BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bingfei Yu

eRA COMMONS USER NAME (credential, e.g., agency login): BIYOO2

POSITION TITLE: Incoming Assistant 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
Xiamen University, Fujian, China	B.S.	07/2009	Biology
Xiamen University, Fujian, China	M.S.	07/2012	Molecular Biology and Biochemistry
University of California, San Diego, CA, USA	Ph.D.	07/2018	Immunology
Stanford University, CA, USA	Postdoc	02/2023	RNA, epigenetics, tech development

A. Personal Statement

I am an immunologist with extensive research experience in single-cell genomics, synthetic biology, and adaptive immunity. I'm interested in developing new approaches to decipher molecular machinery in adaptive immune cells to enhance the immunotherapy of cancer and other diseases. I completed my Ph.D. training in immunology at University of California San Diego where I studied the differentiation and function of CD8+ T cells in killing pathogen-infected cells and tumors. As a graduate student in Dr. Goldrath's lab at UCSD, I established epigenetic profiling platform for primary pathogen-specific T cells and discovered T cell subset-specific transcriptional factor (TF) YY1 and NR3C1 that governs effector and memory precursor transcriptional program respectively. I further co-developed a computational platform with Dr. Wang's lab, applying Google website ranking algorithm to prioritize key TFs in transcriptional network. This led to discovery of TF Runx3 in promoting T cell infiltration into tumors. As a postdoc in Dr. Chang's lab at Stanford, I characterized protein co-factors that bind to female-specific lncRNA XIST in B cells and developed an allelic CRISPR screen to identify key XIST cofactors for silencing of X-linked immune gene. I further developed a computational strategy to track the XIST dysregulation using single-cell RNA-seq data and discovered XIST dysregulation in atypical memory B cells in female-biased autoimmune patients. After charting downstream molecular blueprint in T and B cells, I have recently developed a novel synthetic viral platform to understand how such specific interaction guides the immune system to eradicate tumors. Such platform will serve as a strong foundation for my future research program: how intercellular communication in immune system rewire the downstream epigenetic circuits to orchestrate effective responses against tumors.

Key publications:

Yu B*, Shi Q*, Belk JA, Yost KE, Parker KP, Huang H, Li R, Liu BB, Lingwood D, Greenleaf WJ. Davis MM, Satpathy A, Chang HY. Engineered cell entry links receptor biology with single-cell genomics. ***Cell*** 2022 185(26):4904-4920 * equally contributed

Yu B, Qi Y, Li R, Shi Q, Satpathy A, Chang HY. B cell-specific XIST complex enforces X-inactivation and restrains atypical B cells. ***Cell*** 2021 184(7):1790-1803

Yu B*, Zhang K*, Milner JJ, Toma C, Chen R, Scott-Browne JP, Pereira RM, Crotty S, Chang JT, Pipkin ME, Wang W, Goldrath AW. Epigenetic landscapes reveal transcription factors that regulate CD8+ T cell differentiation. ***Nature Immunology***. 2017 18(5):573-582 * equally contributed

Milner JJ, Toma C*, **Yu B***, Zhang K, Omilusik KD, Phan A, Wang DP, Getzler A, Crotty S, Wang W, Pipkin ME, Goldrath AW. Runx3 programs CD8+ T cell residency in non-lymphoid tissues and tumors. ***Nature***. 2017 552(7684) * equally contributed

Links to full list of public work (including 13 co-authored papers at *Nature Immunology*, *Immunity* and *Cell* etc):
https://pubmed.ncbi.nlm.nih.gov/?term=Bingfei%20Yu

B. Positions and Honors

Positions and Employment

10/2018-02/2023	Postdoctoral Researcher, Stanford University
03/2023	Assistant Professor, USC Keck School of Medicine, Department of Molecular Microbiology & Immunology

Other Experience and Professional Memberships

2013-2015	Member, American Association of Immunologists
2013-2018	Member, The immunological Genome Project
2018-present	Associate Editor, Journal of Translational Medicine IF:4.197

Honors

2022	Parker Bridge Fellow, Parker Institute for Cancer Immunotherapy and the V foundation
2020	AAI trainee abstract award (conference canceled due to pandemic)
2019-2020	Stanford Dean's Postdoctoral Fellowship
2017	La Jolla Immunology Conference Best poster award
2017	UCSD Biology Founding Faculty Award for Graduate Excellence
2016	La Jolla Immunology Conference Best poster award
2016	Marguerite Vogt award (top 1 graduate student based on research excellence)
2015	Best graduate student poster award (UCSD-Salk Retreat)
2012-2014	Dr. Huang Memorial Scholarship

C. Contributions to Science

Decoding and rewiring the immune recognition at the single cell level

The human immune system is remarkably powerful in providing dynamic protection against diverse threats like pathogens and cancers. Decoding the complex underlying signals governing immune responses is essential for optimally harnessing the raw power of immune system for designing next-generation immune therapeutics. To

address this, I developed lentiviral-mediated cell entry by engineered receptor-ligand interaction (ENTER) to display ligand proteins, deliver payloads, and record receptor specificity. We optimize ENTER to decode interactions between T cell receptor (TCR)-MHC peptides, antibody-antigen, and other receptor-ligand pairs. A viral presentation strategy allows ENTER to capture interactions between B cell receptor and any antigen. We engineer ENTER to deliver genetic payloads to antigen-specific T or B cells to selectively modulate cellular behavior in mixed populations. Single-cell readout of ENTER by RNA-sequencing (ENTER-seq) enables multiplexed enumeration of antigen specificities, TCR clonality, cell-type and states of individual T cells. ENTER-seq of CMV-seropositive patient blood samples reveals the viral epitopes that drive effector memory T cell differentiation and inter- vs intra-clonal phenotypic diversity targeting the same epitope. ENTER technology enables systematic discovery of receptor specificity, linkage to cell fates, and antigen-specific cargo delivery.

Yu B*, Shi Q*, Belk JA, Yost KE, Parker KP, Huang H, Li R, Liu BB, Lingwood D, Greenleaf WJ. Davis MM, Satpathy A, Chang HY. Engineered cell entry links receptor biology with single-cell genomics. ***Cell*** 2022 185(26):4904-4920 * equally contributed

Deciphering the role of XIST RNA-protein complex in X-inactivation maintenance in B cells

X chromosome inactivation (XCI) is the fundamental mechanism that equalizes X-linked gene expression between the sexes in every female mammal cell. It is initiated by a female-specific long non-coding RNA (lncRNA) XIST that recruits diverse co-factors to epigenetically silence the prospective inactive X chromosome (Xi) during early embryo development. Once the Xi is established, the Xi “remembers” to maintain silencing in all somatic cells through adulthood, serving as a unique epigenetic memory model without requirement of lncRNA XIST. Surprisingly, I found that XIST is needed again in somatic B cells, a central player of humoral immune response. My postdoc work unveiled an unexpected and central role of XIST in X-inactivation maintenance, a process that impacts female-biased diseases and is long thought to be independent of XIST. I found that (i) XIST is continuously required for XCI maintenance of immune genes with hypomethylated promoters such as TLR7 via deacetylation of H3K27 at enhancers in B cells. (ii) XIST RNA-directed proteomics and CRISPRi screens reveal key B cell-specific XIST cofactors such as TRIM28 that participates in XCI maintenance via preventing transcription elongation. (iii) Single cell analysis of escape of XIST-dependent genes showed that XIST dysregulation occurs at atypical B cells in patients with female-biased autoimmune diseases. (iv) The inactivation of XIST combined with TLR7 stimulation facilitated the formation of atypical B cells, a subset that is abnormally expanded in female-biased autoimmune diseases. This work provides a paradigm shift of our current understanding of XCI maintenance, unveils fundamental rules of RNA-mediated epigenetic memory, and establishes a novel link between female-specific X-inactivation and female-biased autoimmune diseases.

Yu B, Qi Y, Li R, Shi Q, Satpathy A, Chang HY. B cell-specific XIST complex enforces X-inactivation and restrains atypical B cells. ***Cell*** 2021 184(7):1790-1803

Discovering key transcription factors for T cell fate decisions from epigenetic landscapes

In response to infection, naive $CD8^+$ T cells differentiate into a heterogeneous population of pathogen-specific effector $CD8^+$ T cells. While the majority of these T cells undergo apoptosis after pathogen clearance, a small fraction persists as memory cells, providing lasting protection from re-infection. The $CD8^+$ T cell fate decision to be a effector or memory T cell is influenced by both cell-extrinsic factors like inflammation and cell-intrinsic TFs. Numerous TFs have been identified as critical regulators of $CD8^+$ T cell fate. Notably, not all the identified TFs exhibit differential expression between the terminal effector (TE) and memory precursor (MP) subsets, suggesting that additional epigenetic mechanisms contribute to their binding and activity in promoting cell fates. I characterized the epigenetic landscapes of naive, TE, MP and memory $CD8^+$ T cells generated during bacterial infection to identify both enhancer and promoter regions important for $CD8^+$ T cell differentiation. Combining ATAC-seq with motif analysis, I predicted TF candidates and further constructed a transcriptional regulatory network for each subset. To facilitate the identification of key TFs, I developed a new bioinformatics method using the PageRank algorithm to rank the importance of TF in each regulatory network and identified novel TFs for subset differentiation. Finally, I experimentally validated that YY1 and Nr3c1 promote TE and MP differentiation respectively using shRNA knockdown. This PageRank-based computational framework has been applied to other cell types to facilitate the rapid identifications of important TFs.

Yu B, Zhang K, Milner JJ, Toma C, Chen R, Scott-Browne JP, Pereira RM, Crotty S, Chang JT, Pipkin ME, Wang W, Goldrath AW. Epigenetic landscapes reveal transcription factors that regulate CD8+ T cell differentiation. ***Nature Immunology***. 2017 18(5):573-582

Wang D, Diao H, Getzler AJ, Rogal W, Frederick M, Milner J, **Yu B**, Crotty S, Goldrath AW, Pipkin ME. The transcription factor Runx3 establishes chromatin accessibility of cis-regulatory landscapes that drive memory cytotoxic T lymphocyte formation. ***Immunity***. 2018 48(4):659-674

Kakaradov B, Arsenio J, Widjaja CE, He Z, Aigner S, Metz PJ, **Yu B**, Wehrens EJ, Lopez J, Kim SH, Zuniga EI, Goldrath AW, Chang JT, Yeo GW. Early transcriptional and epigenetic regulation of CD8+ T cell differentiation revealed by single-cell RNA sequencing. ***Nature Immunology***. 2017 18(4):422-432

Stone SL, Peel JN, Scharer CD, Risley CA, Chisolm DA, Schultz MD, **Yu B**, Ballesteros-Tato A, Wojciechowski W, Mousseau B, Misra RS, Hanidu A, Jiang H, Qi Z, Boss JM, Randall TD, Brodeur SR, Goldrath AW, Weinmann AS, Rosenberg AF, Lund FE. T-bet Transcription Factor Promotes Antibody-Secreting Cell Differentiation by Limiting the Inflammatory Effects of IFN-gamma on B Cells. ***Immunity***. 2019 50(5):1172-1187

Identification of a novel TF Runx3 in programming tissue-residency of T cells in non-lymphoid tissues and tumors

By developing an understanding of the factors that control anti-pathogen T cell immunity, it may be possible to favor the generation of effector-memory cells (Tem, beneficial in the context of prophylactic vaccines designed to therapeutically boost immunity to chronic infections and tumors); or favor the generation of long-lived central memory cells (Tcm, beneficial in the context of traditional vaccination against infectious diseases, including oncogenic viruses); or favor the generation of tissue-resident memory cells (Trm, beneficial in the context of providing sentinel protection against pathogen and malignancy within non-lymphoid tissues). As an extension of the epigenetic work in effector subsets, I characterized the chromatin accessibility and transcriptional programs in memory subsets using ATAC-seq and RNA-seq and prioritized a list of critical TFs for Trm differentiation. Using in vivo functional screen performed by the postdoctoral researcher Justin Milner in our lab, we confirmed several TF candidates including Runx3 essential for Trm formation. To further understand how Runx3 regulates Trm differentiation, I first identified a core tissue-residency and circulation gene signature across five different non-lymphoid tissues. Then I performed computational analysis to demonstrate that Runx3 promotes tissue-residency gene expression while repressing genes important for egress. Importantly, I discovered that tumor-infiltrating T cells (TILs) share the core tissue residency gene signature with Trm cells, suggesting that the infiltration and survival of TILs in tumor may require the tissue-residency programs which is regulated by Runx3. Indeed, overexpression of Runx3 promotes TILs accumulation and delay tumor growth.

Milner JJ, Toma C*, **Yu B***, Zhang K, Omilusik KD, Phan A, Wang DP, Getzler A, Crotty S, Wang W, Pipkin ME, Goldrath AW. Runx3 programs CD8+ T cell residency in non-lymphoid tissues and tumors. ***Nature***. 2017 552(7684) * equally contributed

Additional publications:

Omilusik KD, Nadjsombati M, Shaw L, **Yu B**, Milner J, Goldrath AW. Sustained regulation of E-protein transcription factors by Id2 enforces terminal differentiation of effector CD8+ T cells. ***Journal of Experimental Medicine***. 2018 215(3):773-783

Dwyer DF, Barrett NA, Austen KF, Kim EY, Brenner MB, Shaw L, **Yu B**, Goldrath AW, Mostafavi S, Regev A et al Expression profiling of constitutive mast cells reveals a unique identity within the immune system. ***Nature Immunology*** 2016 17(7):878-87

Omilusik KD, Best JA, **Yu B**, Goossens S, Weidemann A, Nguyen JV, Seuntjens E, Stryjewska A, Zweier C, Roychoudhuri R, Gattinoni L, Bird LM, Higashi Y, Kondoh H, Huylebroeck D, Haigh J, AW Goldrath. Transcriptional repressor ZEB2 promotes terminal differentiation of CD8+ effector and memory T cell populations during infection. ***Journal of Experimental Medicine***. 2015. 212(12): 2027-39

Robinette M, Fuchs A, Cortez VS, Lee JS, Wang Y, Durum SK, Gilfillan S, Colonna M, Shaw L, **Yu B**, Goldrath AW, Mostafavi S, Regev A et al Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. ***Nature Immunology*** 2015 16(3):306-17

Links to full list of public work:
https://scholar.google.com/citations?user=Mbd1TE8AAAAJ&hl=en

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