

Division Details

Division Data Summary

Research and Training Details

Number of Faculty	15
Number of Research Fellows	3
Number of Support Personnel	11
Direct Annual Grant Support	\$4,880,993
Direct Annual Industry Support	\$831,340
Peer Reviewed Publications	62

Clinical Activities and Training

Number of Clinical Staff	6
Number of Clinical Fellows	5
Number of Other Students	9
Inpatient Encounters	520
Outpatient Encounters	3,888

Division Photo



Row 1: M Weirauch, E Giannini, H Brunner, R Mina
Row 2: J Harley, T Ting, E Morgan-DeWitt
Row 3: K Kaufman, A Grom

Significant Accomplishments

The Division of Rheumatology Maintains International Stature

Rheumatology has had a successful fiscal year with a number of important accomplishments and publications, including: Collaborating with Seattle Children's, Edward Giannini, MSc, DrPH, has shown that aggressive treatment early in the disease course leads to better therapeutic responses and outcomes in juvenile idiopathic arthritis. Michael Henrickson, MD, MPH, published a comprehensive evaluation of the pediatric rheumatology workforce. An institution-wide initiative led by Michael Barnes, PhD, created a biobank for tissues and DNA that is expected to have 750,000 samples before the end of the year; the samples will be useful to research. The continuing efforts of Susan Thompson, PhD, and colleagues led to discovery of a gene important for juvenile idiopathic arthritis.

Work with Micro-RNA's Leads to Important Findings

Nan Shen, MD, has revealed many of the details of how small RNA's, called micro-RNA's, control the production of particular inflammatory mediators known as cytokines. Shen's research has important clinical implications for treating autoimmune diseases such as systemic lupus erythematosus, allergy and asthma.

Center for Autoimmune Genomic Etiology Joins eMERGE Consortium

As a result of the work of John Harley, MD, Cincinnati Children's is now an NIH-funded member of the eMERGE (electronic **M**edical **R**ecords and **G**enomics) Network. This network is a consortium of biorepositories linked to

electronic medical records data for conducting genomic studies. We are helping lead the national initiative to use genetic data with electronic medical records to deepen our understanding of childhood diseases and usher in the coming era of personalized medicine.

Significant Publications

Zhu S, Pan W, Song X, Liu Y, Shao X, Tang Y, Liang D, He D, Wang H, Liu W, Shi Y, **Harley JB**, Shen N, Qian Y. **The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK- α .** *Nat Med.* Jun 3 2012.

IL-17 is an important cytokine in many inflammatory disorders. This study reveals an important role for micro-RNA 236 in the control of IL-17 expression.

Wallace, C. A., **Giannini, E. H.**, Spalding, S. J., Hashkes, P. J., O'Neil, K. M., Zeff, A. S., Szer, I. S., Ringold, S., **Brunner, H. I.**, Schanberg, L. E., Sundel, R. P., Milojevic, D., Punaro, M. G., Chira, P., Gottlieb, B. S., Higgins, G. C., Ilowite, N. T., Kimura, Y., Hamilton, S., Johnson, A., Huang, B., & **Lovell, D. J.** **Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis.** *Arthritis Rheum*, 64(6), 2012-2021. 2012.

The paradigm of treatment whereby children with juvenile idiopathic arthritis are started on a relatively non-aggressive therapeutic regimen has been overturned by this work. This study showed that a high proportion of children treated very aggressively early in their disease course can be brought into a state of inactive disease after only 6 months of therapy initiation.

Henrickson M. Three-Part Series: Policy Challenges for the Pediatric Rheumatology Workforce

Part I. Education and Economics. *Pediatr Rheumatol Online J.* 9:23. 2011.

Part II. Health Care System Delivery and Workforce Supply. *Pediatr Rheumatol Online J.* 9:24. 2011.

Part III. The International Situation. *Pediatr Rheumatol Online J.* 9:26. 2011.

This three-part analysis of current challenges to pediatric rheumatologists regarding barriers to access to care for children with rheumatic disease and to achieving optimal clinical outcomes addresses 1) education and economics, 2) health care system delivery and workforce supply, and 3) the international situation. Dr. Henrickson presents possible solutions to each identified challenge. Per an accompanying editorial (Lindsley CB: Policy challenges for the pediatric rheumatology workforce. *Pediatr Rheumatol Online J* 2012 10:5), **Dr. Henrickson “has initiated an important conversation that has the potential to impact the future of our discipline... Dr. Henrickson has carefully analyzed workforce issues both in the US and internationally and made suggestions that should be seriously considered by the pediatric rheumatology community and implemented where feasible.”**

Niewold TB, Kelly JA, Kariuki SN, Franek BS, Kumar AA, Kaufman KM, Thomas K, Walker D, Kamp S, Frost JM, Wong AK, Merrill JT, Alarcón-Riquelme ME, Tikly M, Ramsey-Goldman R, Reveille JD, Petri MA, Edberg JC, Kimberly RP, Alarcón GS, Kamen DL, Gilkeson GS, Vyse TJ, James JA, Gaffney PM, Moser KL, Crow MK, **Harley JB.** **IRF5 haplotypes demonstrate diverse serological associations which predict serum interferon alpha activity and explain the majority of the genetic association with systemic lupus erythematosus.** *Ann Rheum Dis.* Mar 2012. 71(3):463-8. Epub. Nov 16 2011.

We show that the gene variants at IRF5 influences the differences between patients.

Thompson, S. D., Marion, M. C., Sudman, M., Ryan, M., Tsoras, M., Howard, T. D., Barnes, M. G., Ramos, P. S., Thomson, W., Hinks, A., Haas, J. P., Prahalad, S., Bohnsack, J. F., Wise, C. A., Punaro, M., Rose, C. D., Pajewski, N. M., Spigarelli, M., Keddache, M., Wagner, M., Langefeld, C. D., & **Glass, D. N.** **Genome-wide association**

analysis of juvenile idiopathic arthritis identifies a new susceptibility locus at chromosomal region

3q13.Arthritis Rheum. 2012.

This work represents, to our knowledge, the largest genome-wide association study of JIA cases to date and focuses on the 2 most common subtypes, oligoarticular and RF-negative polyarticular JIA. We report novel JIA-associated loci and supporting eQTL results that extend the JIA associations beyond those previously reported (PTPN2, PTPN22, IL2RA, ADAD1-IL2-IL21, ANGPT1, COG6, C12orf30, and STAT4). The strongest replicated evidence for association with JIA was found at the chromosome 3q13 region, which includes CD80, a co-stimulatory molecule necessary for T cell activation. A novel association was also found near at 10q21 and includes JMJD1C, a gene that encodes a hormone-dependent transcription factor that functions by removing methyl marks on histones. It is noteworthy that a gene expression signature (defined by 50 expression probe sets) for JIA patients with chronically active arthritis also included JMJD1C. The overlap of genetic and gene expression findings cannot be explained by chance and suggests a functional relationship to disease pathogenesis.

Division Publications

1. Anaya JM, Kim-Howard X, Prahalad S, Chernavsky A, Canas C, Rojas-Villarraga A, Bohnsack J, Jonsson R, Bolstad AI, Brun JG, Cobb B, Moser KL, James JA, Harley JB, Nath SK. **Evaluation of genetic association between an ITGAM non-synonymous SNP (rs1143679) and multiple autoimmune diseases.** *Autoimmun Rev.* 2012; 11:276-80.
2. Bronson PG, Goldstein BA, Ramsay PP, Beckman KB, Noble JA, Lane JA, Seldin MF, Kelly JA, Harley JB, Moser KL, Gaffney PM, Behrens TW, Criswell LA, Barcellos LF. **The rs4774 CIITA missense variant is associated with risk of systemic lupus erythematosus.** *Genes Immun.* 2011; 12:667-71.
3. Brunner HI, Mina R, Pilkington C, Beresford MW, Reiff A, Levy DM, Tucker LB, Eberhard BA, Ravelli A, Schanberg LE, Saad-Magalhaes C, Higgins GC, Onel K, Singer NG, von Scheven E, Itert L, Klein-Gitelman MS, Punaro M, Ying J, Giannini EH. **Preliminary criteria for global flares in childhood-onset systemic lupus erythematosus.** *Arthritis Care Res (Hoboken).* 2011; 63:1213-23.
4. Carle AC, Dewitt EM, Seid M. **Measures of health status and quality of life in juvenile rheumatoid arthritis: Pediatric Quality of Life Inventory (PedsQL) Rheumatology Module 3.0, Juvenile Arthritis Quality of Life Questionnaire (JAQQ), Paediatric Rheumatology Quality of Life Scale (PRQL), and Childhood Arthritis Health Profile (CAHP).** *Arthritis Care Res (Hoboken).* 2011; 63 Suppl 11:S438-45.
5. Castillejo-Lopez C, Delgado-Vega AM, Wojcik J, Kozyrev SV, Thavathiru E, Wu YY, Sanchez E, Pollmann D, Lopez-Egido JR, Fineschi S, Dominguez N, Lu R, James JA, Merrill JT, Kelly JA, Kaufman KM, Moser KL, Gilkeson G, Frostegard J, Pons-Estel BA, D'Alfonso S, Witte T, Callejas JL, Harley JB, Gaffney PM, Martin J, Guthridge JM, Alarcon-Riquelme ME. **Genetic and physical interaction of the B-cell systemic lupus erythematosus-associated genes BANK1 and BLK.** *Ann Rheum Dis.* 2012; 71:136-42.
6. Dewitt EM, Grussemeyer CA, Friedman JY, Dinan MA, Lin L, Schulman KA, Reed SD. **Resource use, costs, and utility estimates for patients with cystic fibrosis with mild impairment in lung function: analysis of data collected alongside a 48-week multicenter clinical trial.** *Value Health.* 2012; 15:277-83.
7. Dillon SP, Kurien BT, Li S, Bruner GR, Kaufman KM, Harley JB, Gaffney PM, Wallace DJ, Weisman MH, Scofield RH. **Sex chromosome aneuploidies among men with systemic lupus erythematosus.** *J Autoimmun.* 2012; 38:J129-34.
8. Du F, Lu LJ, Teng JL, Shen N, Ye P, Bao CD. **T-614 alters the production of matrix metalloproteinases (MMP-1 andMMP-3) and inhibits the migratory expansion of rheumatoid synovial fibroblasts, in vitro.** *Int Immunopharmacol.* 2012; 13:54-60.

9. Fukuda T, Brunner HI, Sagcal-Gironella AC, Vinks AA. **Nonsteroidal anti-inflammatory drugs may reduce enterohepatic recirculation of mycophenolic acid in patients with childhood-onset systemic lupus erythematosus.** *Ther Drug Monit.* 2011; 33:658-62.
10. Guo Q, Shen N, Yuan K, Li J, Wu H, Zeng Y, Fox J, 3rd, Bansal AK, Singh BB, Gao H, Wu M. **Caveolin-1 plays a critical role in host immunity against *Klebsiella pneumoniae* by regulating STAT5 and Akt activity.** *Eur J Immunol.* 2012; 42:1500-11.
11. Guthridge JM, Clark DN, Templeton A, Dominguez N, Lu R, Vidal GS, Kelly JA, Kauffman KM, Harley JB, Gaffney PM, James JA, Poole BD. **Effects of IRF5 lupus risk haplotype on pathways predicted to influence B cell functions.** *J Biomed Biotechnol.* 2012; 2012:594056.
12. Henrickson M. **Policy challenges for the pediatric rheumatology workforce: Part II. Health care system delivery and workforce supply.** *Pediatr Rheumatol Online J.* 2011; 9:23.
13. Huang X, Guo Y, Bao C, Shen N. **Multidimensional single cell based STAT phosphorylation profiling identifies a novel biosignature for evaluation of systemic lupus erythematosus activity.** *PLoS One.* 2011; 6:e21671.
14. Hughes T, Adler A, Kelly JA, Kaufman KM, Williams AH, Langefeld CD, Brown EE, Alarcon GS, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Boackle SA, Stevens AM, Reveille JD, Sanchez E, Martin J, Niewold TB, Vila LM, Scofield RH, Gilkeson GS, Gaffney PM, Criswell LA, Moser KL, Merrill JT, Jacob CO, Tsao BP, James JA, Vyse TJ, Alarcon-Riquelme ME, Harley JB, Richardson BC, Sawalha AH. **Evidence for gene-gene epistatic interactions among susceptibility loci for systemic lupus erythematosus.** *Arthritis Rheum.* 2012; 64:485-92.
15. Hughes T, Adler A, Merrill JT, Kelly JA, Kaufman KM, Williams A, Langefeld CD, Gilkeson GS, Sanchez E, Martin J, Boackle SA, Stevens AM, Alarcon GS, Niewold TB, Brown EE, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Criswell LA, Vila LM, Jacob CO, Gaffney PM, Moser KL, Vyse TJ, Alarcon-Riquelme ME, James JA, Tsao BP, Scofield RH, Harley JB, Richardson BC, Sawalha AH. **Analysis of autosomal genes reveals gene-sex interactions and higher total genetic risk in men with systemic lupus erythematosus.** *Ann Rheum Dis.* 2012; 71:694-9.
16. Irwin DE, Gross HE, Stucky BD, Thissen D, DeWitt EM, Lai JS, Amtmann D, Khastou L, Varni JW, DeWalt DA. **Development of six PROMIS pediatric proxy-report item banks.** *Health Qual Life Outcomes.* 2012; 10:22.
17. Irwin DE, Stucky BD, Langer MM, Thissen D, DeWitt EM, Lai JS, Yeatts KB, Varni JW, DeWalt DA. **PROMIS Pediatric Anger Scale: an item response theory analysis.** *Qual Life Res.* 2012; 21:697-706.
18. Isackson PJ, Ochs-Balcom HM, Ma C, Harley JB, Peltier W, Tarnopolsky M, Sripathi N, Wortmann RL, Simmons Z, Wilson JD, Smith SA, Barboi A, Fine E, Baer A, Baker S, Kaufman K, Cobb B, Kilpatrick JR, Vladutiu GD. **Association of common variants in the human eyes shut ortholog (*EYS*) with statin-induced myopathy: evidence for additional functions of *EYS*.** *Muscle Nerve.* 2011; 44:531-8.
19. Jacob CO, Eisenstein M, Dinauer MC, Ming W, Liu Q, John S, Quismorio FP, Jr., Reiff A, Myones BL, Kaufman KM, McCurdy D, Harley JB, Silverman E, Kimberly RP, Vyse TJ, Gaffney PM, Moser KL, Klein-Gitelman M, Wagner-Weiner L, Langefeld CD, Armstrong DL, Zidovetzki R. **Lupus-associated causal mutation in neutrophil cytosolic factor 2 (*NCF2*) brings unique insights to the structure and function of NADPH oxidase.** *Proc Natl Acad Sci U S A.* 2012; 109:E59-67.
20. Kashikar-Zuck S, Ting TV, Arnold LM, Bean J, Powers SW, Graham TB, Passo MH, Schikler KN, Hashkes PJ, Spalding S, Lynch-Jordan AM, Banez G, Richards MM, Lovell DJ. **Cognitive behavioral therapy for the treatment of juvenile fibromyalgia: a multisite, single-blind, randomized, controlled clinical trial.** *Arthritis Rheum.* 2012; 64:297-305.
21. Khanna D, Krishnan E, Dewitt EM, Khanna PP, Spiegel B, Hays RD. **The future of measuring patient-reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS).** *Arthritis Care Res (Hoboken).* 2011; 63 Suppl 11:S486-90.

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- lupus nephritis and focal segmental glomerulosclerosis.** *Arthritis Res Ther.* 2011; 13:R199.
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Faculty, Staff, and Trainees

Faculty Members

John Harley, MD, PhD, Professor

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Edward H. Giannini, MSc, DrPH, Professor

David N. Glass, MD, Professor

Alexei A. Grom, MD, Associate Professor

Michael Henrickson, MD, MPH, Associate Professor

Leadership Clinical Director

Jennifer Huggins, MD, Associate Professor

Leadership Fellowship Director

Kenneth Kaufman, PhD, Professor

Daniel Joe Lovell, MD, MPH, Professor

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Esi Morgan DeWitt, MD, MSCE, Assistant Professor

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Tracy Ting, MD, Assistant Professor

Matthew Weirauch, PhD, Assistant Professor

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- **Janalee Taylor, MSN, RN, CNP**

Trainees

- **Moussa El-Hallak, MD**, PL-5, Memorial University Medical Center
- **Pai-Yue Lu, MD**, PGY-, Cincinnati Children's Hospital Medical Center
- **David Moser, DO**, PL-6, United States Army, Pediatrics
- **Keith Sikora, MD**, PL-6, Johns Hopkins Hospital
- **Patricia Vega-Fernandez, MD**, PL-5, University of Texas Health Science Center at San Antonio, Texas

Grants, Contracts, and Industry Agreements

Grant and Contract Awards Annual Direct

BARNES, M

Expansion of Family Aspects of a DNA Biorepository

National Institutes of Health(University of Cincinnati)

UL1 RR 026314 09/01/11-03/31/12 \$108,944

BRUNNER, H

Towards Measures of Lupus Nephritis Activity & Damage in Children

National Institutes of Health

U01 AR 059509 08/08/10-05/31/13 \$129,719

FLICK, M

Mechanisms Linking the Hemostatic Protease Thrombin to Arthritic Disease

National Institutes of Health

R01 AR 056990 08/10/09-07/31/14 \$171,072

GROM, A

MUNC13-4 Gene Polymorphisms in Macrophage Activation Syndrome and Systemic Juvenile Idiopathic Arthritis

National Institutes of Health

R01 AR 059049 08/08/11-07/31/16 \$225,000

HARLEY, J

Better Outcomes for Children: GWAS & PheWAS in eMERGEII.

National Institutes of Health

U01 HG 006828 05/15/12-04/30/15 \$616,656

Genetic Linkage in Lupus

National Institutes of Health

R37 AI 024717 09/07/10-02/28/15 \$277,494

Genome-Wide Association Study in African-Americans with Systemic Lupus Erythematosus

Department of Defense

W81XWH-10-1-0675 09/01/10-08/31/13 \$269,095

Program Project in the Genetics of SLE-Project 2: Genomics of Lupus Associations in the Hispanic 12q24 Linkage

National Institutes of Health(University of Alabama-Birmingham)

P01 AR 049084 04/01/11-03/31/13 \$90,695

Genomics of Lupus: Administrative Core A

National Institutes of Health(Oklahoma Medical Research Foundation)

P01 AI 083194 08/15/09-07/31/14 \$58,204

Genomics of Lupus: Project 2

National Institutes of Health(Oklahoma Medical Research Foundation)

P01 AI 083194 08/15/09-07/31/14 \$105,933

KAUFMAN, K**Reverse Genomics of Anti-Protective Antigen Response**

National Institutes of Health(Oklahoma Medical Research Foundation)

U19 AI 062629 09/01/11-08/31/14 \$77,582

LOVELL, D**Multidisciplinary Clinical Research Center**

National Institutes of Health

P60 AR 047784 08/18/08-07/31/13 \$847,448

Lovell, D	Administrative Core	\$73,066
Giannini, E	Methods Core	\$115,723
Brunner, H	Project 1	\$165,115
Lovell, D	Project 2	\$180,077
Grom, A	Project 3	\$165,985
Seid, M	Project 4	\$147,482

MORGAN DEWITT, E**Enhancing PROMIS in Pediatric Pain, Rheumatology, and Rehabilitation Research**

National Institutes of Health

U01 AR 057940 09/30/09-07/31/13 \$412,506

Juvenile Arthritis Improvement Network for Clinical Excellence & Safety

Arthritis Foundation

07/01/10-06/30/12 \$93,015

THOMPSON, S**Cincinnati Rheumatic Disease Core Center**

National Institutes of Health

P30 AR 047363 08/25/11-06/30/16 \$400,000

Thompson, S	Administrative Core	\$137,490
Thompson, S	Core 1	\$85,333
Flick, M	Core 2	\$51,759
Thornton, S	Core 3	\$67,086
Wagner, M	Core 4	\$58,332

Gene Expression In Pediatric Arthritis

National Institutes of Health

P01 AR 048929 09/01/11-08/31/16 \$997,630

Thompson, S	Administrative Core	\$163,910
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Thompson, S	Core A	\$133,310	
Wagner, M	Core B	\$155,116	
Harley, J	Project 1	\$58,303	
Lovell, D	Project 2	\$38,399	
Thompson, S	Project 3	\$255,120	
Grom, A	Project 4	\$93,202	
		Current Year Direct	\$4,880,993

Industry Contracts

BRUNNER

Abbott Laboratories	\$19,892
Centocor, Inc.	\$101,974
PAREXEL International LLC	\$9,500
Pfizer, Inc	\$20,611
UCB Biosciences, Inc.	\$9,000

LOVELL

Bristol-Myers Squibb Company	\$202,733
Hoffman-LaRoche, Inc	\$5,974
Novartis Pharmaceuticals	\$170,268
Pfizer, Inc	\$77,405
Roche Laboratories, Inc.	\$213,983

Current Year Direct Receipts **\$831,340,**

Total **\$5,712,333**