BIOGRAPHICAL SKETCH

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NAME: Graham, Daniel Bartholomew

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

POSITION TITLE: Group Leader, Broad Institute of MIT and Harvard
Instructor, Harvard Medical School
Assistant in Immunology, Massachusetts General Hospital
Member, Center for the Study of Inflammatory Bowel Disease, MGH

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
Bates College, Lewison, ME	BS	1998	Biochemistry
Mayo Clinic College of Medicine, Rochester, MN	PhD	2005	Immunology
Washington University School of Medicine, St Louis, MO	Postdoc	2005-2012	Immunobiology

A. Personal Statement

With rapid advancements in genomics technology, the field of immunology faces unprecedented opportunities to decipher the pathophysiological basis of human disease. In this context, we leverage insights gleaned from human genetics to identify key pathways underlying inflammatory bowel disease (IBD). Specifically, we have adopted a multidisciplinary approach to studying IBD that is comprised of (1) single-cell genomics, (2) functional genetic screens to place genes in immune pathways, (3) multi'omic platforms for deep mechanistic characterization of gene function, (4) developing mouse models to discern gene function in the context of complex pathological responses *in vivo*, and (5) identification of novel targets for therapeutic development. Collectively, our work has contributed to the understanding of inflammatory signal transduction pathways that elicit innate effector mechanisms (oxidative burst, natural cytotoxicity) and acquisition of adaptive immunity (antigen presentation, T cell differentiation). This work serves to advance the systematic integration of cell circuits that coordinate innate and adaptive immunity within the gut mucosa.

1. Graham DB, Becker CE, Doan A, Goel G, Villablanca EJ, Knights D, Mok A, Ng AC, Doench JG, Root DE, Clish CB, Xavier RJ. Functional genomics identifies negative regulatory nodes controlling phagocyte oxidative burst. *Nature Communications*. 2015;6:7838. PMID: 26194095; PMCID: PMC4518307.
2. Rivas MA, Graham D, Sulem P, Stevens C, Desch AN, Goyette P, Gudbjartsson D, Jonsdottir I, Thorsteinsdottir U, Degenhardt F, Mucha S, Kurki MI, Li D, D'Amato M, Annese V, Vermeire S, Weersma RK, Halfvarson J, Paavola-Sakki P, Lappalainen M, Lek M, Cummings B, Tukiainen T, Haritunians T, Halme L, Koskinen LL, Ananthakrishnan AN, Luo Y, Heap GA, Visschedijk MC, Consortium UIG, Consortium NIG, MacArthur DG, Neale BM, Ahmad T, Anderson CA, Brant SR, Duerr RH, Silverberg MS, Cho JH, Palotie A, Saavalainen P, Kontula K, Farkkila M, McGovern DP, Franke A, Stefansson K, Rioux JD, Xavier RJ, Daly MJ, Barrett J, de Lane K, Edwards C, Hart A, Hawkey C, Jostins L, Kennedy N, Lamb C, Lee J, Lees C, Mansfield J, Mathew C, Mowatt C, Newman B, Nimmo E, Parkes M, Pollard M, Prescott N, Randall J, Rice D, Satsangi J, Simmons A, Tremelling M, Uhlig H, Wilson D, Abraham C, Achkar JP, Bitton A, Boucher G, Croitoru K, Fleshner P, Glas J, Kugathasan S, Limbergen JV, Milgrom R, Proctor D, Regueiro M, Schumm PL, Sharma Y, Stempak JM, Targan SR, Wang MH. A protein-truncating R179X variant in RNF186 confers protection against ulcerative colitis. *Nature Communications*. 2016;7:12342. PMID: 27503255; PMCID: PMC4980482.

3. O'Connell DJ, Kolde R, Sooknah M, Graham DB, Sundberg TB, Latorre IJ, Mikkelsen TS, Xavier RJ. Simultaneous Pathway Activity Inference and Gene Expression Analysis Using RNA Sequencing. *Cell Systems*. 2016;2(5):323-34. PMID: 27211859; PMCID: PMC5032147.
4. Platt RJ, Chen S, Zhou Y, Yim MJ, Swiech L, Kempton HR, Dahlman JE, Parnas O, Eisenhaure TM, Jovanovic M, Graham DB, Jhunjhunwala S, Heidenreich M, Xavier RJ, Langer R, Anderson DG, Hacohen N, Regev A, Feng G, Sharp PA, Zhang F. CRISPR-Cas9 knockin mice for genome editing and cancer modeling. *Cell.* 2014;159(2):440-55. doi: 10.1016/j.cell.2014.09.014. PMID: 25263330; PMCID: PMC4265475.

B. Positions and Honors

Positions and Employment

2007-2012 Instructor, Dept of Pathology, Washington University School of Medicine, St Louis, MO
2012-2015 Research Scientist, Broad Institute of MIT and Harvard, Cambridge, MA
2012- Instructor, Harvard Medical School, Boston, MA
2012- Assistant in Immunology, Massachusetts General Hospital, Boston, MA
2014- Member, Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, Boston, MA
2015- Group Leader, Broad Institute of MIT and Harvard, Cambridge, MA

Other Experience and Professional Memberships

2006- American Association of Immunologists

Honors

2009-2012 Special Fellow, Leukemia and Lymphoma Society

C. Contribution to Science

1. *Antimicrobial defense.* Genetic studies have highlighted several antibacterial defense mechanisms associated with risk for IBD. However, establishing the immunologic basis of risk-association requires extensive functional characterization. We have contributed novel insights into regulation of the phagocyte oxidative burst and interactions between the innate immune system and bacterial pathogens/commensals. Specifically, our work helped establish a new paradigm in which receptors associated with immunoreceptor tyrosine based activation motifs (ITAMs) constitute a core signaling module that converges with several distinct pathogen sensing receptors. Here, integrin-dependent ITAM signaling through Vav and PLC-γ2 represents the central activation pathway for phagocyte oxidative burst triggered by TLR ligands and cytokines. Further extending this work, we have identified key signaling nodes that negatively regulate oxidative burst by acting at the level of transcription, metabolism, and ubiquitin cycling. Collectively, this work has shed new light on both positive and negative regulation of phagocyte oxidative burst and host defense. Our ongoing work aims to identify novel mechanisms regulating innate immunity.
    a. Graham DB, Becker CE, Doan A, Goel G, Villablanca EJ, Knights D, Mok A, Ng AC, Doench JG, Root DE, Clish CB, Xavier RJ. Functional genomics identifies negative regulatory nodes controlling phagocyte oxidative burst. *Nature Communications*. 2015;6:7838. PMID: 26194095; PMCID: PMC4518307.
    b. Graham DB, Zinselmeyer BH, Mascarenhas F, Delgado R, Miller MJ, Swat W. ITAM signaling by Vav family Rho guanine nucleotide exchange factors regulates interstitial transit rates of neutrophils in vivo. *PLOS ONE*. 2009;4(2):e4652. PMID: 19247495; PMCID: PMC2645696.
    c. Graham DB, Robertson CM, Bautista J, Mascarenhas F, Diacovo MJ, Montgrain V, Lam SK, Cremasco V, Dunne WM, Faccio R, Coopersmith CM, Swat W. Neutrophil-mediated oxidative burst and host defense are controlled by a Vav-PLCgamma2 signaling axis in mice. *The Journal of Clinical Investigation*. 2007;117(11):3445-52. PMID: 17932569; PMCID: PMC2000813.
    d. Miletic AV, Graham DB, Montgrain V, Fujikawa K, Kloeppel T, Brim K, Weaver B, Schreiber R, Xavier R, Swat W. Vav proteins control MyD88-dependent oxidative burst. *Blood*. 2007;109(8):3360-8. PMID: 17158234; PMCID: PMC1852252.
2. *Antigen presentation.* The HLA locus dominates risk associations for multiple autoimmune diseases, and clearly implicates antigen presentation in disease pathogenesis. As our understanding of the cell biology of antigen processing has progressed, insights into the molecular pathways that control these processes have lagged behind. In recent studies, we have identified a key role for ITAM signalling in phagosomal

acidification and processing of exogenous antigens through the proteosomal system during MHCI cross-presentation and CD8 T cell priming. In addition, our work identified a novel role for ITAM signaling and the WASH-retromer complex in CD4 T cell priming. Impaired recycling of MHCII through the retromer pathway leads to rapid lysosomal degradation of peptide-MHCII complexes and severely diminished T cell responses in several models of autoimmunity. Our ongoing functional genetic screens focus on mechanisms of cross-presentation and MHCII presentation.

a. Graham DB, Osborne DG, Piotrowski JT, Gomez TS, Gmyrek GB, Akilesh HM, Dani A, Billadeau DD, Swat W. Dendritic cells utilize the evolutionarily conserved WASH and retromer complexes to promote MHCII recycling and helper T cell priming. *PLOS ONE*. 2014;9(6):e98606. PMID: 24886983; PMCID: PMC4041763.
b. Acton SE, Astarita JL, Malhotra D, Lukacs-Kornek V, Franz B, Hess PR, Jakus Z, Kuligowski M, Fletcher AL, Elpek KG, Bellemare-Pelletier A, Sceats L, Reynoso ED, Gonzalez SF, Graham DB, Chang J, Peters A, Woodruff M, Kim YA, Swat W, Morita T, Kuchroo V, Carroll MC, Kahn ML, Wucherpfennig KW, Turley SJ. Podoplanin-rich stromal networks induce dendritic cell motility via activation of the C-type lectin receptor CLEC-2. *Immunity*. 2012;37(2):276-89. PMID: 22884313; PMCID: PMC3556784.
c. Graham DB, Akilesh HM, Gmyrek GB, Piccio L, Gilfillan S, Sim J, Belizaire R, Carrero JA, Wang Y, Blaufuss GS, Sandoval G, Fujikawa K, Cross AH, Russell JH, Cella M, Swat W. ITAM signaling in dendritic cells controls T helper cell priming by regulating MHC class II recycling. *Blood*. 2010;116(17):3208-18. PMID: 20634378; PMCID: PMC2995352.
d. Graham DB, Stephenson LM, Lam SK, Brim K, Lee HM, Bautista J, Gilfillan S, Akilesh S, Fujikawa K, Swat W. An ITAM-signaling pathway controls cross-presentation of particulate but not soluble antigens in dendritic cells. *The Journal of Experimental Medicine*. 2007;204(12):2889-97. PMID: 17984307; PMCID: PMC2118522.

3. *Lymphocyte differentiation and functional specialization.* Adaptive immunity confers long-term reactivity to commensal microorganisms in IBD, which underlies the relapsing-remitting nature of disease that is so difficult to treat. However, we have an incomplete understanding of the pathways that govern acquisition of adaptive immunity versus tolerance. In recent studies, we have identified that the Dlg1 polarity complex controls development of T cell memory by differentially regulating cell cycle progression versus differentiation. Moreover, we discovered that T cell activation and subsequent entry into the cell cycle requires activation of Vav guanine nucleotide exchange factors to coordinate TCR signaling with cytoskeletal rearrangements that stabilize the immune synapse. In this context, T cell activation through the core TCR signaling pathway is fine-tuned by costimulatory and immunomodulatory receptors. Towards deciphering mechanisms of costimulation, we dissected CD28 signaling motifs to demonstrate cooperative pathway activation and multiple levels of redundancy with respect to augmentation of TCR signaling. In addition to the canonical CD28 costimulatory pathway, several distinct receptors modulate T cell activation. We demonstrated that the SLAM family member Ly9, which is located within an autoimmune risk locus, controls the balance of Th1/Th2 differentiation in CD4 T cells. Our ongoing work aims to elucidate pathways underlying T cell memory versus tolerance and to identify commensal antigens that drive pathological T cell responses in mucosal tissues.

a. Gmyrek GB, Graham DB, Sandoval GJ, Blaufuss GS, Akilesh HM, Fujikawa K, Xavier RJ, Swat W. Polarity gene discs large homolog 1 regulates the generation of memory T cells. *European Journal of Immunology*. 2013;43(5):1185-94. PMID: 23436244; PMCID: PMC3894631.
b. Miletic AV, Graham DB, Sakata-Sogawa K, Hiroshima M, Hamann MJ, Cemerski S, Kloeppel T, Billadeau DD, Kanagawa O, Tokunaga M, Swat W. Vav links the T cell antigen receptor to the actin cytoskeleton and T cell activation independently of intrinsic Guanine nucleotide exchange activity. *PLOS ONE*. 2009;4(8):e6599. PMID: 19672294; PMCID: PMC2719804.
c. Graham DB, Bell MP, Huntoon CJ, Griffin MD, Tai X, Singer A, McKean DJ. CD28 ligation costimulates cell death but not maturation of double-positive thymocytes due to defective ERK MAPK signaling. *Journal of Immunology*. 2006;177(9):6098-107. PMID: 17056536.
d. Graham DB, Bell MP, McCausland MM, Huntoon CJ, van Deursen J, Faubion WA, Crotty S, McKean DJ. Ly9 (CD229)-deficient mice exhibit T cell defects yet do not share several phenotypic characteristics associated with SLAM- and SAP-deficient mice. *Journal of Immunology*. 2006;176(1):291-300. PMID: 16365421.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/44220519/

D. Research Support.
Ongoing Research Support

2017-2022
RC2 DK114784
Systematic Dissection of Gut Cellular Circuits [At Single Cell Resolution]
PI with Ramnik Xavier, Aviv Regev, Vijay Kuchroo, Ruslan Medzhitov