BIOGRAPHICAL SKETCH

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NAME: Lucas, Carrie L.

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

POSITION TITLE: Assistant Professor of Immunobiology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of North Carolina – Chapel Hill, NC	B.S.	05/2006	Biology
Harvard University – Cambridge, MA	Ph.D.	11/2010	BBS/Immunology
National Institutes of Health – Bethesda, MD	(Postdoc)	06/2016	Immunology

A. Personal Statement

My overarching research goal is to discover new and translationally relevant principles of fundamental immunology by defining and studying human immune disorders. To do this, we integrate genomics, *in vitro* studies using primary patient cells, and *in vivo* mouse modeling approaches to gain incisive basic and translational insights.

In early work, we defined the monogenic human disease caused by heterozygous, gain-of-function mutations in the genes encoding the p110δ or p85α PI3K subunits. These individuals suffer from an immunodeficiency and lymphoproliferative disorder now called Activated PI3K-delta Syndrome (APDS), and our efforts have focused on T cell senescence and related DNA damage response pathways (1,2). In a highly collaborative effort, APDS patients were successfully treated in a small clinical trial of a p110δ inhibitor.

Extending beyond APDS, we have also described a new human disease we termed 'Inactivated PI3K-gamma Syndrome' (IPGS) (3). Using patient cells and innovative 'dirty' mouse modeling to better emulate the human condition, we discovered that loss of PI3Kγ causes immunodeficiency and lung/gut immunopathology with humoral defects, hyperinflammatory macrophages, low Tregs, and a Th1-like bias. These findings are highly relevant not only for rare disease research but also for clinical use of PI3Kγ inhibitors in cancer trials.

In ongoing work, we have applied single-cell RNA sequencing to define immunopathology features of 'multisystem inflammatory syndrome in children' (MIS-C) post-SARS-CoV-2 infection (4) and discovered new single-gene defects driving new autoinflammatory and immunodeficiency disorders.

1. **Lucas CL**, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, Avery DT, Moens L, Cannons JL, Biancalana M, Stoddard J, Ouyang W, Frucht DM, Rao VK, Atkinson TP, Agharahimi A, Hussey AA, Folio LR, Olivier KN, Fleisher TA, Pittaluga S, Holland SM, Cohen JI, Oliveira JB, Tangye SG, Schwartzberg PL, Lenardo MJ, Uzel G. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. *Nature Immunology*. 2014; 15(1):88-97. PMCID: PMC4209962.
2. **Lucas CL**, Zhang Y, Venida A, Wang Y, Hughes J, McElwee J, Butrick M, Matthews H, Price S, Biancalana M, Wang X, Richards M, Pozos T, Barlan I, Ozen A, Rao VK, Su HC, Lenardo MJ. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. *The Journal of Experimental Medicine*. 2014; 211(13):2537-47. PMCID: PMC4267241.
3. Takeda AJ, Maher TJ, Zhang Y, Lanahan SM, Bucklin ML, Compton SR, Tyler PM, Comrie WA, Matsuda M, Olivier KN, Pittaluga S, McElwee JJ, Long Priel DA, Kuhns DB, Williams RL, Mustillo PJ, Wymann MP, Rao VK, and **Lucas CL**. Human PI3Kγ deficiency and its microbiota-dependent mouse model reveal immunodeficiency and tissue immunopathology. *Nature Communications*. 2019; 10(1):4364. PMID: 31554793.

4. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, Li N, Liu Y, Shah A, Ravindra NG, Bishai J, Khan A, Lau W, Sellers B, Bansal N, Sparks R, Unterman A, Habet V, Rice AJ, Catanzaro J, Chandnani H, Lopez M, Kaminski N, Dela Cruz CS, Tsang JS, Wang Z, Yan X, Kleinstein SH, van Dijk D, Pierce RW, Hafler DA, **Lucas CL**. Post-infectious inflammatory disease in MIS-C features elevated cytotoxicity signatures and autoreactivity that correlates with severity. *medRxiv*. 2020 Dec 4. PMCID: PMC7724682.

B. Positions and Honors

Positions and Employment

2004-2006 Undergraduate Researcher, Laboratory of Dr. Kathleen Caron, UNC School of Medicine
2005 Summer Research Intern, GlaxoSmithKline, Research Triangle Park, NC
2006-2010 PhD Student, Laboratory of Dr. Megan Sykes, Massachusetts General Hospital, Harvard
2010 Fall Instructor in Biology, BIOL358: Undergraduate Immunobiology, Georgetown University
2011-2016 Postdoctoral Research Fellow, Laboratory of Dr. Michael Lenardo, NIAID/NIH, Bethesda, MD
2016-Present Assistant Professor of Immunobiology, Yale School of Medicine, New Haven, CT

Other Experience and Professional Memberships (as of 2016)

2008 Fall Harvard Teaching Fellow, MCB169: Undergraduate Immunology (Director: Dr. Hidde Ploegh)
2008 Spring Harvard Teaching Fellow, MCB54: Undergraduate Cell Biology (Director: Dr. Rob Lue)
2009, 2010 Admissions Committee Member, Biological and Biomedical Sciences PhD Program, Harvard
2009-2010 Collaborator, Laboratory of Dr. Judy Lieberman, Immune Disease Institute, Harvard
2010 Fall Mirzayan Science and Technology Policy Fellow, The National Academies
2009-2012 Reviewer, *Transplant International*
2014-2015 Steering Committee Member, NIH Immunology Interest Group (IIG)
2015 Lecturer, Immunology (BIOL 556) at Catholic University of America, Washington, DC
2015 Proteomics training, Max Planck Institute of Biochemistry
2017-2019 Member, Faculty Advisory Council, Yale University School of Medicine
2017-2019 Co-chair, Yale Immunobiology Retreat Organizing Committee
2018 Topic Co-Editor: Human Disorders of PI3K Biology, *Frontiers in Immunology*
2019 Clinical Immunology Society (CIS) Nominating Committee
2009-present Member, American Association of Immunologists (AAI)
2014-present Member, Clinical Immunology Society (CIS)
2015-present Member, Federation of Clinical Immunology Societies (FOCIS)
2013-present Faculty of 1000 (Associate of Dr. Ronald Germain until 2016)
2017-present Member, Human and Translational Immunology Steering Committee, Yale University
2017-present Member, Admissions Committee, Yale Immunology PhD Track, BBS Program
2018-present Member, Yale MD/PhD Program Admissions Committee
2019-present Elected Member, Henry Kunkel Society
2019-present Member, Yale Immunobiology Training Grant Diversity and Inclusion Committee
2019-2021 Member, Brown-Coxe Fellowship Selection Committee, Yale University
2020-present Member, Colton Center for Autoimmunity at Yale, Advisory Committee
2020-present Member, Clinical Immunology Society (CIS) Program Committee and Nomination Committee
2020-present American Association of Immunologists (AAI) Travel for Techniques Review Committee

Honors

AWARDS

2005-2006 Barry M. Goldwater Scholarship, UNC Chapel Hill
2008-2010 National Defense Science and Engineering Graduate (NDSEG) Fellowship, Harvard
2009-2010 Albert J. Ryan Fellowship (Illick Fellow), Harvard Medical School
2009 Profiled in Harvard's 2009-2010 Harvard Medical School Dean's Report
2012-2015 Postdoctoral Research Associate (PRAT) Fellowship, NIGMS/NIH
2014 Ray Owen Young Investigator Award: 53rd Midwinter Conference of Immunologists
2014 American Association of Immunologists (AAI)-Life Technologies Trainee Achievement Award
2015 Keystone Symposia Future of Science Fund Scholarship
2016 Fellows Award for Research Excellence, NIH
2017 Rudolph J. Anderson Endowed Postdoctoral Trainee Funding support, Yale University
2017 American Association of Immunologists (AAI) Travel for Techniques Award

2018-2019 Bohmfalk Scholar, Yale University School of Medicine
2020 ICIS Young Investigator Award: Christina Fleischmann Award to Young Women Investigators

SPEAKING ENGAGEMENTS (as of 2016)

2016 Invited Speaker: AAAAI Conference, Los Angeles, CA
2016 Speaker at EMBO Lymphocyte Antigen Receptor Signaling meeting in Siena, Italy
2016 Invited Speaker: Cambridge-Yale MedImmune Annual Conference, Cambridge, England
2017 Platform Talk and Session Chair: Keystone Symposium on PI3K Pathways in Immunology, Growth Disorders, and Cancer, Santa Fe, NM
2017 Invited Speaker: 52nd annual meeting of the Academy of Clinical Laboratory Physicians and Scientists (ACLPS), New Haven, CT
2017 Invited Speaker: Career Options Seminar, NIAID Office of Training and Diversity, Bethesda, MD
2017 Invited Speaker: Cambridge-Yale MedImmune Annual Conference, New Haven, CT
2018 Invited Career Panelist: Harvard Leder Human Biology (LHB) Retreat, Boston, MA
2018 Platform Talk: Clinical Immunology Society (CIS) Meeting, Toronto, ON, Canada
2018 Invited Speaker: EMBO Conference on Lymphocyte Antigen Receptor Signaling, Siena, Italy
2018 Platform Talk and Travel Awardee: European Society for Immunodeficiencies (ESID) Annual Meeting, Lisbon, Portugal
2019-2021 Invited Course Faculty: FOCIS Advanced Course in Basic & Clinical Immunology, La Jolla, CA
2019 Invited Speaker: Henry Kunkel Society Meeting, The Rockefeller University, New York, NY
2019 Invited Speaker: Seminar Series, Cell Biology at the Hospital for Sick Children, Toronto, Ontario, Canada
2019 Invited Speaker: Seminar Series, Division of Cell Pathology at the Children's Hospital of Philadelphia (CHOP), Philadelphia, PA
2019 Invited Speaker: FASEB Signal Transduction in the Immune System, Nova Scotia, Canada
2019 Invited Speaker: The Biochemical Society: PI3K/PTEN pathway: from basic science to clinical translation, Buxton, UK
2019 Invited Speaker: Novartis Autoimmunity, Transplantation, and Inflammation Seminar Series, Basel, Switzerland
2019 Invited Speaker: University of Freiburg, Center for Chronic Immunodeficiency Seminar Series, Freiburg, Germany
2019 Invited Speaker: European Society for Immunodeficiencies (ESID) Focused Meeting: Immunodeficiencies with increased risk of cancer, Brussels, Belgium
2020 Invited Speaker: Keystone Symposium on PI3K and PTEN at the Interface of Cell Growth, Vesicular Trafficking, and Disease, Hannover, Germany – COVID19 cancellation
2020-2021 Faculty Lecturer, AAI Advanced Course (virtual)
2020 Invited Speaker: NIAID Grand Rounds, NIH, Bethesda, MD, USA (virtual)
2020 Invited Speaker: North American Immuno-Hematology Clinical Education and Research (NICER) Symposium (virtual)
2020 Invited Speaker: University of Pittsburgh, Immunology Seminar Series (virtual)
2020 Selected Speaker: ICIS Cytokines Annual Meeting (virtual)
2020 Invited Speaker: NIH/FDA Symposium: The Role of Cytokines in COVID-19 (virtual)
2020 Invited Speaker: American Society of Hematology Annual Meeting (virtual)
2021 Invited Speaker: Tufts University Medical School, Immunology Seminar Series (virtual)
2021 Invited Speaker: Clinical Immunology Society (CIS) Meeting (virtual)
2021 Invited Speaker: Korean Association of Immunologists Annual Meeting (virtual)

Patent: Carrie Lucas, Megan Sykes, Judith Lieberman, Ann Schlesinger, Motomu Shimaoka. Methods for inducing mixed chimerism. PCT/US2009/065945. Fusion protein-siRNA complexes that specifically target activated T cells, and methods of use thereof, are described. WO 2010062966 A3.

C. Contribution to Science (NOTE: Former surname was "Gibbons".)

1. My early publications addressed mechanisms of CD8 T cell tolerance using cellular immunology approaches and *in vivo* mouse modeling. I evaluated mechanisms by which low-dose total body irradiation followed by costimulation blockade using anti-CD40L at the time of BMT deletes donor-reactive CD8 T cells. I found that CD8 T cell-intrinsic PD-1 and NFAT play critical roles and, together with LAG-3 and TGF-β signaling, decrease proliferation and increase apoptosis of donor-reactive CD8 T cells.

a. **Gibbons C** and Sykes M. Manipulating the immune system for anti-tumor responses and transplant tolerance via mixed hematopoietic chimerism. *Immunological Reviews*. 2008; 223:334-60. PMID: 18613846. PMCID: PMC2680695.
b. Haspot F, Fehr T, **Gibbons C**, Zhao G, Hogan T, Honjo T, Freeman G, Sykes M. Peripheral deletional tolerance of alloreactive CD8 but not CD4 T cells is dependent on the PD-1/PD-L1 pathway. *Blood.* 2008; 112(5): 2149-55. PMCID: PMC2518911.
c. Fehr T*****, **Lucas CL***, Kurtz J, Onoe T, Zhao G, Hogan T, Vallot C, Rao A, Sykes M. * Shared first authorship. A CD8 T cell-intrinsic role for the calcineurin-NFAT pathway for tolerance induction in vivo. *Blood.* 2010; 115(6):1280-7. PMCID: PMC2826238.
d. **Lucas CL**, Workman CJ, Beyaz S, LoCascio S, Zhao G, Vignali DAA, and Sykes M. LAG-3, TGF-β, and cell-intrinsic PD-1 inhibitory pathways contribute to CD8 but not CD4 T cell tolerance induced by allogeneic BMT with anti-CD40L. *Blood*. 2011; 117(20):5532-40. PMCID: PMC3109721.

2. As a postdoc, I studied monogenic immune disorders. I was part of a team studying of patients with deficiency in the MAGT1 magnesium transporter resulting in loss of the important NKG2D molecule and EBV susceptibility. Subsequently, I led mechanistic studies to determine the etiology of a disease we found was caused by gain-of-function mutations in either the *PIK3CD* or *PIK3R1* genes encoding the p110δ and p85α PI3K subunits, respectively. I discovered that hyperactive PI3K signaling results in terminal differentiation and senescence of T cells, which contributes to their immunodysregulation.
    a. Chaigne-Delalande B, Li F-Y, O'Connor GM, Lukacs M, Biancalana M, Zheng L, Shatzer A, Pittaluga S, Matthews HF, Jancel T, Hetherington M, Bleesing JJ, Kuijpers TW, **Lucas CL**, Nagpal S, Mehmet H, Su HC, Cohen JI, Uzel G, and Lenardo MJ. Mg^{2+} regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. *Science*. 2013; 341(6142):186-91. PMCID: PMC3894782.
    b. **Lucas CL***, Kuehn HS*, Zhao F*, Niemela JE, Deenick EK, Palendira U, Avery DT, Moens L, Cannons JL, Biancalana M, Stoddard J, Ouyang W, Frucht DM, Rao VK, Atkinson TP, Agharahimi A, Hussey AA, Folio LR, Olivier KN, Fleisher TA, Pittaluga S, Holland SM, Cohen JI, Oliveira JB, Tangye SG, Schwartzberg PL, Lenardo MG, and Uzel G. *Shared first authorship. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. *Nature Immunology*. 2014; 15(1):88-97. Epub 2013 Oct 28. PMCID: PMC4209962.
    c. **Lucas CL**, Zhang Y, Venida A, Wang Y, Hughes J, McElwee J, Butrick M, Matthews M, Price S, Biancalana M, Wang X, Richards M, Pozos T, Barlan I, Ozen A, Rao VK, Su HC, Lenardo MJ. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. *Journal of Experimental Medicine*. 2014; 211(13):2537-47. Epub 2014 Dec 8. PMCID: PMC4267241.
    d. Lenardo M, Lo B, and **Lucas CL**. Genomics of immune diseases and new therapies. *Annual Review of Immunology*. 2016; 20;34:121-49. PMCID: PMC5736009.

3. My lab continues to investigate human PI3Kδ mutations, their consequences in patients, and the basic science lessons that can be gleaned. We have contributed impactful review articles on PI3Kδ and related diseases and expanded the number of known mutation sites and affected p110δ protein domains in PASLI/APDS. Additionally, I collaborated on an exciting clinical trial examining the efficacy of targeted therapy with p110δ-specific inhibitor in PASLI/APDS patients. This precision medicine treatment is ideal for this disorder, and an extension study enrolling additional patients is now ongoing.
    a. **Lucas CL**, Chandra A, Nejentsev S, Condliffe AM, and Okkenhaug K. Activating PI3Kδ mutations and primary immunodeficiency. *Nature Reviews Immunology*. 2016; 16(11):702-714. PMCID: PMC5291318.
    b. Takeda AJ, Zhang Y, Dornan GL, Siempelkamp BD, Jenkins ML, Matthews HF, McElwee JJ, Bi W, Seeborg FO, Su HC, Burke JE, and **Lucas CL**. Novel *PIK3CD* mutations affecting N-terminal residues of p110δ cause hyperactive PI3K signaling and APDS1 in humans. *Journal of Allergy and Clinical Immunology*. 2017; 140(4):1152-1156.e10. PMCID: PMC5632585.
    c. Rao VK, Webster S, Dalm VASH, Šedivá A, van Hagen PM, Holland S, Rosenzweig SD, Christ AD, Sloth B, Cabanski M, Joshi AD, de Buck S, Doucet J, Guerini D, Kalis C, Pylvaenaeinen I, Soldermann N, Kashyap A, Uzel G, Lenardo MJ, Patel DD, **Lucas CL**, Burkhart C. Effective 'Activated PI3Kδ Syndrome'-targeted therapy with the PI3Kδ inhibitor leniolisib. *Blood*. 2017; 130(21):2307-2316. PMCID: PMC5701526.

d. Carpier JM and **Lucas CL**. Epstein–Barr Virus Susceptibility in Activated PI3Kδ Syndrome (APDS) Immunodeficiency. *Frontiers in Immunology*. 2018; 8:2005. PMCID: PMC5776011.

4. More recently, my lab defined the genetic basis of undiagnosed monogenic disorders, including one we called 'Inactivated PI3Kγ Syndrome' (IPGS) from biallelic, loss-of-function variants in *PIK3CG* encoding p110γ. This work advances knowledge of PI3K biology and informs cancer clinical trials targeting PI3Kγ.
    a. Takeda AJ, Maher TJ, Zhang Y, Lanahan SM, Bucklin ML, Compton SR, Tyler PM, Comrie WA, Matsuda M, Olivier KN, Pittaluga S, McElwee JJ, Long Priel DA, Kuhns DB, Williams RL, Mustillo PJ, Wymann MP, Rao VK, and **Lucas CL**. Human PI3Kγ deficiency and its microbiota-dependent mouse model reveal immunodeficiency and tissue immunopathology. *Nature Communications*. 2019; 10(1):4364. PMCID: PMC6761123.
    b. Thian M, Hoeger B, Kamnev A, Poyer F, Köstel Bal S, Caldera M, Jiménez-Heredia R, Huemer J, Pickl WF, Groß M, Ehl S, **Lucas CL**, Menche J, Hutter C, Attarbaschi A, Dupré L, Boztug K. Germline biallelic PIK3CG mutations in a multifaceted immunodeficiency with immune dysregulation. *Haematologica*. 2020; doi: 10.3324/haematol.2019.231399. PMID: 32001535.
    c. Brodsky NN, Boyarchuk O, Kovalchuk T, Hariyan T, Rice A, Ji W, Khokha M, Lakhani S, and **Lucas CL**. Novel compound heterozygous variants in *NHLRC2* in a patient with FINCA syndrome. *J Hum Genet*. 2020; doi: 10.1038/s10038-020-0776-0. PMID: 32435055.
    d. Brooks JP, Rice AJ, Ji W, Lanahan SM, Konstantino M, Dara J, Hershfield MS, Cruickshank A, Dokmeci E, Lakhani S, **Lucas CL**. Uncontrolled Epstein-Barr Virus as an Atypical Presentation of Deficiency in ADA2 (DADA2). *J Clin Immunol*. 2021 Jan 4. PMID: 33394316.
5. We are additionally investigating mechanisms driving pediatric COVID-19 pathology.
    a. Casanova JL, Su HC, COVID Human Genetic Effort (consortium includes **Lucas CL**). A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection. *Cell*. 2020 Jun 11;181(6):1194-1199. PMCID: PMC7218368.
    b. Bastard P, et al., Su HC, Casanova JL. (C-HGE includes **Lucas CL**). Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020. PMID: 32972996.
    c. Zhang Q, et al., Su HC, Casanova JL. (C-HGE includes **Lucas CL**). Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020.PMID: 32972995.
    d. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, Li N, Liu Y, Shah A, Ravindra NG, Bishai J, Khan A, Lau W, Sellers B, Bansal N, Sparks R, Unterman A, Habet V, Rice AJ, Catanzaro J, Chandnani H, Lopez M, Kaminski N, Dela Cruz CS, Tsang JS, Wang Z, Yan X, Kleinstein SH, van Dijk D, Pierce RW, Hafler DA, **Lucas CL**. Post-infectious inflammatory disease in MIS-C features elevated cytotoxicity signatures and autoreactivity that correlates with severity. *medRxiv*. 2020 Dec 4. PMCID: PMC7724682.

Complete List of Published Work: 36 publications
https://www.ncbi.nlm.nih.gov/sites/myncbi/1tyRtgFamYN5-/bibliography/49815344/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

2018-2023	R01AI138141: DNA damage kinases in immune signaling	Lucas (PI)
2020-2023	Mathers Foundation Grant: Genetic drivers of pediatric IBD	Lucas (PI)
2019-2021	CRI CLIP Award: Effects of DDR modulators on cancer immunity	Lucas (PI)
2020-2022	R21AI144315: Immunodysregulation in human PI3Kγ deficiency	Lucas (PI)
2020-2022	3R21AI144315-01A1S1: Mechanisms of severe COVID-19/MIS-C	Lucas (PI)

Completed Research Support

2016-2019	4R00HL125668	Lucas (PI)
2017-2019	Hood Foundation Child Health Research Award	Lucas (PI)
2018-2019	Immune Deficiency Foundation Grant	Lucas (PI)
2019-2020	Yale Cancer Center Pilot Grant	Lucas (PI)