Rheumatology

Division Photo

First Row: E. Giannini, E. Morgan DeWitt, S. Thornton, J. Harley, D. Lovell, H. Brunner, J. Taylor; Second Row: S. Thompson, T. Ting, T. Griffin, M. Henrickson; Not pictured: D. Glass, A. Grom, J. Huggins

Division Data Summary

Research and Training Details	
Number of Faculty	13
Number of Research Students	2
Number of Support Personnel	43
Direct Annual Grant Support	$4,117,231
Direct Annual Industry Support	$817,070
Peer Reviewed Publications	44

Clinical Activities and Training	
Number of Clinical Staff	8
Number of Clinical Fellows	6
Number of Other Students	10
Inpatient Encounters	3,510
Outpatient Encounters	4,006

Significant Publications

. C. H. Hinze, M. Suzuki, M. Klein-Gitelman, M. H. Passo, J. Olson, N. G. Singer, K. A. Haines, K. Onel, K. O'Neil, E. D. Silverman, L. Tucker, J. Ying, P. Devarajan and H. I. Brunner. Neutrophil gelatinase-associated lipocalin is a predictor of the course of global and renal childhood-onset systemic lupus erythematosus disease activity. Arthritis Rheum. 2009;60(9):2772-2781.

This manuscripts reflects a longstanding, very productive collaboration between the Divisions of Rheumatology and Nephrology at CCHMC to identify and validate biomarkers for disease manifestations in childhood-onset systemic lupus erythematosus (cSLE). Neutrophil gelatinase-associated lipocalin measured in the serum was found to accurately predict systemic flares and, if measured in the urine, renal flares, up to three months before any clinical

worsening was evident.

H. I. Brunner, G. C. Higgins, K. Wiers, S. K. Lapidus, J. C. Olson, K. Onel, M. Punaro, J. Ying, M. S. Klein-Gitelman and E. H. Giannini. Prospective validation of the provisional criteria for the evaluation of response to therapy in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62(3):335-344.

This manuscript reflects an ongoing focus of this Division on research in children and adolescents with systemic lupus erythematosus. In this study, our Division designed and coordinated a multi-center study to scientifically validate a standardized definition for response to therapy. This is a critical component to performing effective, valid studies of new therapies in childhood onset SLE.

L. D. Heinlen, L. L. Ritterhouse, M. T. McClain, M. P. Keith, B. R. Neas, J. B. Harley and J. A. James. Ribosomal P autoantibodies are present before SLE onset and are directed against non-C-terminal peptides. J Mol Med. 2010;88(7):719-727.

Autoantibodies to ribosomal P (ribo P) are found in 15-30% of sytemic lupus erythematosus (SLE) patients and are highly specific for SLE. This study provides evidence that antibodies against ribosomal P frequently develop before clinical SLE diagnosis (on average more than a year earlire) and are more broadly reactive than previously thought by targeting regions outside of the C terminus.

T. A. Griffin, M. G. Barnes, N. T. Ilowite, J. C. Olson, D. D. Sherry, B. S. Gottlieb, B. J. Aronow, P. Pavlidis, C. H. Hinze, S. Thornton, S. D. Thompson, A. A. Grom, R. A. Colbert and D. N. Glass. Gene expression signatures in polyarticular juvenile idiopathic arthritis demonstrate disease heterogeneity and offer a molecular classification of disease subsets. Arthritis Rheum. 2009;60(7):2113-2123.

This article builds on longstanding research focus in the Division on the genetic basis for chronic arthritis in children. This manuscript demonstrates that, at the beginning of arthritis, even in children that appear similar clinically, there are very different gene expression profiles and probably different disease processes.

E. H. Giannini, N. T. Ilowite, D. J. Lovell, C. A. Wallace, C. E. Rabinovich, A. Reiff, G. Higgins, B. Gottlieb, Y. Chon, N. Zhang and S. W. Baumgartner. Effects of long-term etanercept treatment on growth in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2010.

This article reflects a long-standing focus of this Division - evaluating new therapies for the children with Juvenile Idiopathic Arthritis (JIA). This study is the first and largest post-marketing safety registry of a biologic agent in JIA patients. This Division designed and coordinated the performance of this study that demonstrated in almost 600 JIA patients that etanercept was safe and led to normalizing growth in this chronically ill population of children.

Faculty Members

John Harley, MD, PhD, Professor ; *Division Director*

Hermine Brunner, MD, MSc, Associate Professor

Edward H. Giannini, MSc, DrPH, Professor

David N. Glass, MD, Professor

Thomas Griffin, MD, PhD, Research Associate Professor

Alexei A. Grom, MD, Research Associate Professor

Michael Henrickson, MD, MPH, Associate Professor Clinical ; *Clinical Director*

Jennifer Huggins, MD, Assistant Professor Clinical ; *Fellowship Director*

Daniel Joe Lovell, MD, MPH, Professor ; *Joseph E. Levinson Endowed Chair in Pediatric Rheumatology*

Esi Morgan DeWitt, MD, MSCE, Assistant Professor

Susan Thompson, PhD, Associate Professor ; *Associate Director*

Sherry Thornton, PhD, Research Assistant Professor

Tracy Ting, MD, Assistant Professor

Clinical Staff Members

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

Trainees

- **Lena Das, MD,** PGY-VI, Memorial University of Newfoundland, Canada
- **Anna Carmela Sagcal, MD,** PGY-VI, University of the Phillipines
- **Rina Mina, MD,** PGY-VI, Downstate Medical Center New York
- **Annette Lopez-Martinez, MD,** PGY-V, University of Puerto Rico Pediatric Hospital
- **David Moser, DO,** PGY-IV, United States Army, Pediatrics
- **Keith Sikora, MD,** PGY-IV, Johns Hopkins Hospital
- **Li Sun, MD,** Children's Hospital of Fudan University, Shanghai, China

Significant Accomplishments

Studying genetic risk factors for JIA

Genetic risk factors identified for juvenile idiopathic arthritis (JIA) may have important implications for the disease. The innovative translational research of Susan Thompson, PhD, David Glass, MD, Alexei Grom, MD, and Thomas Griffin, MD, PhD, continue to be directed towards the understanding the molecular basis of JIA, a heterogeneous disease with several subtypes.

Genomic and gene expression JIA datasets, of unprecedented scope, are being used to define the disease at a molecular level. Recent published data support a reevaluation of the present clinical criteria for defining JIA subtypes. Ongoing research also is focused on providing insight into disease origins and pathogenesis. The data includes high-resolution HLA allele types, single nucleotide polymorphisms (SNP) and gene expression data.

We have identified risk factors in common with other autoimmune diseases and have found evidence in cohorts of JIA patients and controls that associate JIA with 3q13, a region containing the T-cell receptor co-stimulatory molecule CD80. We also identified the gene expression signature of Macrophage Activation Syndrome (MAS); candidate biomarkers for the early diagnosis of MAS; and a novel genetic marker strongly associated with MAS. MAS is a manifestation of JIA associated with high morbidity and is the leading cause of JIA-related mortality.

National leadership in quality improvement

We continue to improve the quality of care and outcomes for children with JIA using quality improvement (QI) techniques. Daniel Lovell, MD, Edward Giannini, MSc, DrPH, Michael Henrickson, MD, MPH, Esi Morgan DeWitt, MD, and Janalee Taylor, RN, PNP, have assumed leadership roles in national QI efforts for children with JIA.

Lovell formed and chaired the national JIA Quality Measures Workgroup that developed quality measures to assess the performance of health care professionals and outcomes for children with JIA. A resulting article, “Measuring process of arthritis care: a proposed set of quality measures for juvenile idiopathic arthritis,” has been accepted for publication in *Arthritis Care Research* this year.

Morgan DeWitt will use these QI measures to lead a national consortium of pediatric rheumatology centers in a coordinated effort starting later this year. She took the consortium, the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN), from concept to reality with funding from the Arthritis Foundation, the Hinchman Family Foundation and Cincinnati Children's Center for Education and Research in Therapeutics.

Advancing lupus research

Hermine Brunner, MD, and her research team identified features that impair the quality of life of children and adolescents with lupus -- fatigue, joint and chest pain, and neurocognitive symptoms.

In multicenter and multinational collaborations, this research team has developed outcome measures for pediatric lupus clinical trials. They established clinically relevant differences in lupus disease activity; developed flare criteria; and created a standardized battery of tests for neurocognitive functioning of children with lupus. With our Division of Nephrology, they also helped develop the first biomarker for lupus nephritis to predict renal flares.

In collaborative research with our Pediatric Pharmacology Unit, they determined the personalized dosing of mycophenolate mofetil for optimal disease control in childhood-onset systemic lupus erythematosis.

Division Publications

1. :

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

Brunner, H

Efficacy Measures for Pediatric Lupus Studies
National Institutes of Health
U01 AR 055054 — 08/17/07 - 07/31/10 — $132,061 / $396,400

Forecasters of Future and Progressive Chronic Kidney Disease in Patients with Microvascular Glomerular Injury
Ohio State University (National Institutes of Health)
U01 DK 085673 — 10/01/09 - 09/30/14 — $11,284 / $511,284

Early Agressive Therapy in Juvenile Idiopathic Arthritis
Children's Hosp & Reg Med Ct-Seattle (National Institutes of Health)
R01AR049762 — 09/01/06 - 08/31/11 — $20,117 / $119,884

Efficacy Measures in Pediatric Lupus
National Institutes of Health
U01 AR 055054 — 09/18/09 - 09/17/10 — $87,811 / $87,811

Flick, M

Mechanisms Linking the Hemostatic Protease Thrombin to Arthritic Disease
National Institutes of Health
R01 AR 056990 — 08/10/09 - 07/31/14 — $180,000 / $960,000

Glass, D

Research Registry for Juvenile Rheumatoid Arthritis
National Institutes of Health
N01 AR 042272 — 09/30/04 - 03/31/11 — $853,693 / $5,059,660

HLA/KIR Region Genetics in Pediatric Arthritis
National Institutes of Health
U01 AI 67150 — 09/01/09 - 03/31/11 — $200,716 / $200,716

HLA/KIR Region Genetics in Pediatric Arthritis
National Institutes of Health
U01 AI 67150 — 06/28/10 - 03/31/11 — $184,232 / $184,232

Griffin, T

HLA-B27 Misfolding an the UPR in Spondyloarthritis
National Institutes of Health
R01 AR 046177 — 09/01/06 - 06/30/11 — $269,451 / $1,357,821

Lovell, D

Early Aggressive Therapy in Juvenile Idiopathic Arthritis
Children's Hosp & Reg Med Ct-Seattle (National Institutes of Health)
09/01/06 - 04/30/11 — $108,780 / $401,811

Multidisciplinary Clinical Research Center
National Institutes of Health
P60 AR 047784 — 08/18/08 - 07/31/13 — $829,776 / $4,210,600

Lovell, D	Administrative Core	68,872
Giannini, E	Methodology Core	109,718
Brunner, H	Project 1	175,862
Lovell, D	Project 2	168,915
Grom, A	Project 3	159,616
Seid, M	Project 4	148,793

IL-1 Trap for Treatment of Familial Mediterranean Fever
Cleveland Clin Lerner Col of Med of CWRU
R01 FD 003435 03/01/09 - 02/28/11 $77,731 / $123,896

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 $324,401 / $1,297,604

Thompson, S

Cincinnati Rheumatic Disease Core Center
National Institutes of Health
P30 AR 047363 09/01/06 - 06/30/11 $406,233 / $1,971,433

Thompson, S	Administrative Core	123,566
Thompson, S	Core 1 - Tissue	29,791
Degen, J	Core 2 - Animal Models of Arthritis/Inflammatory Disease	65,815
Thornton, S	Core 3 - Phenotyping	79,964
Wagner, M	Core 4 - Informatics	57,097
Strait, R	P&F Study	50,000

IL-1 Inhibition in Systemic Juvenile Idiopathic Arthritis
Albert Einstein College of Medicine (National Institutes of Health)
HHSN268200700015C 08/15/07 - 08/14/11 $22,828 / $77,773

Genetics of Juvenile Idiopathic Arthritis and Subtypes
Wake Forest University (National Institutes of Health)
R01 AR 057106 09/24/09 - 08/31/11 $45,721 / $92,814

Defining the Complex Genetics of Juvenile Idiopathic Arthritis
National Institutes of Health
RC1 AR 058587 09/28/09 - 08/31/11 $333,333 / $666,666

CARRA: Accelerating Toward an Evidence Based Culture in Pediatric Rheumatology
Duke University (National Institutes of Health)
RC2 AR 058934 09/30/09 - 09/29/11 $29,063 / $48,697

Current Year Direct **$4,117,231**

Industry Contracts

Brunner, H

Pfizer, Inc	$ 49,159
Abbott Laboratories	$ 35,933

Lovell, D

Pfizer, Inc	$ 105,027
Roche Laboratories, Inc.	$ 259,313
Novartis Pharmaceuticals	$ 367,638

Current Year Direct Receipts **$817,070**

Total $4,934,301