engineering of Chimeric Antigen Receptor T Cells with integrin αEβ7 Results in Augmented Therapeutic Efficacy against E-cadherin positive tumor. bioRxiv preprint doi: https://doi.org/10.1101/727446.
e. Zhao E, Mai T, Kryczek I, Li W, Wu K, Zhao L, Wei S, Crespo J, Wan S, Vatan L, Szeliga W, Shao I, Wang Y, Liu Y, Varambally S,Chinnaiyan AM, Welling TH, Marquez V, Kotarski J, Wang H, Wang Z, **Zhang Y,** Liu R, Wang G, Zou W. Cancer mediates effector T cell dysfunction by targeting microRNAs and EZH2 via glycolysis restriction. Nat Immunol. 2015, doi: 10.1038/ni.3313.
f. 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.

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

ACTIVE

5R01AI143256-02, NIH/NIAID (PI: Zhang) 08/12/2019 - 12/31/2023

Synthetic rescue of antigen-driven T cells and alloimmunity

Goals: Whereas STIM1-KO T cells fail to be activated, activated Ezh2-null T cells experience massive cell death. We find that deletion of these 2 genes restores T cell activation, with implications to the development of GVL and GVHD.

1R01HL154757-01A1, NIH/NHLBI (PI: Zhang) 04/2021 – 03/2025

Title: Dot1l, Plasmacytoid Dendritic Cells and Alloimmunity

Goals: To determine the Dot1l-mediate epigenetic mechanisms that regulate reconstitution of donor plasmacytoid dendritic cells and develop of novel pDC-based cellular therapy to inhibit GVHD.

1 P50 CA254897-01, The SPORE (NIH), Project-1: Epigenetic Therapy

Co-leader (Zhang, 33% of the total projet-1 budget), 06/2021 – 05/2026

Title: Cyclin Dependent Kinases as Epigenetic Therapy Targets

Goals: A) study immune-sensitization by inhibition of CDK9; B) discover whether other additional and clinically targeted CDKs are also epigenetic regulators; and C) conduct pre-clinical and clinical studies of combined epigenetic therapy and immunotherapy using CDK inhibitors, DNMT inhibitors and immune checkpoint inhibitors.

R01, NIH/NIAMS, Zhang (Co-investigator) 04/01/2020 - 03/31/2025

Goals: To determine the hypothesis that TCR engagement stimulates EGR-mediated STIM1 upregulation in naïve T cells that initiate Ca^{2+} clearance inhibition, critical for the maintenance of NFAT/NF-κB activation and subsequent T cell activation.