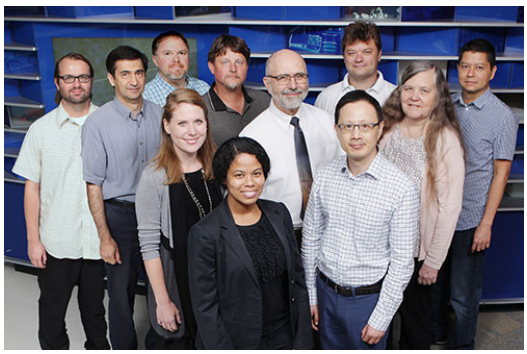
Center for Autoimmune Genomics and Etiology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**11**
Joint Appointment Faculty	**3**
Research Fellows and Post Docs	**8**
Research Graduate Students	**12**
Total Annual Grant Award Dollars	**$5,802,219**
Total Publications	**40**



Row 1: H Moncrieffe, N Shen

Row 2: L Kottyan, J Harley, S Thompson

Row 3: B Namjou-Khales, K Kaufman, A Porollo, I Chepelev

Row 4: M Weirauch, S Waggoner

Research Highlights

Protein Evolution

Researchers are making extraordinary progress by applying ever better sequencing technologies to biological problems. This is particularly true of DNA and protein sequencing. The linear sequences of nucleic acid bases and amino acids constituting the building blocks that provide this kind of essential information for every known variety of life is extraordinary. We have trillions of these building blocks of sequence. But the sequence is only part of the answer. DNA does not exist only as a sequence and neither do proteins. They interact and influence each other with evolutionary consequences. Alexey Porollo, PhD, with gifted undergraduate, Frasier Baker, published a new informatics tool, called CoeViz, which finds pairwise changes in the amino acid structure of a protein. This means that if a certain amino acid is changed in a certain way, then the new approach predicts what second changes would occur at another amino acid which would be likely to preserve the critical function of that protein. This approach provides insight into evolutionary alterations in proteins of different species.

Super-women in Autoimmunity

You know that nearly all men have an X and Y chromosome, and women have two X chromosomes. Did you know that one in a thousand women has three X chromosomes? These super-women tend to be about an inch taller than women with only two X chromosomes, but usually they are in the normal range for most everything else. Ke Liu, PhD, Ken Kaufman, PhD, Leah Kottyan, PhD, and John Harley, MD, PhD, along with 75 collaborators from around the world collected patients with systemic lupus erythematosus and a dry eye and mouth disease called Sjogren's syndrome; both are predominately female diseases 1:10 and 1:20, respectively, male to female. As predicted, the super-females with three X chromosomes have both of these disorders at a higher rate than women with two X chromosomes, consistent with the idea that the number of X chromosomes influences the risk for these diseases where men with one have a much lower risk than women with two who are also at a lower risk than these super-women with three.

Matt of All Trades

Transcription factors help decide what cell and when genes are expressed. This happens when scientists copy the DNA code to the RNA. Then the RNA influences what the cell does on its own or it translates into proteins. These transcription factors, and what they do, are at the center of much of the progress now made in medical research. Matt Weirauch, PhD, has made himself an expert in this area of biology. He has had the critical informatic role in expanding what we know about the DNA sequences that these proteins bind, and has found himself involved in a wide variety of different projects that are all biology. For example, he not only helped the group headed by Rafi Kopan, PhD, in the Division of Developmental Biology to develop a new method which would reveal when transcription factors were working very close to each other on the genome, the deeper meaning of the actions of PLZF, and worked on the sequences of DNA that particular transcription factors prefer; but he also helped interpret the genomes of both a plant *(Arabidosis thaniana)* and of bed bugs. This is a scientist with abiding curiosity into all forms of life on earth.

Success with extramural funding of research

Sue Thompson, PhD and Leah Kottyan, PhD both have done their part for the Center for Autoimmune Genomics and Etiology (CAGE) by bring wonderful success in the very competitive world of grant funding. Sue managed to renew the funding that provides infrastructure for the investigative commitment that Cincinnati Children's has traditionally made to juvenile idiopathic arthritis. This will provide support for many new projects meant to understand and treat this condition better than we have in the past. Leah has led a long term collaboration with the Allergy Division for the genetics of eosinophilic esophagitis. These children have swelling and edema of their esophagus to the point that they cannot swallow. Success with this project has been made possible by the infrastructure composed by her collaborator, Marc Rothenberg, MD, PhD. The studies to follow their discoveries are so compelling that she was awarded support as the Principal Investigator by the National Institute of Allergy and Infectious Diseases to pursue these new ideas for the next five years.

New Ideas Must Run the Gauntlet Before They are Accepted

Steve Waggoner, PhD, has been disrupting our thinking for a number of years now with the idea that a kind of immune system cell called "natural killer" cells actually act to inhibit our own immune responses. Many scientists had their doubts, and it required years of experiments to convince them. If we had the capacity to manipulate this phenomenon, then we might be able to help the body cure chronic infections like HIV, the human immunodeficiency virus, or some cancers; or going in the other direction, inhibit destructive autoimmune responses in thyroid disease, lupus or rheumatoid arthritis. Dr. Waggoner has had a major role in showing that these natural killers modulate immune responses; ideas that have not been easily accepted by our professional scientific colleagues. In the past year, he finally reached the point where his ideas published are reviews of progress in the field of immunology, and appear to now be part of the lexicon of accepted knowledge. This is an important milestone in science—when your work is on its way to the textbooks introductory students learn from when first entering a field.

Future

The faculty and staff of the Center for Autoimmune Genomics and Etiology (CAGE) have at least 40 different scientific initiatives underway. These initiatives promise to provide important future advances for the coming versions of this report, most in ways that we least expect as the montage of progress we assemble will be one where chance favors fertile minds prepared for new discovery.

Significant Publications

Alipanahi B, Delong A, **Weirauch MT**, Frey BJ. **Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning**. *Nat Biotechnol*. 2015 Aug;33(8):831-8.

> Knowing the sequence specificities of DNA- and RNA-binding proteins is essential for developing models of the regulatory processes in biological systems and for identifying causal disease variants. In this study, we show that sequence specificities ascertained from experimental data with 'deep learning' techniques, offer a scalable, flexible and unified computational approach for pattern discovery.

Zhou S, Wang Y, Meng Y, Xiao C, Liu Z, Brohawn P, Higgs BW, Jallal B, Jia Q, Qu B, Huang X, Tang Y, Yao Y, **Harley JB**, **Shen N**. **In Vivo Therapeutic Success of MicroRNA-155 Antagomir in a Mouse Model of Lupus Alveolar Hemorrhage**. *Arthritis Rheumatol*. 2016

Apr;68(4):953-64.

Micro-RNA inhibitors are modified RNA molecules themselves, called antagomirs, hold promise as a new class of therapeutic agents. They are anticipated to have broad applicability, efficacy, and utility. Here we show that a particular antagomer is a very effective treatment in an animal model of a very deadly form of systemic lupus erythematosus.

Liu K, Kurien BT, Zimmerman SL, **Kaufman KM**, **Taft DH**, **Kottyan LC**, **Lazaro S**, **Weaver CA**, Ice JA, Adler AJ, Chodosh J, Radfar L, Rasmussen A, Stone DU, Lewis DM, Li S, Koelsch KA, Igoe A, Talsania M, Kumar J, Maier-Moore JS, Harris VM, Gopalakrishnan R, Jonsson R, Lessard JA, Lu X, Gottenberg JE, Anaya JM, Cunninghame-Graham DS, Huang AJ, Brennan MT, Hughes P, Illei GG, Miceli-Richard C, Keystone EC, Bykerk VP, Hirschfield G, Xie G, Ng WF, Nordmark G, Eriksson P, Omdal R, Rhodus NL, Rischmueller M, Rohrer M, Segal BM, Vyse TJ, Wahren-Herlenius M, Witte T, Pons-Estel B, Alarcón-Riquelme ME, Guthridge JM, James JA, Lessard CJ, Kelly JA, **Thompson SD**, Gaffney PM, Montgomery CG, Edberg JC, Kimberly RP, Alarcón GS, Langefeld CL, Gilkeson GS, Kamen DL, Tsao BP, Joseph McCune W, Salmon JE, Merrill JT, Weisman MH, Wallace DJ, Utset TO, Bottinger EP, Amos CI, Siminovitch KA, Mariette X, Sivils KL, **Harley JB**, Scofield RH. **X Chromosome Dose and Sex Bias in Autoimmune Diseases: Increased Prevalence of 47,XXX in Systemic Lupus Erythematosus and Sjögren's Syndrome**. *Arthritis Rheumatol*. 2016 May;68(5):1290-300.

The reasons for female dominance of autoimmune diseases has been a long-standing and unsolved mystery. Here we show, for the first time, that the increased frequency of women who have the 47,XXX genotype are at increased risk for systemic lupus erythematosus and Sjogren's syndrome, thereby further supporting a gene dose effect of the X chromosome as an explanation for female dominance.

Namjou B, Marsolo K, Lingren T, Ritchie MD, Verma SS, **Cobb BL**, Perry C, Kitchner TE, Brilliant MH, Peissig PL, Borthwick KM, Williams MS, Grafton J, Jarvik GP, Holm IA, **Harley JB**. **A GWAS Study on Liver Function Test Using eMERGE Network Participants**. *PLoS One*. 2015 Sep 28;10(9):e0138677.

Bahram Namjou, MD, and colleagues used the electronic medical record and pre-existing genotyping results from other studies to show that DNA variants at the UGT1A gene govern the level of bilirubin in the blood, confirming that this is the most important locus for the level of bilirubin in pediatric populations.

Clement CC, **Moncrieffe H**, **Lele A**, Janow G, Becerra A, Bauli F, Saad FA, Perino G, Montagna C, Cobelli N, Hardin J, Stern LJ, Ilowite N, Porcelli SA, Santambrogio L. **Autoimmune response to transthyretin in juvenile idiopathic arthritis**. *JCI Insight*. 2016 Feb;1(2).

The cause of JIA is, by definition, unknown. This study provides evidence for an autoimmune response to a protein called transthyretin (TTR) in patients with JIA. This was reported in an international online news update as "Protein that triggers JIA identified". This study describes the JIA synovial fluid proteome, degradome and identifies increased post-translational modifications in the JIA inflamed site. This study detected autoantibodies to TTR in JIA patient serum and synovial fluid. Proinflammatory cytokines IFN-g and TNF-a was produced and increased immune cell proliferation occurred in response to TTR.

Division Publications

1. Alarcon-Riquelme ME, Ziegler JT, Molineros J, Howard TD, Moreno-Estrada A, Sanchez-Rodriguez E, Ainsworth HC, Ortiz-Tello P, Comeau ME, Rasmussen A, Kelly JA, Adler A, Acevedo-Vazquez EM, Cucho-Venegas JM, Garcia-De la Torre I, Cardiel MH, Miranda P, Catoggio LJ, Maradiaga-Cecena M, Gaffney PM, et al. **Genome-Wide Association Study in an Amerindian Ancestry Population Reveals Novel Systemic Lupus Erythematosus Risk Loci and the Role of European Admixture.** *Arthritis Rheumatol*. 2016; 68:932-43.
2. Alipanahi B, Delong A, Weirauch MT, Frey BJ. **Predicting the Sequence Specificities of DNA- and Rna-Binding Proteins by Deep Learning.** *Nat Biotechnol*. 2015; 33:831-8.
3. Angeles-Han ST, McCracken C, Yeh S, Jang SR, Jenkins K, Cope S, Bohnsack J, Hersh A, Thompson SD, Prahalad S. **Hla Associations in a Cohort of Children with Juvenile Idiopathic Arthritis with and without Uveitis.** *Investigative Ophthalmology & Visual Science*. 2015; 56:6043-48.

4. Baker FN, Porollo A. **Coeviz: A Web-Based Tool for Coevolution Analysis of Protein Residues.** *BMC Bioinformatics*. 2016; 17:119.

5. Benoit JB, Adelman ZN, Reinhardt K, Dolan A, Poelchau M, Jennings EC, Szuter EM, Hagan RW, Gujar H, Shukla JN, Zhu F, Mohan M, Nelson DR, Rosendale AJ, Derst C, Resnik V, Wernig S, Menegazzi P, Wegener C, Peschel N, et al. **Unique Features of a Global Human Ectoparasite Identified through Sequencing of the Bed Bug Genome.** *Nat Commun*. 2016; 7:10165.

6. Bouffi C, Kartashov AV, Schollaert KL, Chen X, Bacon WC, Weirauch MT, Barski A, Fulkerson PC. **Transcription Factor Repertoire of Homeostatic Eosinophilopoiesis.** *J Immunol*. 2015; 195:2683-95.

7. Brothers KB, Holm IA, Childerhose JE, Antommaria AH, Bernhardt BA, Clayton EW, Gelb BD, Joffe S, Lynch JA, McCormick JB, McCullough LB, Parsons DW, Sundaresan AS, Wolf WA, Yu JH, Wilfond BS, Pediatrics Workgroup of the Clinical Sequencing Exploratory Research Consortium, Pediatrics Workgroup of the Clinical Sequencing Exploratory Research CSER Consortium. **When Participants in Genomic Research Grow Up: Contact and Consent at the Age of Majority.** *J Pediatr*. 2016; 168:226-31 e1.

8. Caster DJ, Korte EA, Merchant ML, Klein JB, Wilkey DW, Rovin BH, Birmingham DJ, Harley JB, Cobb BL, Namjou B, McLeish KR, Powell DW. **Autoantibodies Targeting Glomerular Annexin A2 Identify Patients with Proliferative Lupus Nephritis.** *Proteomics Clin Appl*. 2015; 9:1012-20.

9. Chen X, Ernst K, Soman F, Borowczak M, Weirauch MT. **Cressint: A User-Friendly Web Resource for Genome-Scale Exploration of Gene Regulation in Arabidopsis Thaliana.** *Curr Plant Biol*. 2015; 3-4:48-55.

10. Chiaroni-Clarke RC, Li YR, Munro JE, Chavez RA, Scurrah KJ, Pezic A, Akikusa JD, Allen RC, Piper SE, Becker ML, Thompson SD, Lie BA, Flato B, Forre O, Punaro M, Wise C, Saffery R, Finkel TH, Hakonarson H, Ponsonby AL, et al. **The Association of Ptpn22 Rs2476601 with Juvenile Idiopathic Arthritis Is Specific to Females.** *Genes Immun*. 2015; 16:495-8.

11. Chimote AA, Hajdu P, Kottyan LC, Harley JB, Yun Y, Conforti L. **Nanovesicle-Targeted Kv1.3 Knockdown in Memory T Cells Suppresses Cd40l Expression and Memory Phenotype.** *J Autoimmun*. 2016; 69:86-93.

12. Clement CC, Moncriefe H, Lele A, Janow G, Becerra A, Bauli F, Saad FA, Perino G, Montagna C, Cobelli N, Hardin J, Stern LJ, Ilowite N, Porcelli SA, Santambrogio L. **Autoimmune Response to Transthyretin in Juvenile Idiopathic Arthritis.** *JCI Insight*. 2016; 1:e85633.

13. Cokelaer T, Bansal M, Bare C, Bilal E, Bot B, Chaibub N, E, Eduati F, de l, Fuente, A, Gönen M, Hill S. **Dreamtools: A Python Package for Scoring Collaborative Challenges.** *F1000Research*. 2016; 4.

14. Davis B, Stucke E, Khorki M, Litosh V, Rymer J, Rochman M, Travers J, Kottyan L, Rothenberg M. **Eosinophilic Esophagitis-Linked Calpain 14 Is an Il-13-Induced Protease That Mediates Esophageal Epithelial Barrier Impairment.** pmc/PMC4855700. *JCI Insight*. 2016; 1:e86355.

15. Davis BP, Epstein T, Kottyan L, Amin P, Martin LJ, Maddox A, Collins MH, Sherrill JD, Abonia JP, Rothenberg ME. **Association of Eosinophilic Esophagitis and Hypertrophic Cardiomyopathy.** *J Allergy Clin Immunol*. 2016; 137:934-6 e5.

16. Deng Y, Zhao J, Sakurai D, Sestak AL, Osadchiy V, Langefeld CD, Kaufman KM, Kelly JA, James JA, Petri MA, Bae SC, Alarcon-Riquelme ME, Alarcon GS, Anaya JM, Criswell LA, Freedman BI, Kamen DL, Gilkeson GS, Jacob CO, Merrill JT, et al. **Decreased Smg7 Expression Associates with Lupus-Risk Variants and Elevated Antinuclear Antibody Production.** *Ann Rheum Dis*. 2016.

17. Finkel TH, Li J, Wei Z, Wang W, Zhang H, Behrens EM, Reuschel EL, Limou S, Wise C, Punaro M, Becker ML, Munro JE, Flato B, Forre O, Thompson SD, Langefeld CD, Glass DN, Glessner JT, Kim CE, Frackelton E, et al. **Variants in Cxcr4 Associate with Juvenile Idiopathic Arthritis Susceptibility.** *BMC Med Genet*. 2016; 17:24.

18. Hall MA, Verma SS, Wallace J, Lucas A, Berg RL, Connolly J, Crawford DC, Crosslin DR, de Andrade M, Doheny KF, Haines JL, Harley JB, Jarvik GP, Kitchner T, Kuivaniemi H, Larson EB, Carrell DS, Tromp G, Vrabec TR, Pendergrass SA, et al. **Biology-Driven Gene-Gene Interaction Analysis of Age-Related Cataract in the Emerge Network.** *Genet Epidemiol*. 2015; 39:376-84.

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22. Li YR, Zhao SD, Li J, Bradfield JP, Mohebnasab M, Steel L, Kobie J, Abrams DJ, Mentch FD, Glessner JT, Guo Y, Wei Z, Connolly JJ, Cardinale CJ, Bakay M, Li D, Maggadottir SM, Thomas KA, Qui H, Chiavacci RM, et al. **Genetic Sharing and Heritability of Paediatric Age of Onset Autoimmune Diseases.** *Nat Commun*. 2015; 6:8442.

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Identifies New Sle Risk Variants in Individuals with Asian Ancestry. *Nat Genet*. 2016; 48:323-30.

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39. Zhao J, Giles BM, Taylor RL, Yette GA, Lough KM, Ng HL, Abraham LJ, Wu H, Kelly JA, Glenn SB, Adler AJ, Williams AH, Comeau ME, Ziegler JT, Marion M, Alarcon-Riquelme ME, Biolupus Genles Networks, Alarcon GS, Anaya JM, Bae SC, et al. **Preferential Association of a Functional Variant in Complement Receptor 2 with Antibodies to Double-Stranded DNA.** *Ann Rheum Dis*. 2016; 75:242-52.

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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Iouri Chepelev, PHD	Psoriatic Arthritis Causal Noncoding Genetic Variants in IL-23 Pathway	National Psoriasis Foundation	ANRF_Chepelev	7/1/2015 - 6/30/2017	$100,000
Iouri Chepelev, PHD	Identification of Lupus Causal Variants at BLK Locus by Mapping 3D Genome	Lupus Research Institute	LRI_Chepelev	1/1/2015 - 12/31/2017	$100,000
Stacey Ann Cranert, PHD	An Innate Helping Hand for B Cells on the Margin during Chronic Viral Infections	American Association of Immunologists	AAI_Cranert	5/1/2016 - 5/31/2016	$625
Stacey Ann Cranert, PHD	Using Cells to Treat Pediatric Blood Cancers	Cancer Free Kids	CFK_Cranert	7/1/2015 - 6/30/2016	$45,000
John Harley, MD-PHD	X Chromosome Gene Ddx3x is involved in B-cell Development	American Association of Immunologists	AAI_Harley	5/1/2016 - 5/31/2016	$750

John Harley, MD-PHD	Lupus Association with Signal Transducer and Activator of Transcription 4	Department of Veteran Affairs	IPA_Lazaro	7/1/2015 - 6/30/2016	$67,340
John Harley, MD-PHD	Lupus Association with Signal Transducer and Activator of Transcription 4	Department of Veteran Affairs	IPA_Magnusen	7/1/2014 - 6/30/2016	$63,710
John Harley, MD-PHD	Lupus Association with Signal Transducer and Activator of Transcription 4	Department of Veteran Affairs	IPA_Taft	7/1/2015 - 6/30/2016	$53,833
John Harley, MD-PHD	Genetic Linkage in Lupus	National Institutes of Health	R01 AI024717	6/16/2016 - 5/31/2021	$390,000
John Harley, MD-PHD	Better Outcomes for Children: Promoting Excellence in Healthcare Genomics to Inform Policy	National Institutes of Health	U01 HG008666	9/1/2015 - 5/31/2019	$1,710,578
Kenneth Kaufman, PHD	Genetic Susceptibility for Occupational Asthma	National Institute Occupational of (University of Cincinnati)	R01 OH008795	4/1/2016 - 8/31/2017	$22,461
Leah C. Kottyan, PHD	Mechanisms of genetic risk at 2p23 in Eosinophilic Esophagitis	Am Partnership for Eosinophilic Disorder	Kottyan_Apfed	4/12/2016 - 4/11/2018	$50,000
Alexey Porollo, PHD	GM-CSF-Induced Metal Sequestration and Histoplasma	National Institutes of Health (University of Cincinnati)	R01 AI106269	5/15/2013 - 4/30/2018	$59,153
Alexey Porollo, PHD	Directed Culturing of Pneumocystis Using Metatranscriptomics	National Institutes of Health (University of Cincinnati)	R01 HL119190	5/22/2013 - 2/28/2018	$3,036
Carolyn Rydyznski	Natural Killer Cells: Innate Regulators of Humoral Responses	American Association of Immunologists	AAI_Rydyznski	5/1/2016 - 5/31/2016	$300
Carolyn Rydyznski	A Follicular Regulatory Subset of Natural Killer Cells	National Institutes of Health	F32 AI118179	5/3/2015 - 5/2/2018	$36,036
Susan D Thompson, PHD	Gene Expression In Pediatric Arthritis	National Institutes of Health	P01 AR048929	9/1/2011 - 8/31/2016	$1,366,469
Susan D Thompson, PHD	Cincinnati Rheumatic Disease Core Center	National Institutes of Health	P30 AR047363	8/25/2011 - 6/30/2017	$585,023
Stephen Waggoner, PHD	AAI Early Career Faculty Travel Grant	American Association of Immunologists	AAI_Waggoner	5/1/2016 - 5/31/2016	$1,250
Stephen Waggoner, PHD	A Revolutionary Approach to an Efficacious HIV Vaccine	National Institutes of Health	DP1DA038017	6/1/2014 - 5/31/2019	$772,200
Stephen Waggoner, PHD	Effect of Aging on Natural Killer Cell Regulation of T Cell	Ellison Medical Foundation	Ellison_Waggoner	7/1/2013 - 6/30/2016	$100,000

	in Viral Pathogenesis				
Matthew Tyson Weirauch, PHD	A Free Website for Discovering Non-coding Lupus-associated Variant Function	Lupus Research Institute	LRI_Weirauch	1/1/2016 - 12/31/2018	$100,000
Matthew Tyson Weirauch, PHD	Effect of Disease-associated Genetic Variants on Viral Protein DNA Binding	National Institutes of Health	R21 HG008186	12/15/2014 - 11/30/2017	$156,000
Matthew Tyson Weirauch, PHD	Data Coordination and Integration Center for LINCS-BD2K	National Institutes of Health (Icahn School of Medicine @ Mt Sinai)	U54 HL127624	9/29/2014 - 4/30/2019	$18,455
Total Annual Grant Award Dollars					**$5,802,219**