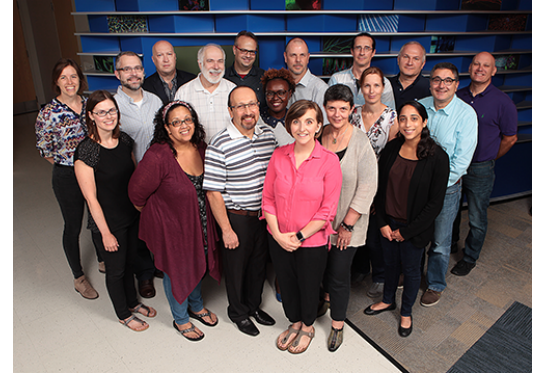


Immunobiology

Division Details

RESEARCH AND TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	1
Research Fellows and Post Docs	16
Research Graduate Students	18
Total Annual Grant Award Dollars	\$5,621,163
Total Annual Industry Award Dollars	\$313,860



Row 1: I Castro, M Khodoun, C Kinder, C Chougnat, T Alenghat

Row 2: K McLay, A Herr, F Finkelman, K Cole, E Janssen, H Singh

Row 3: E Miraldi, J Hogenesch, K Roskin, K Hoebe, I Lewkowich, HL Grimes, J Katz

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Division Highlights

Research Advances

Faculty in the division made a wide-ranging set of fundamental and translational advances. These have provided strong insights into the functioning of the immune system in health and disease.

A collaboration among the [Grimes](#), [Singh](#), and Salomonis labs using the tools of systems and computational biology, led to the discovery of rare mixed-lineage intermediates that are precursors of monocytes and neutrophils in the bone marrow. They uncovering of these rare cells occurred using single-cell RNA-Seq methodology. They appear to manifest an unusual cellular state referred to as “dynamic instability” which poises the intermediates to give rise to one of two different stable cellular fates. Dynamic instability can propose to underlie binary cell fate choice in a variety of developmental systems.

The [Hildeman](#) laboratory has elucidated an important function for the methyl transferase Dnmt3a in the generation of CD8 T cell memory. Curiously, their findings demonstrate that loss of Dnmt3a increases the frequency of CD8 memory T cells that generate upon infection of mice with LCMV. This result is somewhat counterintuitive in that DNA methylation of control regions in the genome by de novo methyltransferases such as Dnmt3a promotes the generation of cellular memory. Uncovering the precise molecular mechanisms by which Dnmt3a antagonizes memory CD8 T cell formation as well as its functions in other memory T and B cell responses is an exciting area of future exploration.

The [Divanovic](#) laboratory has demonstrated that thermoneutral housing provides a greatly improved, sex-independent, model of exacerbated non-alcoholic fatty liver disease (NAFLD) in mice. This translational advance represents a novel approach for analysis of cellular and molecular mechanisms underlying disease pathogenesis. NAFLD exacerbation at thermoneutrality conserved across multiple mouse strains, and associates with augmented intestinal permeability, an altered microbiome and activation of inflammatory pathways

associated with the disease in humans. Notably, female mice, typically resistant to high fat diet (HFD)-induced obesity and NAFLD, developed full disease characteristics at thermoneutrality. These findings have important biomedical implications as NAFLD, which often leads to cirrhosis and hepatocellular carcinoma, is the most common chronic liver disease worldwide.

A longstanding and productive collaboration among the Jordan, [Katz](#), and Hildeman labs has made considerable progress on its primary goal of controlling autoreactive T cells as a means of treating ongoing autoimmune disease. The use of p53 potentiation, with checkpoint abrogation (PPCA) therapy, demonstrates remarkable efficacy in mouse models of multiple sclerosis (MS) and type 1 diabetes (T1D). With T1D, the data shows that new onset diabetic NOD mice benefit from PPCA therapy with an increase in the remission period or outright reversal of T1D. As part of our center for transplant immunology, to both solid organ (heart, islet) transplant models, expanded use of this new therapeutic approach is showing signs of success.

Inter-Disciplinary Collaborations and Grants

[Dr. Claire Chougnet, PhD](#), is leading an [ARC](#) proposal focused on inflammation and pre-term birth that has obtained an [NIH UO1 award](#). This will enable the collaborative team to robustly advance the primate model for analysis of pre-term birth complications as well as gain fundamental insights into the development and functioning of the neonatal and infant immune systems.

[Dr. David Hildeman, PhD](#), in collaborations with [Dr. Steve Woodle, MD](#), from the [University of Cincinnati College of Medicine](#), are focusing on targeting of allograft immune responses in kidney transplantation. Funding obtained from [Novartis](#) and [Sanofi](#) will allow exploration of lymphocyte responses and resistance mechanisms in patients on therapies.

[Dr. Harinder Singh, PhD](#), in a collaboration with Dr. Woodle and [Dr. Jim Driscoll, MD, PhD](#), both from University of Cincinnati College of Medicine, launched a collaborative effort to uncover genomic responses and molecular pathways that underlie resistance and rebound of plasma cells to proteasome inhibitor therapy. This therapeutic modality is being tested clinically to achieve desensitization in patients with pre-existing allo-reactive antibodies before organ transplantation.

Faculty Development, Promotion, and Recruitment

[Dr. Mike Jordan, MD](#), promoted to a full professor based on his outstanding research accomplishments in elucidating the cellular and molecular bases of HLH as well as other genetically caused immune deficiencies.

Cincinnati Children's recruited John Hogenesch to a joint appointment in the Division of Immunobiology and research space in the Center for Systems Immunology (T5). John is an accomplished systems biologist with a focus on the circadian clock. He plans to collaborate with immunologists in exploring the actions of the circadian clock on immune responses.

[Dr. Emily Miraldi, PhD](#), obtained a trustee award to advance her promising career in computational immunology.

Training Grants

National Institutes of Health (NIH) awarded NIH T32 (2016-21) funding to Cincinnati Children's due to the tireless and superb efforts of [Dr. Dave Hildeman, PhD](#), as well as faculty mentors along with past and current PhD trainees. This is a first for the [Immunology Graduate Program](#) at Cincinnati Children's. It is a highly competitive award that represents a superb return on a long term academic vision and investment in Immunology. The [DFG](#) sponsored IRTG (2017-21) has been successfully renewed. The continuation of this international training program with Universities of [Lubeck](#) and [Kiehl](#) in Germany is a superb testimonial to our faculty, and students, who gave compelling research presentations and testimonials at a site visit in Lubeck.

Division Publications

1. Olsson A; Venkatasubramanian M; Chaudhri VK; Aronow BJ; Salomonis N; Singh H; Grimes HL. [Single-cell analysis of mixed-lineage states leading to a binary cell fate choice](#). *Nature*. 2016; 537:698-702.

2. Fischer K; Ruiz HH; Jhun K; Finan B; Oberlin DJ; van der Heide V; Kalinovich AV; Petrovic N; Wolf Y; Clemmensen C. **Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis.** *Nature Medicine*. 2017; 23:623-630.
3. Kesarwani M; Kincaid Z; Gomaa A; Huber E; Rohrabough S; Siddiqui Z; Bouso MF; Latif T; Xu M; Komurov K. **Targeting c-FOS and DUSP1 abrogates intrinsic resistance to tyrosine-kinase inhibitor therapy in BCR-ABL-induced leukemia.** *Nature Medicine*. 2017; 23:472-482.
4. Fang J; Liu X; Bolanos L; Barker B; Rigolino C; Cortelezzi A; Oliva EN; Cuzzola M; Grimes HL; Fontanillo C. **A calcium- and calpain-dependent pathway determines the response to lenalidomide in myelodysplastic syndromes.** *Nature Medicine*. 2016; 22:727-734.
5. Karwacz K; Miraldi ER; Pokrovskii M; Madi A; Yosef N; Wortman I; Chen X; Watters A; Carriero N; Awasthi A. **Critical role of IRF1 and BATF in forming chromatin landscape during type 1 regulatory cell differentiation.** *Nature Immunology*. 2017; 18:412-421.
6. Gray J; Oehrlé K; Worthen G; Alenghat T; Whitsett J; Deshmukh H. **Intestinal commensal bacteria mediate lung mucosal immunity and promote resistance of newborn mice to infection.** *Science Translational Medicine*. 2017; 9:eaaf9412.
7. Hall SL; Baker T; Lajoie S; Richgels PK; Yang Y; McAlees JW; van Lier A; Wills-Karp M; Sivaprasad U; Acciani TH. **IL-17A enhances IL-13 activity by enhancing IL-13-induced signal transducer and activator of transcription 6 activation.** *Journal of Allergy and Clinical Immunology*. 2017; 139:462-471.e14.
8. Chandrakasan S; Jayavaradhan R; Ernst J; Shrestha A; Loberg A; Dexheimer P; Jordan M; Pang Q; Aronow B; Malik P. **KIT blockade is sufficient for donor hematopoietic stem cell engraftment in Fanconi anemia mice.** *Blood*. 2017; 129:1048-1052.
9. Lo B; Fritz JM; Su HC; Uzel G; Jordan MB; Lenardo MJ. **CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency.** *Blood*. 2016; 128:1037-1042.
10. Lages CS; Simmons J; Maddox A; Jones K; Karns R; Sheridan R; Shanmukhappa SK; Mohanty S; Kofron M; Russo P. **The Dendritic Cell-T Helper 17-Macrophage Axis Controls Cholangiocyte Injury and Disease Progression in Murine and Human Biliary Atresia.** *Hepatology*. 2017; 65:174-188.
11. Vollmer LL; Ghosal S; McGuire JL; Ahlbrand RL; Li KY; Santin JM; Ratliff-Rang CA; Patrone LGA; Rush J; Lewkowich IP. **Microglial Acid Sensing Regulates Carbon Dioxide-Evoked Fear.** *Biological Psychiatry*. 2016; 80:541-551.
12. Li KP; Shanmuganad S; Carroll K; Katz JD; Jordan MB; Hildeman DA. **Dying to protect: cell death and the control of T-cell homeostasis.** *Immunological Reviews*. 2017; 277:21-43.
13. McNally JP; Millen SH; Chaturvedi V; Lakes N; Terrell CE; Elfers EE; Carroll KR; Hogan SP; Andreassen PR; Kanter J. **Manipulating DNA damage-response signaling for the treatment of immune-mediated diseases.** *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114:E4782-E4791.
14. Ladle BH; Li KP; Phillips MJ; Pucsek AB; Haile A; Powell JD; Jaffee EM; Hildeman DA; Gamper CJ. **De novo DNA methylation by DNA methyltransferase 3a controls early effector CD8+ T- cell fate decisions following activation.** *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113:10631-10636.
15. Vander Lugt B; Riddell J; Khan AA; Hackney JA; Lesch J; DeVoss J; Weirauch MT; Singh H; Mellman I. **Transcriptional determinants of tolerogenic and immunogenic states during dendritic cell maturation.** *The Journal of Cell Biology*. 2017; 216:779-792.
16. Berberich I; Hildeman DA. **The Bcl2a1 gene cluster finally knocked out: first clues to understanding the enigmatic role of the Bcl-2 protein A1.** *Cell Death and Differentiation*. 2017; 24:572-574.
17. Navabi N; Whitt J; Wu SE; Woo V; Moncivaiz J; Jordan MB; Vallance BA; Way SS; Alenghat T. **Epithelial Histone Deacetylase 3 Instructs Intestinal Immunity by Coordinating Local Lymphocyte Activation.** *Cell Reports*. 2017; 19:1165-1175.

18. Vignesh KS; Figueroa JAL; Porollo A; Divanovic S; Caruso JA; Jr DGS. **IL-4 Induces Metallothionein 3-and SLC30A4-Dependent Increase in Intracellular Zn²⁺ that Promotes Pathogen Persistence in Macrophages.** *Cell Reports*. 2016; 16:3232-3246.
19. Alder MN; Opoka AM; Lahni P; Hildeman DA; Wong HR. **Olfactomedin-4 Is a Candidate Marker for a Pathogenic Neutrophil Subset in Septic Shock.** *Critical Care Medicine*. 2017; 45:e426-e432.
20. Woo V; Alenghat T. **Host-microbiota interactions: epigenomic regulation.** *Current Opinion in Immunology*. 2017; 44:52-60.
21. Senthamaraiakannan P; Presicce P; Rueda CM; Maneenil G; Schmidt AF; Miller LA; Waites KB; Jobe AH; Kallapur SG; Chougnet CA. **Intra-amniotic Ureaplasma parvum-Induced Maternal and Fetal Inflammation and Immune Responses in Rhesus Macaques.** *Journal of Infectious Diseases*. 2016; 214:1597-1604.
22. Xie W; Chen S; Strong JA; Li AL; Lewkowich IP; Zhang JM. **Localized Sympathectomy Reduces Mechanical Hypersensitivity by Restoring Normal Immune Homeostasis in Rat Models of Inflammatory Pain.** *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2016; 36:8712-8725.
23. Giles DA; Ramkhelawon B; Donelan EM; Stankiewicz TE; Hutchison SB; Mukherjee R; Cappelletti M; Karns R; Karp CL; Moore KJ. **Modulation of ambient temperature promotes inflammation and initiates atherosclerosis in wild type C57BL/6 mice.** *Molecular Metabolism*. 2016; 5:1121-1130.
24. Li KP; Fähnrich A; Roy E; Cuda CM; Grimes HL; Perlman HR; Kalies K; Hildeman DA. **Temporal Expression of Bim Limits the Development of Agonist-Selected Thymocytes and Skews Their TCR beta Repertoire.** *Journal of immunology (Baltimore, Md. : 1950)*. 2017; 198:257-269.
25. Schmidt AF; Kannan PS; Chougnet CA; Danzer SC; Miller LA; Jobe AH; Kallapur SG. **Intra-amniotic LPS causes acute neuroinflammation in preterm rhesus macaques.** *Journal of Neuroinflammation*. 2016; 13:238.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Claire A Chougnet, PhD	Host-microbe Cross-talk and Pregnancy Outcomes	Burroughs Wellcome Foundation (University of Cincinnati)	CHougnet BWF 1010626	06/01/2013 - 03/31/2018	\$150,000
Ian P Lewkowich	Mechanisms of IL-17A-mediated Enhancement of Asthma Severity	National Institutes of Health	R01 HL122300	05/01/2014 - 02/28/2019	\$555,697
Alexey Porollo, PhD	Suppression of IgE-Mediated Disease by Polyclonal Rapid Desensitization	National Institutes of Health (University of Cincinnati)	R01 AI113162	07/15/2014 - 06/30/2018	\$89,784
Michael B Jordan, MD David A Hildeman, PhD	Exploiting the DNA Damage Response to Selectively Sculpt the T Cell Repertoire	National Institutes of Health	R01 AI109810	07/15/2014 - 03/31/2018	\$390,000
James Mulloy, PhD	Rapid Suppression of Food Allergy with Anti-FcεRIα Antibody	Intermountain Medical Center (University of Cincinnati)	Finkelman/Krishnamur	07/22/2014 - 09/29/2017	\$84,128
Harinder Singh, PhD	Distinct functional Outcomes	National Institutes of Health	R01 AR066808	03/12/2015	\$68,640

	of BCR/TLR7 and BCR/TLR9 Co-Engagement	Health (Univ of Massachusetts Medical School)		- 02/29/2020	
Edith Janssen, PhD	CD244 Targeting Therapeutics in SLE	Lupus Research Institute	LRI_Janssen	01/01/2015 - 12/31/2017	\$100,000
Julio Aliberti, PhD	Lipoxins and Control of Inflammation during Cerebral Malaria	National Institutes of Health	R21 AI118302	07/01/2015 - 09/16/2016	\$195,000
Heping Xu, PhD	Interplay of IRF4 and IRF8 in Orchestrating Cell Fate Dynamics of Germinal Center B Cells	The Leukemia and Lymphoma Society	Xu LLS CDP	07/01/2015 - 06/30/2018	\$55,000
Theresa Alenghat	Epigenomic Regulation of the Host-commensal Relationship	Burroughs Wellcome Foundation (University of Cincinnati)	Alenghat UC/BWF	09/01/2014 - 08/31/2019	\$140,000
Theresa Alenghat	Epigenomic regulation of Host-microbiota Interactions	The Pew Charitable Trusts	Alenghat PEWS 15-16	08/01/2015 - 07/31/2019	\$60,000
Harry Leighton Grimes, PhD	Mechanisms of Granulocyte Homeostasis	National Institutes of Health	R01 HL122661	07/01/2015 - 04/30/2019	\$390,000
Senad Divanovic, PhD	Immune Mechanisms of Inflammation-induced Preterm Birth	Burroughs Wellcome Foundation (University of Cincinnati)	Senad BWF 1015032	06/01/2015 - 03/31/2019	\$150,000
Edith Janssen, PhD	Effect of Different MRgHIFU Approaches on Anti-tumor Responses	National Institutes of Health	R03 CA201918	01/19/2016 - 12/31/2017	\$78,000
Theresa Alenghat	Epigenomic Integration of Microbiota-derived Signals in the Pathogenesis of IBD	Crohn's & Colitis Foundation of America	Alenghat CCFA 2015	10/01/2015 - 09/30/2018	\$100,000
Ian P Lewkowich	Study of Activity-Dependent Sympathetic Sprouting	National Institutes of Health (University of Cincinnati)	R01 NS045594	02/01/2016 - 01/31/2021	\$7,499
David A Hildeman, PhD	Pathogenesis and Therapeutic Targeting of Immune Disorders	National Institutes of Health	T32 AI118697	07/01/2016 - 06/30/2021	\$140,586
Claire A Chougnnet, PhD	Mechanistic and Therapeutic Role of the CD137-CD137L Axis in Type 1 Diabetes	National Institutes of Health (University of Cincinnati)	R01 DK107541	07/21/2016 - 06/30/2021	\$36,743
David A Hildeman, PhD	PEARL: Pathway Exploration and Analysis in Renal Lupus	National Institutes of Health (Feinstein	UH2 AR067688	06/01/2015 -	\$86,561

		Institute for Medical Research)			05/31/2019	
Harry Leighton Grimes, PhD	A Rapid Spontaneous Murine Model of CN-AML	National Institutes of Health	R01 CA196658	09/01/2016	\$625,379	-
				08/31/2019		
Ian P Lewkowich	Studies to Assess Inflammation and Microglial Activation in Panic/PTSD Animal Models	Department of Veteran Affairs	Lewkowich IPA 16-18	03/01/2016	\$9,798	-
				02/28/2018		
Michael B Jordan, MD	Mechanisms of LRBA-mediated Immune Regulation	Jeffrey Modell Foundation	Jordan JMF Translati	09/01/2016	\$50,000	-
				08/31/2018		
Harinder Singh, PhD	Murine Memory B Cell Development and Function	National Institutes of Health (University of Pittsburgh)	R56 AI043603	08/22/2016	\$59,280	-
				07/31/2021		
Harry Leighton Grimes, PhD	Novel Targets to Cure Pediatric Leukemia	Cancer Free Kids	Grimes CFK 2016	07/01/2016	\$50,000	-
				06/30/2017		
Ian P Lewkowich	Impact of Prenatal HDM Exposure in Severely Asthmatic Mothers on Offspring Asthma	National Institutes of Health	R21 AI119385	12/01/2016	\$234,000	-
				11/30/2018		
Claire A Chougnet, PhD	Direct Interactions with HDL Promote Regulatory T Cells Survival	National Institutes of Health	R21 AI128218	12/01/2016	\$248,945	-
				11/30/2018		
Senad Divanovic, PhD	Immunopathogenesis of Non-alcoholic Fatty Liver Disease	National Institutes of Health	R01 DK099222	08/01/2016	\$332,775	-
				07/31/2018		
Harry Leighton Grimes, PhD	American Society of Hematology Career Development	American Society of Hematology	ASH Career Developme	07/01/2016	\$42,000	-
				06/30/2017		
Janssen PhD,Edith Chougnet PhD,Claire A	Metabolic Alterations in Age-associated Dendritic Cell Dysfunction	National Institutes of Health	R01 AG053498	03/01/2017	\$507,778	-
				02/28/2022		
Jordan MD,Michael B Herr PhD,Andrew	Mechanisms of LRBAmediated control of CTLA4	National Institutes of Health	R21 AI132822	06/01/2017	\$234,000	-
				05/31/2019		
Harry Leighton Grimes, PhD	Translational Utility of New Models of Human AML	Alex's Lemonade Stand Foundation		06/19/2017	\$5,000	-
				08/20/2017		
Suhas G Kallapur, MD David A Hildeman, PhD Andrew Herr, PhD	Novel Therapeutic Target for Intrauterine Inflammation	National Institutes of Health	R21 HD090856	12/10/2016	\$156,000	-
				11/30/2018		

Louis Muglia	Maternal Temperament,	National Institutes of	R01 HD078127	09/01/2016	\$188,569.50
Claire A Chougnat,	Stress, and Inflammation in	Health		-	
PhD	Preterm Birth			08/31/2017	

Total Annual Grant Award Dollars

\$5,621,162.50

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Andrew Herr, PhD	Airway Therapeutics & Steve Linberg	\$33,710
Edith Janssen, PhD	Roche Laboratories, Inc.	\$228,150
Michael B Jordan, MD	NantKwest, Inc.	\$52,000
Total Annual Industry Award Dollars		\$313,860
