**2013 Research Annual Report**

**Rheumatology**

**Division Details**

**Division Data Summary**

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**Significant Accomplishments**

**New Therapies for Juvenile Idiopathic Arthritis (JIA)**

Phase 3 clinical trials were published by Daniel Lovell, MD, MPH, and Hermine Brunner, MD, MSc, MBA, as contributors to large collaborator studies, for treatments of the systemic form of JIA that block the cytokines IL-1 and IL-6, respectively, canukinumab and tocilizumab. These therapies are highly effective for the systemic form of JIA, which accounts for 75 percent of the deaths associated with JIA.

**New Informatic Tools**

Transcription factors are very important in the coordination of gene expression, making possible nearly all cellular processes. Understanding the precise sequence that they bind in DNA is important to explaining how healthy cellular processes occur (growth, division, differentiation) as well as pathological processes (cancer, anemia, inflammation). Matthew Weirauch, PhD, with colleagues in Toronto evaluated the relative merit of alternative ways of evaluating the transcription factor binding, leading to important methodologic advances for understanding these enigmatic and critically important proteins.

**Micro-RNAs in Inflammation**

Small RNAs called micro-RNAs appear to inhibit the expression of specific genes in cells. Nan Shen, MD and John Harley, MD, PhD have collaborated with scientists in China to explore the properties of these enigmatic...
molecules in inflammation. Their work shows that micro-RNA 31 contributes to the impaired production of the cytokine IL-2 in systemic lupus erythematosus. They also show that the cytokine IL-17 contributes to autoimmune pathogenesis by suppressing the expression of micro-RNA 23b, which is in turn inhibits expression of IL-17, TNFα, and IL-1β making a complex web of gene expression control.

**Research Highlights**

**Esi Morgan DeWitt, MD**

Patient Reported Outcomes Measurement Information System (PROMIS) partnering with researchers in Behavioral Medicine and Clinical Psychology, Susmita Kashikar-Zuck, PhD, and Lori Crosby, PsyD; Physical Medicine and Rehabilitation, Jilda Vargus-Adams, MD; Anesthesia (Pain Management) Kenneth Goldschneider, MD; and UC Department of Anthropology, C. Jeffrey Jacobson – have conducted validation studies of PROMIS measures in children with Juvenile Idiopathic Arthritis, chronic pain, cerebral palsy. We have developed new measures to assess pain behaviors and pain quality in children with chronic pain. Having completed the data collection portion of the study, we are in the analysis phase.

Pediatric Rheumatology Care and Outcomes Improvement Network – development of shared decision making aid to facilitate discussion and collaboration with families with JIA making treatment decisions. Partnership with Bill Brinkman, MD of the Anderson Center's Evidence and Measures team, and Ellen Lipstein, MD of Adolescent Medicine (and Anderson Center). Funded by AHRQ Center for Education and Research on Therapeutics, PI Carole Lannon.

**Iouri Chepelev, PhD**

*Functional characterization of noncoding autoimmune disease-predisposing DNA sequence variants.*

Recent genome-wide association studies have revealed that majority of disease-susceptibility loci in autoimmune diseases lie outside of the coding regions of genes and are assumed to influence transcriptional regulation rather than gene function by altering the activities of underlying regulatory elements of transcription such as enhancers and long noncoding RNAs. Our goal is to functionally characterize the role of gene-regulatory elements in the autoimmune disease etiology. Since joining the CAGE/Cincinnati Children’s faculty four months ago, my laboratory has been actively developing high-throughput experimental methods to investigate long-range chromatin interactions of enhancers and gene promoters, and a potential role of long noncoding RNAs as facilitators of these interactions.

*DNA methylation, alternative pre-mRNA splicing and lupus.*

The epigenome is a sensor of environmental stimuli and may thus be involved in the autoimmune disease etiology. Variants within methyl-CpG-binding protein MeCP2, a key transcription regulator which binds methylated DNA, are associated with increased susceptibility to lupus and differential gene expression in patients with SLE. CD4⁺ T cells isolated from active lupus patients demonstrate global DNA hypomethylation. Aberrations in alternative splicing occur in SLE, and aberrant processing of transcripts can lead to the altered function of genes involved in the immune control. Our goal is to investigate a potential mechanistic link between these two types of aberrations in SLE. As a step toward this goal, we have recently completed and published a study on the role of DNA methylation and MeCP2 in pre-mRNA splicing.

**Halima Moncrieffe, PhD**
Novel biomarker for identifying a subset of JIA patients who will respond to medication.

Juvenile Idiopathic Arthritis is the most common rheumatologic childhood disease. When children with arthritis fail to respond to medication this can result in disease progression, reduced quality of life and increased risk of disability. Identifying JIA patients who will respond to the standard treatment of methotrexate is an important goal. We have contributed to that goal by identifying a novel biomarker found in the serum of blood that is elevated in a subset of patients with childhood arthritis who will respond well. The article (Moncrieffe et al, Rheumatology, 2013) was featured on the MDLinx website “the world's most current index of articles that matter in the daily lives of physicians”.

P30 Pilot and Feasibility Research Funding.

Halima Moncrieffe was awarded $60,000 for research entitled “A novel method of inducing suppressive T cells in juvenile arthritis” for two years commencing July 1st, 2013. This project was selected on a competitive basis and aims to investigate the first steps in feasibility and potential of a novel approach to therapy in childhood arthritis.

New Cincinnati Children’s mentoring partnership with the ROSE program.

Halima Moncrieffe became the first mentor at Cincinnati Children's to become a partner with the ROSE (Research, Observation, Service and Education) program at the University of Cincinnati. ROSE students are “high ability, intellectually curious pre-medical college students” and integrate into the laboratory over two consecutive summers.

American Association of Immunology Award.

Dr. Moncrieffe was the recipient of an American Association of Immunology Abstract Award for an abstract entitled “Autoimmune susceptibility gene critically influences CD39 T cell expression and function in modulating human inflammation.” The award included $750 travel expenses to present these findings at the AAI 100th Annual Meeting.

Matthew Weirauch, PhD

Evaluation of methods for modeling transcription factor sequence specificity (first author paper in Nature Biotechnology)


Transcription factors (TFs) control gene expression by binding to short genomic sequences near the genes they control. Understanding the rules governing these binding events is crucial to understanding genome function and evolution, and also the etiology of diseases. Many approaches have been developed to model and learn a TF’s sequence binding specificity; consequently, preferences for the particular models (and methods) are very contentious. Due to the central importance of this problem to any analysis involving scanning DNA sequences for potential TF binding sites, Dr. Weirauch co-sponsored a “contest” with Tim Hughes at U. Toronto as part of the “DREAM challenge” series, which is part of the RECOMB computational biology meetings. This challenge enabled them to systematically compare a total of 26 algorithms for modeling the binding of a diverse panel of
Currently, about 80% of patients are consented during registration and agree to participate. We also have DNA from over 15,500 patients. The Cincinnati Biobank has led the institution’s sample collection project, Better Outcomes for Children. This project obtains consent from patients as they register at the hospital to allow use of residual clinical samples for research. In the summer of 2012, we began an expansion effort to extend this project to as many areas of the hospital as possible. We are currently operating said project in 26 clinics and eight satellite campuses.

### Division Publications


Marsolo K, Vivo M, identify a novel methylated sequence bound by the CEBPB|ATF4 heterodimer that is active in


19. Marsolo K, Corsmo J, Barnes MG, Pollick C, Chalfin J, Nix J, Smith C, Ganta R. Challenges in creating...


Faculty, Staff, and Trainees

Faculty Members

John B. Harley, MD, PhD, Professor
  Leadership Division Director

Michael Barnes, PhD, Assistant Professor
  Leadership Director of Cincinnati Biobank

Hermine Brunner, MD, MSc, MBA, Professor

Iouri Chepelev, PhD, Assistant Professor

Edward H. Giannini, MSc, DrPH, Professor Emeritus

David Glass, MD, Professor Emeritus
  Leadership Emeritus Associate Director of the Cincinnati Children's Research Foundation

Alexei A. Grom, MD, Associate Professor

Michael Henrickson, MD, MPH, Associate Professor

Jennifer Huggins, MD, Associate Professor
  Leadership Fellowship Director

Kenneth Kaufman, PhD, Professor

Daniel Joe Lovell, MD, MPH, Professor
  Leadership Joseph E. Levinson Endowed Chair in Pediatric Rheumatology; Associate Division Director; Clinic Co-Director

Rina Mina, MD, Assistant Professor

Halima Moncrieffe, PhD, Instructor

Esi Morgan DeWitt, MD, MSCE, Assistant Professor

Alexey Porollo, PhD, Assistant Professor

Nan Shen, MD, Associate Professor

Susan Thompson, PhD, Professor
  Leadership Associate Division Director

Sherry Thornton, PhD, Assistant Professor
  Leadership Director of the Flow Cytometry Core

Tracy Ting, MD, Assistant Professor
  Leadership Clinic Co-Director

Stephen Waggoner, PhD, Assistant Professor

Matthew Weirauch, PhD, Assistant Professor
Clinical Staff Members

Janalee Taylor, MSN, RN, CNP

Trainees

Moussa El-Hallak, MD, PGY6, Memorial University Medical Center
Pai-Yue Lu, MD, PGY6, New York Medical College
Jordan Jones, MD, PGY4, Des Moines University College of Osteopathic Medicine
Khalid Abulaban, MD, PGY5, Gulf Medical College Amjan
Patricia Vega-Fernandez, MD, PGY6, University of Texas Health Science Center at San Antonio, Texas
Ke Liu, BS, 2003, Nanchang University
Samuel Vaughn, BS, 2004, Brigham Young University
Jiadi Xu, BS, 2010, China Agricultural University
Leah Kottyan, PhD, 2010, University of Cincinnati
Bahram Namjou, MD, 1989, Oklahoma Medical Research Foundation
Erin Zoller, PhD, 2011, University of Cincinnati
Dong Liang, PhD, 2010, Université Paris Descartes

Division Collaboration

Division of Biostatistics and Epidemiology » Bin Huang
   Analyzed data from multiple clinical trials of agents for the treatment of pediatric and adult rheumatic diseases.

Division of Behavioral Medicine and Clinical Psychology »
   Ongoing studies of pediatric fibromyalgia.

Division of Infectious Diseases » Margaret Hostetter
   Study of a new mechanism of biofilm formation by Candida albicans. Analysis of de novo mutations as possible causative factors for osteomyelitis and recurrent staph infection.

Division of Neonatology and Pulmonary Biology » Bruce Trapnell
   Analysis of possible functional implications of de novo mutations is associated with tracheal ring deformity.

Division of Hematology » Matthew Flick
   Examining the effects of deficits in hemostatic factors on the pathogenesis of arthritis. We have shown that several hemostatic factors, including fibrinogen and specific regulatory domains of fibrinogen, play key roles in the pathogenesis of arthritis.

Division of Emergency Medicine » Richard Strait
   Mechanism of IgG Inhibition in Inflammatory Arthritis. Our studies indicate that deficiency in IgG exacerbates arthritis in animal models. We are examining the potential mechanisms of IgG1 inhibition of inflammatory arthritis.

Division of Biomedical Informatics » Bruce Aronow and Anil Jegga
   We are building an integrated computational system for data mining of huge datasets relevant to human diseases.

Division of Allergy and Immunology » Mark Rothenberg
   Dr. Weirauch is involved in at least four different projects examining how transcription factor binding events contribute to the development of Eosinophilic Esophagitis.

Division of Human Genetics » C. Alexander Valencia
Dr. Weirauch has provided Bioinformatic analysis for a paper characterizing the targets of Granzyme B. Drs. Valencia and Weirauch are also applying for funding together for a joint experimental/computational platform for identifying transcription factor binding events that are disrupted by a given disease-associated genetic variant.

**Division of Pediatric Urology** » Joo-Seop Park

Dr. Weirauch aided in analysis of ChIP-seq results.

**Division of Developmental Biology** » Yutaka Yoshida

Dr. Weirauch is helping decipher the gene regulatory network controlling the expression of PLEXINA1 in the human brain.

**Division of Dermatology** » Kara Shah

Dr. Ting continues to have a joint Dermatology/ Rheumatology clinic with Dr. Kara Shah on a quarterly basis. This is a joint clinic to treat patients with identified or potential rheumatologic/ dermatologic conditions.

**Division of Behavioral Medicine and Clinical Psychology** » Dennis Drotar

Adherence in JIA and effect on outcomes.

**Division of Behavioral Medicine and Clinical Psychology** » Susmita Kashikar-Zuck

Dr. Ting collaborates with Dr. Kashikar-Zuck and her lab in behavioral medicine and clinical psychology for continued research in juvenile fibromyalgia. They continue to publish the findings from the longitudinal follow-up study and are working on the development of a new combined neuromuscular training and CBT program.

**Division of Human Genetics** » Taosheng Huang

Collaboration with Dr. Huang to help him find a "safe place" to target a TALEN protein to the OPA1 promoter, with the goal of establishing a therapy to increase its expression levels and prevent optic atrophy.

**Division of Human Genetics** » Kejian Zhang and Greg Grabowski

Drs. Harley and Kaufman have been working closely with Drs. Zhang and Grabowski on the development of exome sequencing as a clinical test.

**Division of Developmental Biology** » Brian Gebelein

Dr. Weirauch is helping elucidate the regulatory logic of an important enhancer in Drosophila development.

**Division of Allergy and Immunology** » Marc Rothenberg

Drs. Harley and Kaufman are collaborating with Dr. Rotherberg on the GWAS of Eosinophilic Esophagitis.

**Division of Human Genetics; Division of Endocrinology** » Lisa Martin and Nancy Crimmins

Dr. Harley is collaborating on the genetics of early childhood obesity.

**Division of Biomedical Informatics** » John Hutton, Imre Solti, Keith Marsolo, and Michael Wagner

Dr. Harley, Cincinnati Children's site leader for the eMERGE Network project, is working closely with Drs. Hutton, Solti, Marsolo and Wagner.

**Division of Neonatology and Pulmonary Biology** » Louis Muglia

Genetics of prematurity - with Drs. Harley and Kaufman

**Division of Pediatric Ophthalmology** » Richard Lang

Genetics of retinal toxicity of prematurity - with Drs. Harley and Kaufman.

**Division of Human Genetics** » Mehdi Keddache

Exome sequencing - Drs. Harley and Kaufman

**Division of Human Genetics; Division of Anesthesia** » Cindy Prows and Senthil Sadhasivam

Return of genetic results - Dr. Harley collaborates with Nurse Prows and Dr. Sadhasivam on various ROR
Division of Clinical Pharmacology ; Division of Human Genetics » Sander Vinks , Kejian Zhang, and Cindy Prows

Dr. Harley collaborates with Drs. Vinks, Zhang and Nurse Prows on CYP2D6 data generation and incorporation with next generation pharmacogenomics data.

Division of Immunobiology » Lee Grimes

Drs. Harley and Kaufman collaborate with Dr. Grimes on exome sequencing in severe congenital neutropenia.

Division of Neonatology and Pulmonary Biology » Paul Kingma

Drs. Harley and Kaufman collaborate with Dr. Kingma on the genetics of congenital diaphragmatic hemia.

Division of Neonatology and Pulmonary Biology » Paul Kingma and James Greenberg

Drs. Harley and Kaufman collaborate with Dr. Kingma and Dr. Greenberg on various genomics projects: Polymicrogyria, Esophageal Atresia, Situs Inversus.

Division of Infectious Diseases » Peggy Hostetter

Drs. Harley and Kaufman collaborate with Dr. Hostetter on the genetics of Disseminated staph.

Division of Anesthesia » Vidya Chidambaran and Senthil Sadhasavam

Depressed Respiratory Condition with Opioid Use/Treatment - Dr. Harley

Division of Neonatology and Pulmonary Biology » Bruce Trapnell

Tracheal Ring Deformity - Dr. Harley

Division of Endocrinology » Nancy Crimmins

Early onset obesity - Dr. Harley

Division of Neonatology and Pulmonary Biology » Ardythe Morrow

Genetics of neonatal necrotizing colitis - Dr. Harley

Division of Asthma Research » Neeru Hershey

Genetics of asthma - Dr. Harley

Division of Developmental & Behavioral Pediatrics » Patty Manning

Genetics of autism - Dr. Harley

Division of Bone Marrow Transplantation & Immune Deficiency ; Division of Immunobiology » Kasiani Myers and Lee Grimes

Bone marrow failure syndromes including neutropenia - Dr. Harley

Division of Experimental Hematology » Jame Mulloy

Lente virus vector construction for ionizing radiation project - Dr. Harley

Division of Human Genetics ; Division of Occupational and Physical Therapy ; Division of Child Life ; Division of Behavioral Medicine and Clinical Psychology »

Dr. Ting acts as the medical leader for the Intensive Physical Therapy Program for children and adolescents with joint hypermobility and chronic pain. This recurring two week program has continued to prove successful and is quickly increasing in size. We hope to recruit additional patients for the coming year and to begin evaluating outcomes of the program.

Division of Biomedical Informatics »

Ongoing project with PR-COIN (led by Dr. Morgan DeWitt) on upload of Epic electronic health record data into the PR-COIN registry, this facilitates participation of Cincinnati Children's in the national QI learning network to
improve care and outcomes of children with JIA. This allows a data-in-once strategy, with data entered at point of care to be used for quality improvement and research.

Grants, Contracts, and Industry Agreements

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| **BRUNNER, H**            |               |
| **Amgen TREAT**           |               |
| Amgen, Inc. (Children's Hospital & Regional Medical Center-Seattle) | $5,000 |
| 10/14/08-06/30/13 |   |
| **An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis** |               |
| Bristol -Myers Squibb     |               |
| 02/01/13-01/31/23 | $252,616 |
| **Forecasters of Future and Progressive CKD in Patients with Microvascular Glomerular Injury** |               |
| National Institutes of Health (Ohio State University) |               |
| U01 DK 085673 | 10/01/09-04/30/13 |
| **Progression of Autoimmunity During Puberty in SLE** |               |
| National Institutes of Health (Indiana University) | $38,504 |
| R56 AI 085258 | 04/01/12-08/31/13 |
| **Standardizing and Optimizing Treatment for Lupus Nephritis in Children** |               |
| Lupus Foundation (The Regents of the University of California) | $12,402 |
| 10/01/11-09/27/13 |   |
| **Childhood Arthritis and Rheumatology Research Alliance Registry (“CARRA Registry”)** |               |
| Duke University | $1,125 |
| 09/01/12-08/31/13 |   |

| **GROM, A**               |               |
| **MUNC13-4 gene Polymorphisms in Macrophage Activation Syndrome and Systemic Juvenile Idiopathic Arthritis** | $225,000 |
| National Institutes of Health |               |
| R01 AR 059049 | 08/08/11-07/31/16 |

| **HARLEY, J**             |               |
| **Better Outcomes for Children: GWAS & PheWAS in eMERGEII** | $1,038,586 |
| National Institutes of Health |               |
| U01 HG 006828 | 05/15/12-04/30/15 |

| **Genetic Linkage in Lupus** |               |
National Institutes of Health

R37 AI 024717 09/07/10-02/28/15 $260,844

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

W81XWH-10-1-0675 09/01/10-08/31/13 $168,159

Genomics of Lupus
National Institutes of Health(Oklahoma Medical Research Foundation)
P01 AI 083194 08/01/11-07/31/14 $172,577

Identification of Diagnostic Markers for Lupus Nephritis
National Institutes of Health(University of Louisville)
R21 AI 103980 01/18/13-12/31/14 $50,000

Genetic Lupus Associations in the Hispanic 12q24 Linkage (Project 2)
National Institutes of Health(University of Alabama-Birmingham)
P01 AR 49084 04/01/11-03/31/13 $90,695

HUGGINS, J.

ACR REF / AMGEN Rheumatology Fellowship Training Award
Rheumatology Research Foundation
07/01/13-06/30/2014 $25,000

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 $30,108

KOTTYAN, L

Center for Environmental Genetics (Kotyan)
National Institutes of Health(University of Cincinnati)
P30 ES 006096 04/01/11-03/31/12 $1,080

LOVELL, D

Camp Wekandu at Camp Joy 2013
The Dayton Foundation
04/01/13-03/31/14 $1,800

Multidisciplinary Clinical Research Center
National Institutes of Health
P60 AR 047784 08/18/08-07/31/13 $837,145

Lovell, Daniel Administrative Core $70,673
Giannini, Edward Methods Core $151,589
Brunner, Hermine Project 1 $238,624
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**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 $415,393

**THOMPSON, S**

**Gene Expression In Pediatric Arthritis**
National Institutes of Health

P01 AR 048929 09/01/11-08/31/16 $971,484

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**THOMPSON, S**

**Cincinnati Rheumatic Disease Core Center**
National Institutes of Health

P30 AR 047363 08/25/11-06/30/16 $395,722

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## Exome Sequencing Studies in Juvenile Idiopathic Arthritis

**Arthritis Foundation**

01/01/13-12/31/14  $92,593

### Current Year Direct

$5,167,310

### Industry Contracts

#### BRUNNER, H

- Abbott Laboratories  $35,989
- Centocor, Inc  $120,460
- Eli Lilly and Company  $2,986
- GlaxoSmithKline  $7,007
- Pharmanet LLC  $3,157
- UCB Pharma, Inc  $44,792

#### GROM, A

- Roche Laboratories, Inc  $10,318

#### LOVELL, D

- Astrazeneca  $8,701
- Bristol-Myers Squibb  $304,446
- Centocor, Inc  $65,895
- Hoffman-LaRoche, Inc  $4,390
- Novartis Pharmaceuticals  $153,511
- Roche Laboratories, Inc  $80,785

### Current Year Direct Receipts

$842,437

### Total

$6,009,747