BIOGRAPHICAL SKETCH

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NAME: Zhiheng He

eRA COMMONS USER NAME (credential, e.g., agency login): ZHIHENGHE1

POSITION TITLE: Assistant Professor, Department of Molecular Microbiology & Immunology

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
Huazhong University of Science and Technology, Wuhan, P.R.China	B.S.	07/2004	Public Health
Chinese Academy of Sciences, Wuhan, P.R.China	M.S.	07/2007	Molecular Biology
Chinese Academy of Sciences, Shanghai, P.R.China	Ph.D.	07/2011	Microbiology
University of Southern California, CA, USA	Postdoctoral	06/2013	Immunology
Beckman Research Institute of City of Hope, CA, USA	Postdoctoral	06/2018	Immunology
Beckman Research Institute of City of Hope, CA, USA	Staff Scientist	08/2019	Immunology

A. Personal Statement

Research in my laboratory uses a combination of molecular approaches and animal models in the analysis of IL-17-producing T helper cells (Th17 cells) in autoimmune diseases, and other inflammatory disorders including immunotherapy-induced autoimmune colitis. Th17 cells are under extensive study as a promising target for the treatment of autoimmune diseases. However, Th17 cells play major roles in both autoimmunity (pathogenic Th17) and defensive immunity against pathogen infections (beneficial Th17). The inhibitors that non-specifically block Th17 function often lead to dramatically increased susceptibility to infections and tumors. Our research is focused on the transcriptional and metabolic regulation of Th17 populations, specifically asking how beneficial and pathogenic Th17 populations are differentially regulated. My study has led the efforts to precisely arrest Th17-mediated immunity without disturbing normal development of other lineages of T cells. My lab continues to work in the area of Th17 immunity to identify molecular mechanisms underlying autoimmunity, for developing treatment specially targeting pathogenic Th17 without disturbing protective immune responses.

a. Bouch RJ, Zhang J, Miller BC, Robbins CJ, Mosher TH, Li W, Krupenko SA, Nagpal R, Zhao J, Bloomfeld RS, Lu Y, Nikiforov MA, Song Q, **He Z**. Distinct inflammatory Th17 subsets emerge in autoimmunity and infection. ***J. Exp. Med***. 2023 Jun 27; 220(10). Doi: 10.1084/jem.20221911.
b. Zhong X, Wu H, Zhang W, Gwack Y, Shang W, Lee KO, Isakov N, **He Z***, Sun Z*. Decoupling the role of RORγt in the differentiation and effector function of TH17 cells. ***Sci Adv*.** 2022 Oct 21;8(42): eadc9221. doi: 10.1126/sciadv.adc9221. Epub 2022 Oct 21. PMID: 36269826; PMCID: PMC9586477. *Corresponding author.
c. J Zhang, R Bouch, M Blekhman, **Z He**. "USP19 suppresses Th17-driven pathogenesis in autoimmunity", ***J Immunol***. 2021. Jun 16:ji2100205. doi: 10.4049/jimmunol.2100205. Epub ahead of print. PMID: 34135062.
d. **Z He**, J Ma, F Wang, R Wang, Z Huang, J Zhang, S Sen, E Rothenberg and Z Sun. "Two amino acid mutation disrupts RORγt function in Th17 differentiation but not thymocyte development", ***Nat. Immunol***, 2017 Oct;18(10):1128-1138. doi: 10.1038/ni.3832. Epub 2017 Aug 28.

Current Research Support

1. NIH-NIAID, R21 1R21AI166159-01A1– PI 07/01/2022-06/30/2024
   Distinguishing inflammatory Th17 subsets through using an autoimmune Th17-selective inhibitor
2. NIH-NIAID, R21 1R21AI171359-01– PI 07/01/2022-06/30/2024
   Determining the mechanisms by which a circular RNA regulates the function of Th17 cells
3. NIH-NIAID, R01 1R01AI173277-01– PI 10/01/2022-09/30/2027
   Dissecting functions of IL-23-dependent inflammatory Th17 cells

Completed Research Support

1. NIH-NCI, P30CA012197– PI 07/01/2020-06/30/2021
   Identification of a biomarker for immunotherapy-induced colitis
2. Wake Forest Clinical and Translational Science Institute (CTSI) – PI 10/07/2021-01/07/2022
   Determining the therapeutic effects of a pathogenic Th17 selective inhibitor for autoimmune diseases
3. Wake Forest Clinical and Translational Science Institute (CTSI) – PI 07/02/2021-12/31/2022
   Understanding pathogenic potential of autoimmune Th17 cells generated in vivo
4. Errett Fisher Foundation – PI 01/01/2022-12/31/2022
   Selectively probing autoimmune Th17 cells in vivo
5. Wake Forest Clinical and Translational Science Institute (CTSI) – PI 07/01/2022-12/30/2022
   Determining the potential of a FDA-approved pathogenic-immune cell selective inhibitor to treat human IBD

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2023- Assistant Professor (Tenure-Track), Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, CA, USA
2019-2023 Assistant Professor (Tenure-Track), Department of Microbiology and Immunology, Wake Forest School of Medicine, NC, USA
2018-2019 Staff Scientist, Beckman Research Institute of City of Hope, CA, USA
2013-2018 Postdoctoral Associate, Beckman Research Institute of City of Hope, CA, USA
2011-2013 Postdoctoral Fellow, University of Southern California, CA, USA

Scientific Appointments

2017- Member, The American Association of Immunologists

Academic Honors

2019 Travel Award, The American Association of Immunologists
2018 Travel Award, The American Association of Immunologists
2010 Pfizer special award, Pfizer-SIBS

C. Contributions to Science

1. We showed for the first time that inflammatory Th17 cells engaged in autoimmunity is experimentally and therapeutically distinguishable from inflammatory Th17 cells responsible for the clearance of pathogen infection. This is significant because present inflammatory Th17 inhibitors relieve autoimmunity at the cost of susceptibility to pathogen infections. Dissecting defensive and pro-autoimmune functions of inflammatory Th17 cells is critically needed. These exciting data is the first to provide a strong proof-of-concept that pro-autoimmune and anti-infection Th17 subsets can be selectively targeted based on their altered metabolic programming and reveal a pro-autoimmune Th17-selective inhibitor as a potential therapeutic for autoimmune diseases.

   a. Bouch RJ, Zhang J, Miller BC, Robbins CJ, Mosher TH, Li W, Krupenko SA, Nagpal R, Zhao J, Bloomfeld RS, Lu Y, Nikiforov MA, Song Q, **He Z**. Distinct inflammatory Th17 subsets emerge in autoimmunity and infection. ***J. Exp. Med***. 2023 Jun 27; 220(10). Doi: 10.1084/jem.20221911.

b. J Zhang, R Bouch, M Blekhman, **Z He**. "USP19 suppresses Th17-driven pathogenesis in autoimmunity", ***J Immunol***. 2021. Jun 16:ji2100205. doi: 10.4049/jimmunol.2100205. Epub ahead of print. PMID: 34135062.

2. With the initial goal of developing treatment precisely targeting autoimmune disorders without disturbing normal T cell immunity, I dissected pleiotropic functions of transcription factor RORγt, which play major roles in both Th17-mediated autoimmunity and T cell maturation in thymus. This study demonstrates the possibility and importance of genetic dissection of protein functions in order to manipulate transcription factors to specifically control gene expression and cell differentiation, open the way to generation of drugs precisely targeting Th17-mediated pathology.

   a. Zhong X, Wu H, Zhang W, Gwack Y, Shang W, Lee KO, Isakov N, **He Z***, Sun Z*. Decoupling the role of RORγt in the differentiation and effector function of TH17 cells. ***Sci Adv*.** 2022 Oct 21;8(42): eadc9221. doi: 10.1126/sciadv.adc9221. Epub 2022 Oct 21. PMID: 36269826; PMCID: PMC9586477. *Corresponding author.
   b. **Z He**, J Zhang, Z Huang, Q Du, N Li, Q Zhang, Y Chen, Z Sun. "Sumoylation of RORγt regulates Th17 differentiation and thymocyte development", ***Nat Commun***. 2018 Nov 19;9(1):4870. doi: 10.1038/s41467-018-07203-z.
   c. **Z He**, J Ma, F Wang, R Wang, Z Huang, J Zhang, S Sen, E Rothenberg and Z Sun. "Two amino acid mutation disrupts RORγt function in Th17 differentiation but not thymocyte development", ***Nat. Immunol***, 2017 Oct;18(10):1128-1138. doi: 10.1038/ni.3832. Epub 2017 Aug 28.
   d. **Z He**, J Zhang, Q Du, J Xu, Y Gwack, Z Sun. "SRC3 is a co-factor for RORγt in Th17 differentiation but not thymocyte development", ***J Immunol***. 2018 Dec 19; pii: ji1801187. doi: 10.4049/jimmunol.1801187.

3. Attempt to better understand mechanisms regulating Th17 cells differentiation, my research began to characterize on the roles of post-translational modification and the dynamic composition of transcription factor complexes. My study found that modifications on master transcription factor RORγt integrate multiple inputs to recruit distinct molecules correspondingly, and thus precisely regulate cytokine expression and Th17 functions.

   a. **Z He**, F Wang, J Zhang, S Sen, Q Pang, S Luo, Y Gwack and Z Sun. "Regulation of Th17 differentiation by IKKα-dependent and -independent phosphorylation of RORγt", ***J Immunol***. 2017 Aug 1;199(3):955-964. doi: 10.4049/jimmunol.1700457.
   b. **Z He,** F Wang, J Ma, S Sen, J Zhang, Y Gwack, Y Zhou, Z Sun. "Ubiquitination of RORγt at Lysine 446 limits Th17 differentiation by controlling coactivator recruitment", ***J Immunol***. 2016 Aug 15;197(4):1148-58. doi: 10.4049/jimmunol.1600548.
   c. S Sen, F Wang, J Zhang, **Z He**, J Ma, Y Gwack, J Xu, Z Sun. "SRC1 promotes Th17 differentiation by overriding Foxp3 suppression to stimulate RORγt activity in a PKC-θ-dependent manner", ***Proc Natl Acad Sci U S A***. 2018 Jan 16;115(3):E458-E467. doi: 10.1073/pnas.1717789115.

4. I demonstrated that innate immune responses are critical for the establishment of herpesvirus persistent infection. During my experiences as a graduate student and early stage of postdoctoral fellow, I demonstrated the mechanisms how herpesvirus establishes latent infection in human cells. Virus hijacks innate immune effectors--IKKβ and IKKε--activated by viral infection to sequentially phosphorylate and repress viral transcription factor RTA to quench lytic gene expression. RTA also recruits host co-repressor TLE2 to maintain stable latent infection. These findings reveal novel targets for generating drugs eradiating herpesvirus from host cells.

   a. **Z He**, J Zhao, J Zhang, JU Jung, P Feng. "NF-κB activation coordinated by IKKβ and IKKε enables latent infection of Kaposi's sarcoma-associated herpesvirus", ***J Virol***. 2014 Jan;88(1):444-55. doi: 10.1128/JVI.01716-13.
   b. **Z He**, Y Liu, D Liang, Z Wang, ES Robertson, K Lan. "Cellular corepressor TLE2 inhibits replication-and-transcription-activator-mediated transactivation and lytic reactivation of Kaposi's sarcoma-associated herpesvirus", ***J Virol*.** 2010 Feb;84(4):2047-62. doi: 10.1128/JVI.01984-09

c. **Z He** and K Lan. Latency associated nuclear antigen (LANA) of Kaposi's sarcoma associated herpesvirus: Structure and function. *Molecular Biology of Tumor Virus Gene Products*. ISBN: 978-81-308-0324-1

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