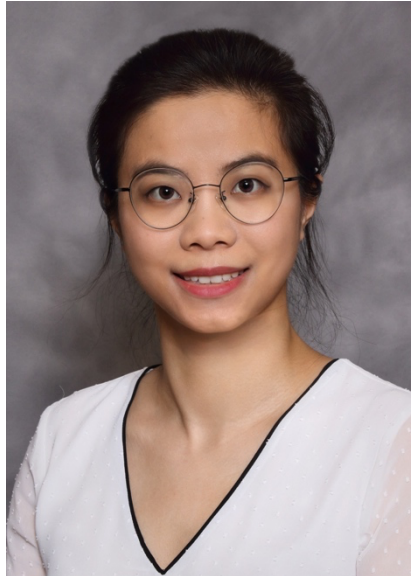


MCW  Graduate School
Dissertation Defense Announcement



Yao Chen

“BATF regulates progenitor to cytolytic effector CD8⁺ T cell transition during chronic viral infection”

Candidate for Doctor of Philosophy in Microbiology and Immunology
Graduate School of Biomedical Sciences
Medical College of Wisconsin

Friday, July 2nd, 2021, 9:00 AM (CST)
Live Public Viewing (Zoom):

<https://mcw-edu.zoom.us/j/95814353262?pwd=MGI3cDJkRSt2S21wYnYzTUVxRzZlNQ09>

Committee in Charge:

Dr. Weiguo Cui (Advisor)
Dr. Bryon Johnson
Dr. Debra Newman
Dr. Sridhar Rao
Dr. Subramaniam Malarkannan

Graduate Studies

- Biochemistry of the Cell
- Intro to Biomedical Research
- Techniques in Molecular & Cell
- Molecular and Cellular Biology
- Mechanism of Cellular Signaling
- Classical and Molecular Genetics
- Ethics & Integrity in Science
- Cellular and Microbiology Immunology
- Tumor Immunology
- Immunological Tolerance
- Immunology Journal Club
- Career Development Biomed Science
- Reading and Research
- Microbiology and Immunology Seminar
- Doctoral Dissertation

Abstract:

During chronic viral infection, CD8⁺ T cells develop into three major phenotypically and functionally distinct subsets: Ly108⁺ TCF1⁺ progenitor, Ly108⁻ CX3CR1⁻ terminally exhausted, and recently identified CX₃CR1⁺ cytotoxic effector cells. Nevertheless, how CX₃CR1⁺ effector CD8⁺ T cell differentiation is transcriptionally and epigenetically regulated remains elusive. Here, our single-cell transcriptomics and epigenetic assays revealed that CD8⁺ T cell subsets were governed by distinct gene regulatory networks (GRNs) and epigenetic landscapes. Computational analyses demonstrated a striking similarity between CX₃CR1⁺ cytotoxic cells responding to chronic infection and short-lived effector cells (SLECs) from acute infection. Consistently, genetic deletion of T-bet significantly diminished the formation and function of the CX₃CR1⁺ subset. Importantly, we identify a previous unappreciated role of BATF in maintaining a permissive chromatin structure that allows the differentiation transition from TCF1⁺ progenitor to CX₃CR1⁺ effector cells. Intriguingly, haploinsufficiency of BATF in CD8⁺ T cells abolished CX₃CR1⁺ effector subset formation. Lastly, we found that BATF directly bound to key genetic regions such as *Tbx21* and *Klf2*, modulating their enhancer accessibility to facilitate progenitor to CX₃CR1⁺ effector CD8⁺ T cell transition. These mechanistic insights can potentially be harnessed to overcome T cell exhaustion in treating chronic infections and cancer.

Curriculum Vitae

Yao Chen

Versiti Blood Center of Wisconsin 8727 Watertown Plank Rd. Milwaukee, WI 53226
Phone: 414-458-3371 E-mail: yachen@mcw.edu

Education

- Ph.D. 2016-present Microbiology & Immunology, Medical College of Wisconsin, WI. USA
Interdisciplinary Doctoral Program in Biomedical Sciences (IDP).
Laboratory of Weiguo Cui, MD, PhD.
- M.S. 2013-2016 Kinesiology, Beijing Sport University, China.
Department of Exercise Physiology.
- B.S. 2009-2013 Kinesiology, Beijing Sport University, China.

Research Experience

- 2016-present **Research assistant in Dr. Weiguo Cui's Lab**, Versiti Blood Center of Wisconsin. USA.
- Studied the transcriptional and epigenetic regulation in CD8 T cell differentiation following acute and chronic viral infection.
 - Combining single-cell RNA sequencing and single-cell TCR sequencing technology to trace the clonal expansion, differentiation trajectory, and lineage commitment of virus-specific CD8 T cells during memory formation and chronic viral infection.
 - Single-cell transcriptional profiling of immune cells in mouse non-small-cell lung cancer and melanoma models.
- 2014-2016 **Research assistant in Dr. Qing-song Liu's Lab**, Department of Pharmacology & Toxicology, Medical College of Wisconsin. USA.
- Studied the neural circuit mechanisms of drug addiction and depressive behavior.
 - Studied the endocannabinoid signaling contributes to addictive-like behavior.
- 2009-2014 **Research assistant in Dr. Li Zhao's Lab**, Department of Exercise Physiology, Beijing Sport University. China.

- Studied how aerobic exercise regulates synaptic transmission in the paraventricular nucleus of spontaneously hypertensive rats.
- Studied the beneficial effects of aerobic exercise in a mouse model of Alzheimer's disease.

Honors and Awards:

2020	\$2500 travel award from MCW Center for Immunology
2020	\$600 travel award from MCW Graduate Student Travel Award Fund
2014	China National Scholarship for graduate students.
2013	“Outstanding Poster Award” in 2013 Chinese Society of Exercise Physiology Professional Committee Annual Conference— “Sport and Health” Symposium, China.
2013	The Third Prize in the Seventh “Challenge Cup” Academic Science and Technology Contest for College Students, Beijing, China.
2012	Award from National Undergraduate Training Programs for Innovation and Entrepreneurship, China.

Skills

- Familiar with 10x Genomics single cell sequencing technology and Illumina NextSeq and MiSeq sequencing systems.
- Familiar with Single cell RNA sequencing, bulk RNA sequencing, ATAC-sequencing, CUT&Tag and CUT&RUN ChIP-sequencing, Single cell TCR sequencing, 16S Microbial Sequencing.
- Familiar with sequencing data analysis and coding in R and Linux.
- Familiar with animal works, such as tissue collecting, intraperitoneal injection, intravenous injection, making mixed bone marrow chimeras, implanting electrodes into a live mouse brain for EEG recording.
- Flow cytometry, cell sorting, cell culture, immunocytochemistry, qPCR, molecular cloning, fluorescence microscopy, western blotting, molecular cloning, CRISPR/Cas9-based genome editing

- Setup protocol in Eppendorf epMotion.
- Familiar with Incucyte Live-Cell Analysis Systems
- Electrophysiology. Familiar with Axon Patch-Clamp technique and Cerebus multichannel data acquisition system.

Professional activities

1. 2020 Keystone Symposia Conference: T Cell Memory, **oral presentation**.
2. **Oral presentation** at 11th Annual Immunology Scientific Retreat of Center for Immunology, Medical College of Wisconsin, 2020.
3. 2019 Medical College of Wisconsin Graduate Student Association symposium poster presentation.
4. Finished the Linux Basics for NGS Data Analysis and mRNAseq Workshop provided by The University of Wisconsin Biotechnology Center, UW-Madison.
5. Reviewed two manuscripts for the journal of Metabolic Brain Disease.

Community activities

1. 2017- present. President of the Chinese Student & Scholars Association at Medical College of Wisconsin.

Publications :

First author papers:

1. **Chen Y**, Zander, R, Wu X, Schauder DM, Kasmani MY, Shen J, Zheng S, Burns R, Taparowsky EJ, Cui W. BATF regulates progenitor to cytolytic effector CD8+ T cell transition during chronic viral infection. **Nature Immunology. (2021) (accepted)**
2. Pan J*, **Chen Y***, Zhang Q*, Khatun A, Xin G, Wang L, Palen K, Yang C, Johnson BD, Sei S, Shoemaker HR, Lubet RA, Wang Y, Cui W[#] and You M[#]. Inhibition of lung tumorigenesis by a novel small molecule CA170 targeting the immune checkpoint protein VISTA. **Communications Biology. (2021) (accepted)**
3. **Chen Y**, Zander R, Khatun A, Schauder DM and Cui W. Transcriptional and Epigenetic Regulation of Effector and Memory CD8 T Cell Differentiation. **Review, Frontiers in Immunology. (2018)**
4. **Chen Y**, Liu X, Vickstrom CR, Liu MJ, Zhao L, Viader A, Cravatt BF, Liu QS. Neuronal and Astrocytic Monoacylglycerol Lipase Limit the Spread of Endocannabinoid Signaling in the Cerebellum. **eNeuro. (2016)**

5. **Chen Y**, Gu BY, Zhao L. Effect of Creatine Supplementation on BKCa Current Variation and Intracellular Free Calcium Concentration Induced by Glucose Deprivation. **Journal of Beijing Sport University, Journal in Chinese. (2017)**

Co-authoring papers:

1. Xin G, **Chen Y**, Topchyan P, Kasmani MY, Burns R, Volberding PJ, Wu X, Cohn A, Chen Y, Lin CW, Ho PC, Silverstein R, Cui W. Targeting PIM1-Mediated Metabolism in Myeloid Suppressor Cells to Treat Cancer. **Cancer Immunology Research. (2021)**
2. Schauder DM, Shen J, **Chen Y**, Kasmani MY, Burns R, Cui W. E2A-regulated epigenetic landscape is required for memory CD8 T cell differentiation. **PNAS. (2021)**
3. Topchyan P, Xin G, **Chen Y**, Zheng S, Burns R, Shen J, Kasmani MY, Kudek M, Yang N, Cui W. Harnessing the IL-21-BATF Pathway in the CD8+ T Cell Anti-Tumor Response. **Cancers. (2021)**
4. Son YM, Cheon IS, Wu Y, Li C, Wang Z, **Chen Y**, Takahashi Y, Dent AL, Kaplan MH, Fu Y, Taylor JJ, Cui W, Sun J. Tissue-resident CD4+ T helper cells assist the development of protective respiratory mucosal B and CD8+ T cell memory responses. **Science Immunology. (2020)**
5. Xin G, Khatun A, Topchyan P, Zander R, Volberding PJ, **Chen Y**, Shen J, Fu C, Jiang A, See WA and Cui W. Pathogen-boosted adoptive cell transfer therapy induces endogenous antitumor immunity through antigen spreading. **Cancer Immunology Research. (2019)**
6. Xin G*, Zander R*, Schauder DM*, **Chen Y**, Weinstein JS, Drobyski W, Tarakanova V, Craft J, Cui W. Single-cell RNA sequencing unveils an IL-10-producing helper subset that sustains humoral immunity during persistent infection. **Nature Communications. (2018)**
7. Liu X, **Chen Y**, Vickstrom CR, Li Y, Viader A, Cravatt BF, Liu QS. Coordinated regulation of endocannabinoid-mediated retrograde synaptic suppression in the cerebellum by neuronal and astrocytic monoacylglycerol lipase. **Sci Rep. (2016)**
8. Liu X, **Chen Y**, Tong J, Reynolds AM, Proudfoot SC, Qi J, Penzes P, Lu Y, Liu QS. Epac Signaling Is Required for Cocaine-Induced Change in AMPA Receptor Subunit Composition in the Ventral Tegmental Area. **J Neurosci. (2016)**
9. Hurley MM, Maunze B, Block ME, Frenkel MM, Reilly MJ, Kim E, **Chen Y**, Li Y, Baker DA, Liu QS, Choi S. Pituitary Adenylate-Cyclase Activating Polypeptide Regulates Hunger- and Palatability-Induced Binge Eating. **Neuropsychopharmacology. Front Neurosci. (2016)**

10. Ogasawara D, Deng H, Viader A, Baggelaar MP, Breman A, Dulk H, Nieuwendijk AM.C.H, Soethoudt M, Wel T, Zhou J, Overkleeft HS, Sanchez-Alavez M, Mori S, Nguyen W, Bruno C, Liu XJ, **Chen Y**, Liu QS, Cravatt BF, Stelt M. Rapid and profound rewiring of brain lipid signaling networks by acute diacylglycerol lipase inhibition. **PNAS. (2015)**
11. Forest J, Miao ZJ, Zhao L, **Chen Y**, Li W. Auricular Tensing for Indication of Intent on a Visual Selection Vector. **Presence Teleoperators & Virtual Environments. (2015)**
12. Forest J, Miao ZJ, Zhao L, **Chen Y**, Lv YY. Optical fiber light source directs neurite growth. **Biomed Opt Express. (2013)**
13. Li Z, **Chen Y**, Gong LJ, Lv YY. A Modified Method for Primary Culture of Newborn Rat Cortical Neurons and Its Basic Electrophysiological Property. **Journal of Beijing Sport University, Journal in Chinese. (2012)**