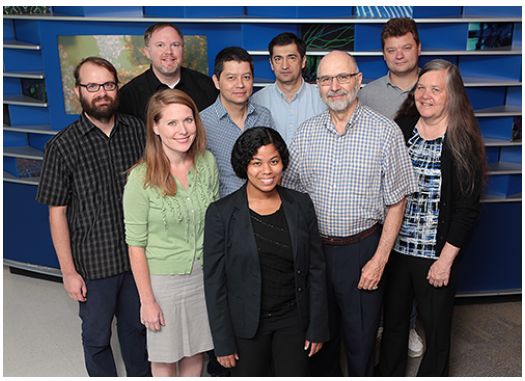
Center for Autoimmune Genomics and Etiology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**11**
Joint Appointment Faculty	**3**
Research Fellows and Post Docs	**9**
Research Graduate Students	**10**
Total Annual Grant Award Dollars	**$4,503,474**



Row 1: H Moncrieffe, L Kottyan, J Harley, M Weirauch, I Chepelev, S Thompson, S Waggoner, B Namjou, A Porollo

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Division Highlights

John Harley, MD, PhD, joins the Autoimmune Disease Prevention Network

An important research accomplishment has been the funding of U01AI130830 for the Autoimmune Disease Prevention Network and becoming the administrative site for the Infrastructure and Opportunities Fund for this initiative from the National Institute of Allergy and Infectious Diseases (NIAID). Indeed, this accomplishment makes Cincinnati Children's one of the premier institutions for autoimmune research and a collaborative member of the best investigative units in the country, led by investigators at the University of Colorado and Stanford University, to mention two of the other five members of this consortium.

Multiple Sclerosis funding awarded to first time R01 recipient, Matthew Weirauch, PhD

Another important accomplishment has been the funding of Dr. Matthew Weirauch's first R01 focused on Multiple Sclerosis (MS). Indeed, it is quite unusual for someone who has never published on this disease to be able to obtain National Institutes of Health R01 funding. This speaks to the importance of our preliminary data. We have found associations using the transcription factors made from the DNA of a virus with the genes that alter the risk of MS. These associations nominate molecular interactions that may show us how the virus causes MS. Work by others has led the community of investigators trying to solve the origins of MS to conclude the involvement of Epstein-Barr virus in causing MS. Our work holds great promise to reveal how this happens, thereby providing the insights and basic knowledge that will lead to new management and therapies for MS patients.

Kenneth Kaufman, PhD, made new discoveries regarding the pathogenesis of rheumatoid arthritis

Working with colleagues, Drs. John Harley, MD, PhD, and Matthew Weirauch, PhD, in the Center for Autoimmune Genomics and Etiology, and the University of Michigan, Dr. Kenneth Kaufman, PhD, has been studying viral infection in the fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis. Identification of viral DNA in the FLS from all rheumatoid arthritis and osteoarthritis samples tested was surprising. Currently, Dr. Kaufman is working on identifying the strain of the virus infecting these cells, characterizing the frequency of infection in the cells and studying the effect the virus has on human gene expression. Interestingly, Dr. Weirauch's work has shown that

rheumatoid arthritis genetic risk loci are statistically enriched for specific viral transcription binding sites. These findings suggest that the effect of viral infection on human gene expression may differ based on the presence or absence of rheumatoid arthritis risk alleles and that these differences may play a role in the pathogenesis of rheumatoid arthritis.

Dr. Kaufman continues to work with many collaborators at Cincinnati Children's to utilize next-generation DNA sequencing and micro array technologies to identify polymorphisms that lead to disease. These studies cover a wide range of phenotypes and diseases including: eosinophilic esophagitis with Dr. Marc Rothenberg, PhD (Division of Allergy and Immunology), macrophage activation syndrome with Dr. Alexi Grom, MD (Division of Rheumatology), cardiomyopathy in patients with sickle cell anemia with Dr. Punam Malik, MD (Division of Experimental Hematology and Cancer Biology), tracheal ring deformity with Dr. Paul Kingma, MD, PhD (Divisions of Neonatology and Pulmonary Biology), and others.

Susan Thompson, PhD, performs ongoing JIA genetic studies

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, and describes a group of clinically heterogeneous arthritides which begin before the age of 16 years, persist for at least six weeks and have an unknown cause. Genome-wide association (GWAS) and Immunochip studies led by the Thompson lab using high-density single nucleotide polymorphism (SNP) arrays have identified 35 associations to date between common genetic variations (minor allele frequency (MAF) > 5%) and JIA. Interestingly, while JIA patients share clinical and pathological features with adult rheumatoid arthritis (RA) patients, we have found that only about 1/2 of the genetic associations reported in JIA overlap with those reported in adult rheumatoid arthritis. Comparing adult and pediatric forms of arthritis has the potential to identify disease mechanisms and causes specific to the developing pediatric immune system. Fine mapping within the HLA has allowed us to classify subcategories of JIA and delineate differences from adult arthritis based on unique amino acids present in the antigen binding pocket of the class II HLA-DRB1 molecule. Genetic approaches application can assist in understanding response to medications. For example, methotrexate, is a drug that is widely used to treat arthritis in children, but it is only effective in ~30% of patients. Identification of genetic variation that will predict patient response to methotrexate and molecular markers of methotrexate metabolism is being used to generate genomic profiles that will help clinicians choose the most appropriate therapy for rapid and effective treatment of childhood arthritis.

Alexey Porollo, PhD, published results from pneumocystis pneumonia (PCP) pathogenesis R01

The study of pneumocystis pneumonia (PCP) pathogenesis in the mouse model has National Institutes of Health (NIH) funding for five years, R01HL119190. Dr. Alexey Porollo, PhD, has completed an RNA-seq analysis of the host, pathogen, and associated lung microbiome. The identified mouse genes perturbed through the progress of PCP, enabling the elucidation of biological pathways and cell types involved in combating the fungal infection. Functional genomics of the pathogenic fungus (pneumocystis murina), its metabolic strategies for acquiring nutrients and interaction with the revealation of the host. Directed supplementation experiments established a long term culture for the non-cultivable fungus. To perform a metatranscriptome analysis of the RNA-seq data containing a complex mixture of host, pathogen and bacterial transcripts, researchers developed a new computational workflow. Published results are in peer-reviewed journals, including *mBio* and *Microbiome*. The study lays the foundation for a formulation of the culture media permitting a long term cultivation of the parasitic fungus and for identifying new drug targets within the persistent opportunistic pathogen.

Nan Shen, MD, PhD, identified a functional genetic variant causing amino acid replacement in neutrophil cystolic factor 1

Working with colleagues at the Medical University of South Carolina and Shanghai Jiao Tong University, Dr. Shen's group has identified a functional genetic variant causing amino acid replacement in neutrophil cystolic factor 1 (NCF1), leading to a lower capacity of inducing oxidative burst, that is strongly associated with several common autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome among different ethnic patients' cohorts. The published study is found in *Nature Genetics*. The data provide an elegant strategy to define the genetic causal variant located at a complex genomic region missed by a conventional genome wide association study (GWAS) approach and highlight the pathogenic role of reduced reactive oxygen species in autoimmune disease development.

Improved understanding of lupus and psoriatic arthritis etiology; Iouri Chepelev, PhD

In studies funded by the Lupus Research Institute, Arthritis National Research Foundation and National Psoriasis Foundation, Iouri Chepelev, PhD, has been investigating genetic and molecular mechanisms of regulation of some genes implicated in the pathogenesis of systemic lupus erythematosus and psoriatic arthritis. His laboratory has mapped out detailed 3-dimensional structures of human genome in immune cells to better understand the regulation of these genes. The data generated in these studies will reveal some genetic interactions involved in the etiology of lupus, and psoriatic arthritis, and will provide a strong foundation for his future studies on the genetic basis of these diseases.

Natural killer cells in cytomegalovirus vaccination; new findings by Stephen Waggoner, PhD

In this Center for Clinical & Translational Science & Training (CCTST) funded study, Dr. Stephen Waggoner, PhD, and colleagues, evaluated the functionality and inducibility of unique subsets of human natural killer cells associated with cytomegalovirus infection. The goal was to determine whether subsets of natural killer cells normally present only in cytomegalovirus infected individuals, can develop if stimulated following administration of a cytomegalovirus vaccine. A secondary goal was to determine the functional contribution of these cells as a means to ascertain the value of intentionally triggering the development of these cells during immunization. The study involved a collaboration with Drs. David Bernstein, MD, MA (Division of Infectious Diseases) and Yenan Bryceson, PhD (Karolinska Institute), and made use of a unique set of longitudinal blood samples collected from adolescent cytomegalovirus-negative women receiving an experiment cytomegalovirus vaccine. The results reveal important functions of these natural killer cells, and remarkably demonstrate the appearance of the natural killer subset in cytomegalovirus-negative individuals at time points after vaccine administration. These findings will be important in the design of next generation vaccines to prevent diseases associated with congenital cytomegalovirus infection.

Bahram Namjou, MD, continues to uncover genetic associations of NAFLD, appendicitis and early onset migraine

In this National Human Genome Research Institute (NHGRI) funded study (U01HG008666; PI Harley), Bahram Namjou-Khales, MD, and colleagues from the Electronic Medical Records and Genomics (eMERGE) Network developed NLP phenotype algorithms, identified and obtained cases and controls from the Cincinnati Biobank, and genotyped new subjects for eMERGE Network-wide GWAS and PheWAS studies. The goal of these projects is to expand the genetic knowledgebase for different phenotypes, specifically those important in pediatrics. In FY 17, finalization of phenotype algorithms for non-alcoholic fatty liver condition (NAFLD/NASH), appendicitis and early onset migraine occurred.

Ongoing genomic discovery in the laboratory of Leah Kottyan, PhD

The Kottyan lab continues their work elucidating the genetic causal variants at the risk loci associated with systemic lupus erythematosus and eosinophilic esophagitis. Through collaboration, the lab is also participating in functional genomic projects to understand preterm birth, autoimmune liver disease, and response to therapy in patients with attention deficit hyperactivity disease (ADHD).

Halima Moncrieffe, PhD, transcriptional profiles of JIA patient blood with subsequent poor response to methotrexate

Dr. Halima Moncrieffe, PhD, and colleagues, performed a multi-site study to identify a gene expression profile that associates with response to methotrexate in children with juvenile idiopathic arthritis (JIA). Methotrexate remains the first line disease-modifying anti-rheumatic drugs (DMARD) therapy for patients with JIA,; with a good response seen in less than half of patients. The first signs of a good response are not usually seen until at least six-eight weeks into the treatment, and it may take several months to achieve the full benefit of this treatment. To our knowledge, this is the first demonstration that suggests a cell-type specific signature associated with MTX non-response in patients with JIA. This method of identifying gene expression patterns specific to cell populations may be a valuable tool in understanding the complex mechanisms of drug response and enable greater precision in treatment selection for patients with JIA.

Division Publications

1. Fang J; Bolanos LC; Choi K; Liu X; Christie S; Akunuru S; Kumar R; Wang D; Chen X; Greis KD. **Ubiquitination of hnRNPA1 by TRAF6 links chronic innate immune signaling with myelodysplasia.** *Nature Immunology*. 2017; 18:236-245.

2. Almoguera B; Vazquez L; Mentch F; Connolly J; Pacheco JA; Sundaresan AS; Peissig PL; Linneman JG; McCarty CA; Crosslin D. **Identification of Four Novel Loci in Asthma in European American and African American Populations.** *American journal of respiratory and critical care medicine*. 2017; 195:456-463.

3. Litosh VA; Rochman M; Rymer JK; Porollo A; Kottyan LC; Rothenberg ME. **Calpain-14 and its association with eosinophilic esophagitis.** *Journal of Allergy and Clinical Immunology*. 2017; 139:1762-1771.e7.

4. Ombrello MJ; Arthur VL; Remmers EF; Hinks A; Tachmazidou I; Grom AA; Foell D; Martini A; Gattorno M; Özen S. **Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications.** *Annals of the rheumatic diseases*. 2017; 76:906-913.

5. Hinks A; Bowes J; Cobb J; Ainsworth HC; Marion MC; Comeau ME; Sudman M; Han B; Juvenile Arthritis Consortium for Immunochip; Becker ML. **Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases.** *Annals of the rheumatic diseases*. 2017; 76:765-772.

6. Young KA; Munroe ME; Guthridge JM; Kamen DL; Niewold TB; Gilkeson GS; Weisman MH; Ishimori ML; Kelly J; Gaffney PM. **Combined role of vitamin D status and CYP24A1 in the transition to systemic lupus erythematosus.** *Annals of the rheumatic diseases*. 2017; 76:153-158.

7. Deng Y; Zhao J; Sakurai D; Sestak AL; Osadchiy V; Langefeld CD; Kaufman KM; Kelly JA; James JA; Petri MA. **Decreased SMG7 expression associates with lupus-risk variants and elevated antinuclear antibody production.** *Annals of the rheumatic diseases*. 2016; 75:2007-2013.

8. Munroe ME; Lu R; Zhao YD; Fife DA; Robertson JM; Guthridge JM; Niewold TB; Tsokos GC; Keith MP; Harley JB. **Altered type II interferon precedes autoantibody accrual and elevated type i interferon activity prior to systemic lupus erythematosus classification.** *Annals of the rheumatic diseases*. 2016; 75:2014-2021.

9. Guo H; Cranert SA; Lu Y; Zhong MC; Zhang S; Chen J; Li R; Mahl SE; Wu N; Davidson D. **Deletion of Slam locus in mice reveals inhibitory role of SLAM family in NK cell responses regulated by cytokines and LFA-1.** *The Journal of Experimental Medicine*. 2016; 213:2187-2207.

10. Mao AP; Constantinides MG; Mathew R; Zuo Z; Chen X; Weirauch MT; Bendelac A. **Multiple layers of transcriptional regulation by PLZF in NKT-cell development.** *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113:7602-7607.

11. Cox JW; Ballweg RA; Taft DH; Velayutham P; Haslam DB; Porollo A. **A fast and robust protocol for metataxonomic analysis using RNAseq data.** *Microbiome*. 2017; 5:7.

12. 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.

13. Imai F; Chen X; Weirauch MT; Yoshida Y. **Requirement for Dicer in Maintenance of Monosynaptic Sensory-Motor Circuits in the Spinal Cord.** *Cell Reports*. 2016; 17:2163-2172.

14. 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.

15. Lu R; Munroe ME; Guthridge JM; Bean KM; Fife DA; Chen H; Slight-Webb SR; Keith MP; Harley JB; James JA. **Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies.** *Journal of Autoimmunity*. 2016; 74:182-193.

16. Li H; Reksten TR; Ice JA; Kelly JA; Adrianto I; Rasmussen A; Wang S; He B; Grundahl KM; Glenn SB. **Identification of a Sjogren's syndrome susceptibility locus at OAS1 that influences isoform switching, protein expression, and responsiveness to type I interferons.** *PLoS genetics*. 2017; 13:e1006820.

17. Verma SS; Cooke Bailey JN; Lucas A; Bradford Y; Linneman JG; Hauser MA; Pasquale LR; Peissig PL; Brilliant MH; McCarty CA. **Epistatic Gene-Based Interaction Analyses for Glaucoma in eMERGE and NEIGHBOR Consortium.** *PLoS genetics*. 2016; 12:e1006186.

18. Bush WS; Crosslin DR; Owusu-Obeng A; Wallace J; Almoguera B; Basford MA; Bielinski SJ; Carrell DS; Connolly JJ; Crawford D. **Genetic variation among 82 pharmacogenes: The PGRNseq data from the eMERGE network..** *Clinical Pharmacology and Therapeutics*. 2016; 100:160-169.

19. Cushion MT; Collins MS; Sesterhenn T; Porollo A; Vadukoot AK; Merinod EJ. **Functional Characterization of Pneumocystis carinii Inositol Transporter 1.** *mBio*. 2016; 7:e01851-16.

20. Kottyan LC; Rothenberg ME. **Genetics of eosinophilic esophagitis.** *Mucosal immunology*. 2017; 10:580-588.

21. Merkel PA; Xie G; Monach PA; Ji X; Ciavatta DJ; Byun J; Pinder BD; Zhao A; Zhang J; Tadesse Y. **Identification of Functional and Expression Polymorphisms Associated With Risk for Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis.** *Arthritis and Rheumatology*. 2017; 69:1054-1066.

22. Munroe ME; Young KA; Kamen DL; Guthridge JM; Niewold TB; Costenbader KH; Weisman MH; Ishimori ML; Wallace DJ; Gilkeson GS. **Discerning Risk of Disease Transition in Relatives of Systemic Lupus Erythematosus Patients Utilizing Soluble Mediators and Clinical Features.** *Arthritis and Rheumatology*. 2017; 69:630-642.

23. Han X; Wang Y; Zhang X; Qin Y; Qu B; Wu L; Ma J; Zhou Z; Qian J; Dai M. **MicroRNA-130b Ameliorates Murine Lupus Nephritis Through Targeting the Type I Interferon Pathway on Renal Mesangial Cells.** *Arthritis and Rheumatology*. 2016; 68:2232-2243.

24. Schulert GS; Fall N; Harley JB; Shen N; Lovell DJ; Thornton S; Grom AA. **Monocyte MicroRNA Expression in Active Systemic Juvenile Idiopathic Arthritis Implicates MicroRNA-125a-5p in Polarized Monocyte Phenotypes.** *Arthritis and Rheumatology*. 2016; 68:2300-2313.

25. Dauber A; Cunha-Silva M; Macedo DB; Brito VN; Abreu AP; Roberts SA; Montenegro LR; Andrew M; Kirby A; Weirauch MT. **Paternally Inherited DLK1 Deletion Associated With Familial Central Precocious Puberty.** *Journal of Clinical Endocrinology and Metabolism*. 2017; 102:1557-1567.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Alexey Porollo, PhD	GM-CSF-Induced Metal Sequestration and Histoplasma	National Institutes of Health (University of Cincinnati)	R01 AI106269	05/15/2013 - 04/30/2018	$29,789
Alexey Porollo, PhD	Directed Culturing of Pneumocystis Using Metatranscriptomics	National Institutes of Health (University of Cincinnati)	R01 HL119190	05/22/2013 - 02/28/2018	$227,931
Stephen Waggoner, PhD	A Revolutionary Approach to an Efficacious HIV Vaccine	National Institutes of Health	DP1 DA038017	06/01/2014 - 05/31/2019	$780,000
Matthew Tyson Weirauch,	Effect of Disease-associated	National Institutes of Health	R21 HG008186	12/15/2014	$156,000

PhD	Genetic Variants on Viral Protein DNA Binding			- 11/30/2017	
Iouri Chepelev, PhD	Identification of Lupus Causal Variants at BLK Locus by Mapping 3D Genome	Lupus Research Institute	LRI_Chepelev	01/01/2015 - 12/31/2017	$100,000
Carolyn Rydyznski	A Follicular Regulatory Subset of Natural Killer Cells	National Institutes of Health	F31 AI118179	05/03/2015 - 05/02/2018	$36,504
Iouri Chepelev, PhD	Psoriatic Arthritis Causal Noncoding Genetic Variants in IL-23 Pathway	National Psoriasis Foundation	ANRF_Chepelev	07/01/2015 - 06/30/2017	$100,000
John Harley, MD, PhD	Better Outcomes for Children: Promoting Excellence in Healthcare Genomics to Inform Policy	National Institutes of Health	U01 HG008666	09/01/2015 - 05/31/2019	$117,184
Matthew Tyson Weirauch, PhD	Data Coordination and Integration Center for LINCS-BD2K	National Institutes of Health (Icahn School of Medicine @ Mt Sinai)	U54 HL127624	09/29/2014 - 04/30/2019	$18,455
Matthew Tyson Weirauch, PhD	A Free Website for Discovering Non-coding Lupus-associated Variant Function	Lupus Research Institute	LRI_Weirauch	01/01/2016 - 12/31/2018	$100,000
Susan D Thompson, PhD	Cincinnati Rheumatic Diseases Resource Center	National Institutes of Health	P30 AR070549	08/01/2016 - 07/31/2021	$785,983
Leah C. Kottyan, PhD	Mechanisms of Genetic Risk at 2p23 in Eosinophilic Esophagitis	National Institutes of Health	R01 DK107502	09/01/2016 - 08/31/2021	$351,000
John Harley, MD, PhD	Genetic Linkage in Lupus	National Institutes of Health	R01 AI024717	06/16/2016 - 05/31/2021	$390,000
Leah C. Kottyan, PhD	Mechanisms of Genetic Risk at 2p23 in Eosinophilic Esophagitis	Am Partnership for Eosinophilic Disorder	Kottyan_Apfed	04/12/2016 - 04/11/2018	$50,000
Halima Moncrieffe	AAI Travel Grant for the International Congress of Immunology 2016	American Association of Immunologists	AAI_Moncrieffe	08/01/2016 - 09/30/2016	$2,500
Stephen Waggoner, PhD	Cytotoxic Control of Immunoglobulin A and Colitis by Innate Lymphoid Cells	Crohn's & Colitis Foundation of America	439543	05/29/2016 - 08/28/2016	$2,500
Seth Reighard	Treatment of Lupus Nephritis using PD-L1-expressing Natural Killer Cells	Lupus Foundation of America	LF_Reighard	05/16/2016 - 10/15/2016	$4,000

Kenneth Kaufman, PhD	Genetic Susceptibility for Occupational Asthma	National Institutes of Health (University of Cincinnati)	R01 OH008795	04/01/2016 - 08/31/2017	$55,519
John Harley, MD, PhD	Gene Regulation as a Foundation for Autoimmune Disease Prevention	National Institutes of Health	U01 AI130830	05/31/2017 - 05/31/2022	$547,118
Stephen Waggoner, PhD	Harnessing Natural Killer Cells to Treat Lupus and Other Autoimmune Diseases	Dr. Ralph & Marian Falk Med Res Trust Aw	Falk_Waggoner	01/31/2017 - 01/30/2018	$300,000
Matthew Tyson Weirauch, PhD	Binding of Epstein Barr Virus EBNA2 unifies Multiple Sclerosis Genetic Mechanisms	National Institutes of Health	R01 NS099068	04/01/2017 - 12/31/2021	$346,991
Halima Moncrieffe	Identifying Signaling Aberrations in JIA Synovial Mononuclear Cells	Brigham & Women's Hospital	JBC_Moncrieffe	11/11/2016 - 11/10/2017	$2,000
Total Annual Grant Award Dollars					**$4,503,474**