Brent Yasuda Chick, MA

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EDUCATION

Ph.D. in Biological Sciences, 2020-2025 (expected)
University of California San Diego, San Diego, CA
Advisor: Diana C. Hargreaves, Associate Professor of Molecular and Cell Biology Laboratory
Thesis: Characterizing the epigenetic mechanisms of ERK signal decoding in cell fate decisions

M.A. in Molecular, Cellular, and Developmental Biology, 2018-2020
University of California Santa Barbara, Goleta, CA
Advisor: Maxwell Z. Wilson, Assistant Professor of Molecular, Cellular, and Developmental Biology

B.S. in Molecular Biology, 2010-2015
University of California San Diego, San Diego, CA
Advisor: Stephen Hedrick, Distinguished Professor Emeritus of Molecular Biology

PUBLICATIONS

SELECTED PUBLICATIONS

- Cannonical BAF complex activity shapes the enhancer landscape that licenses CD8$^+$ T cell effector and memory fates
  Chick BY*, McDonald B*, Ahmed NS, Burns M, Ma S, Casillas E, Chen D, Mann T, O'Connor C, Hah N, Hargreaves DC, Kaech S (**co-first authors*)
  Submitted (2022)

  Description: CD8+ T cells provide a critical layer of host protection against infectious pathogens by differentiating into distinct subsets of effector and memory cells. Chromatin remodeling is essential for cellular differentiation, but the mechanisms that control site-specific opening and closing of gene regulatory elements in differentiating CD8+ T cells are unknown. We identified that in effector antiviral CD8+ T cells, the ARID1A-containing canonical BAF (cBAF) complex opens thousands of enhancers that are bound by effector-associated transcription factors (TFs) including T-bet, BATF, and ETS1. In the absence of Arid1a these TFs could not bind because of reduced accessibility, leading to abnormal proliferation, gene expression and failure to differentiate into terminal effector and tissue-resident memory cells. Thus, cBAF governs the enhancer landscape of activated CD8+ T cells that orchestrates TF activity and the acquisition of specific effector and memory differentiation states.

- In vitro recapitulation of murine thymopoiesis from single hematopoietic stem cells
  Montel-Hagen A, Sun V, Casero D, Tsai S, Zampieri A, Jackson N, Li S, Lopez S, Zhu Y, Chick BY, He C, De Barros SC, Seet CS, Crooks GM
  Cell Reports (2020)

  Description: We report a serum-free, 3D murine artificial thymic organoid (M-ATO) system that mimics normal murine thymopoiesis with the production of all T cell stages, from early thymic progenitors to functional single-positive (CD8SP and CD4SP) TCRαβ and TCRγδ cells. RNA sequencing aligns M-ATO-derived populations with phenotypically identical primary thymocytes. M-ATOs initiated with defined hematopoietic stem cells (HSCs) and lymphoid progenitors from marrow and thymus generate each of the downstream differentiation stages, allowing the kinetics of T cell differentiation to be tracked. Remarkably, single HSCs deposited into each M-ATO generate the complete trajectory of T cell differentiation, producing diverse TCR repertoires across clones that largely match endogenous thymus. M-ATOs represent a highly reproducible and efficient experimental platform for the interrogation of clonal thymopoiesis from HSCs.

- Pleiotropic Roles of VEGF in the Microenvironment of the Developing Thymus
  De Barros SC, Suterwala B, He C, Ge S, Chick BY, Blumberg GK, Kim K, Klein S, Zhu Y, Wang X, Casero D, Crooks GM
  The Journal of Immunology (2020)

  Description: Neonatal life marks the apogee of murine thymic growth. Over the first few days after birth, growth slows and the murine thymus switches from fetal to adult morphology and function. In this study, we show for the first time the critical role of vascular endothelial growth factor (VEGF) on thymic morphogenesis beyond its well-known role in angiogenesis. During a brief window a few days after birth, VEGF inhibition induced rapid and profound remodeling of the endothelial, mesenchymal and epithelial thymic stromal compartments, mimicking changes seen during early adult maturation. Rapid transcriptional changes were seen in each compartment after VEGF inhibition, including genes involved in migration, chemotaxis, and cell adhesion as well as induction of a proinflammatory and proadipogenic signature in endothelium, pericytes, and mesenchyme. Expression patterns and

functional blockade of the receptors VEGFR2 and NRP1 demonstrated that VEGF mediates its pleiotropic effects through distinct receptors on each microenvironmental compartment of the developing mouse thymus.

- Organoid-induced differentiation of conventional T cells from human pluripotent stem cells
  Montel-Hagen A, Seet CS, Li S, Chick BY, Zhu Y, Chang P, Tsai S, Sun V, Lopez S, Chen H, He C, Chin CJ, Casero D, Crooks GM
  Cell Stem Cell (2019)

  Description: The ability to generate T cells from pluripotent stem cells (PSCs) has the potential to transform autologous T cell immunotherapy by facilitating universal, off-the-shelf cell products. However, differentiation of human PSCs into mature, conventional T cells has been challenging with existing methods. We report that a continuous 3D organoid system induced an orderly sequence of commitment and differentiation from PSC-derived embryonic mesoderm through hematopoietic specification and efficient terminal differentiation to naive CD3+CD8αβ+ and CD3+CD4+ conventional T cells with a diverse T cell receptor (TCR) repertoire. Introduction of an MHC class I-restricted TCR in PSCs produced naive, antigen-specific CD8αβ+ T cells that lacked endogenous TCR expression and showed anti-tumor efficacy in vitro and in vivo. Functional assays and RNA sequencing aligned PSC-derived T cells with primary naive CD8+ T cells. The PSC-artificial thymic organoid (ATO) system presented here is an efficient platform for generating functional, mature T cells from human PSCs.

- Generation of mature T cells from human hematopoietic stem and progenitor cells in artificial thymic organoids
  Seet CS, He C, Bethune MT, Li S, Chick BY, Gschweng EH, Zhu Y, Kim K, Kohn DB, Baltimore D, Crooks GM, Montel-Hagen A
  Nature Methods (2017)

  Description: Studies of human T cell development require robust model systems that recapitulate the full span of thymopoiesis, from hematopoietic stem and progenitor cells (HSPCs) through to mature T cells. Existing in vitro models induce T cell commitment from human HSPCs; however, differentiation into mature CD3+TCR-αβ+ single-positive CD8+ or CD4+ cells is limited. We describe here a serum-free, artificial thymic organoid (ATO) system that supports efficient and reproducible in vitro differentiation and positive selection of conventional human T cells from all sources of HSPCs. ATO-derived T cells exhibited mature naive phenotypes, a diverse T cell receptor (TCR) repertoire and TCR-dependent function. ATOs initiated with TCR-engineered HSPCs produced T cells with antigen-specific cytotoxicity and near-complete lack of endogenous TCR Vβ expression, consistent with allelic exclusion of Vβ-encoding loci. ATOs provide a robust tool for studying human T cell differentiation and for the future development of stem-cell-based engineered T cell therapies.

ADDITIONAL PUBLICATIONS

- Notch signaling regulates the differentiation of CLEC9A+ dendritic cells from human and mouse hematopoietic stem and progenitor cells
  Seet CS, Li S, Chick BY, Casero D, Kim J, Gschweng E, Chen H, Zhu Y, Lopez S, Miao R, Montel-Hagen A, Kohn D, Sehl M, Crooks GM
  Experimental Hematology (2018)
- Directed differentiation of conventional T cells from human pluripotent stem cells in an artificial organoid system
  Montel-Hagen A, Seet CS, Li S, Chick BY, Zhu Y, Lopez S, Chang P, Tsai S, He C, Chin CJ, Casero D, Crooks GM
  Experimental Hematology (2018)
- VEGF affects postnatal thymic development through distinct receptor pathways
  De Barros SC, Suterwala B, Ge S, He C, Kim K, Zhu Y, Chick BY, Wang X, Casero D, Crooks GM
  Experimental Hematology (2018)
- Direct notch signaling promotes the differentiation of human CLEC9A+ dendritic cells from hematopoietic stem and progenitor cells
  Seet CS, Li S, Chick BY, Casero D, Gschweng EH, Zhu Y, Miao R, Montel-Hagen A, Kohn D, Sehl M, Crooks GM
  Blood (2017)
- In vitro generation of human pluripotent stem cell-derived T cells for immunotherapy
  Montel-Hagen A, Seet CS, Li S, Chick BY, Chang P, Zhu Y, He C, Lopez S, Crooks GM
  Blood (2017)
- Artificial thymic organoids permit allelic exclusion and efficient generation of naïve TCR-engineered T cells from human hematopoietic stem cells in vitro
  Seet CS, He C, Bethune MT, Li S, Chick BY, Gschweng EH, Zhu Y, Kim K, Baltimore D, Kohn D, Montel-Hagen A, Crooks GM
  Blood (2016)

FUNDING, AWARDS, AND HONORS

NIH T32 Pathways in Biological Sciences (PiBS) Training Grant
McElroy Award
UCSD Provost Honors

CONFERENCES AND PRESENTATIONS

2022 La Jolla Immunology Conference – Abstract submitted
2022 Salk Post-translational Regulation of Cell Signaling Meeting Attendee
2019 Kavli Institute for Theoretical Physics – qBio Morphogenesis summer course: TA and Attendee
2018 ASCB | EMBO Meeting Attendee
2017 La Jolla Immunology Conference Attendee

SERVICE AND LEADERSHIP

2022 Project LEAD Volunteer (Educating breast cancer advocates on cancer epigenetics)
Graduate Student Seminar Series Student Organizer – Chromatin and Transcriptional Regulation 2022
UCSD Biological Sciences Peer Mentorship Program (2021-2022)

REFERENCES

Available upon request