Rheumatology

Division Photo

Front row (seated): H. Brunner; J. Taylor; D. Lovell; E. Giannini; Second row (standing): S. Thompson; J. Huggins; M. Flick; G. Layh Schmitt; S. Thornton; T. Griffin

Division Data Summary

Research and Training Details

<table>
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<tr>
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Clinical Activities and Training

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<tr>
<td>Outpatient Encounters</td>
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Faculty Members

Robert Colbert, MD, PhD,  Professor
Hermine Brunner, MD, MSc,  Associate Professor
Matthew Flick, PhD,  Research Instructor
Edward H. Giannini, MSc, DrPH,  Professor
David N. Glass, MD,  Professor
T. Brent Graham, MD,  Assistant Professor Clinical
Thomas Griffin, MD, PhD,  Research Assistant Professor
Clinical Staff Members

- Janalee Taylor, MSN, RN, CNP

Trainees

- Lisa K. Petiniot, MD, PGY-VIII, Cincinnati Children's Hospital Medical Center
- Kristina M. Wiers, MD, PGY-VI, Maimonides Medical Center
- Claas Hinze, MD, PGY-V, Cincinnati Children's Hospital Medical Center
- Tracy V. Ting, MD, PGY-V, Cleveland Clinic Foundation
- Lena Das, MD, PGY-IV, Memorial University of Newfoundland, Canada
- Anna Carmela Sagcal, MD, PGY-IV, University of the Philippines
- XueMei Tang, MD, Chongqing Medical University

Significant Accomplishments in FY08

Juvenile Arthritis Treatment Research

The Division serves as the coordinating center for an international group of over 70 pediatric rheumatology centers dedicated to performing clinical trials in children with Juvenile Idiopathic Arthritis (JIA) called The Pediatric Rheumatology Collaborative Study Group (PRCSG). Daniel Lovell, MD, MPH serves as the chairman of this group and beginning in 2007 Hermine Brunner, MD, MSc began serving as the Scientific Director. For the prior 30 years Edward Giannini, MSc, DrPH, also a member of our Division had served in that role. In 2007, a double-blind randomized controlled trial that had been performed by members of the PRCSG served as the basis for appreciation of pediatric specific dosing issues and safety concerns for a frequently used biologic therapy, infliximab, for the treatment of children with severe, treatment resistant polyarticular JIA. Dr. Giannini has served for the past 7 years of the recently completed study entitled “Etanercept Registry in Juvenile Idiopathic Arthritis”. This study enrolled 601 patients who were followed for up to 3 years to determine the longer-term safety of etanercept, a TNF inhibitor. The resulting database constitutes the largest safety database in existence of any biologic in children with arthritis. Division members serve as the overall study coordinating center for an innovative NIH funded randomized, placebo controlled trial of combination therapy in new onset JIA to induce remission (NIH/NIAMS RO1 “Early Aggressive Therapy in Juvenile Idiopathic Arthritis”) and an FDA funded investigator initiated randomized trial in patients with Familial Mediterranean Fever. Division investigators serve as principal investigators on a study determining the long term safety of etanercept in children with JIA and are leading in the development of trials of biologic agents blocking interleukin1 and interleukin 6 in children with Systemic JIA.


Systemic Lupus Erythematosus Research

The CCHMC Division of Rheumatology has engaged in several externally funded research projects in SLE. Dr. Brunner serves as the overall study PI for several multi-center studies, including a FDA-funded Phase I/II trial to test the safety of
Genomic studies of Juvenile Idiopathic Arthritis

And multiple sclerosis. Thus, progress in other autoimmune disease results in the identification of candidate genes is not limited to juvenile idiopathic arthritis (JIA). Some susceptibility polymorphisms are unique to JIA or its subtypes while other polymorphisms influence the risk to a variety of autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and autoimmune kidney disease). Gene-environment interactions also play a role in the etiology of JIA.

A central focus of the laboratory research efforts of the Division for many years has been to better understand the role of genes and their expression patterns in the subtypes of JIA. The genetic features of JIA are complex and it is clear that additional research is needed to identify the genetic factors involved in JIA.


Genomic studies of Juvenile Idiopathic Arthritis

A central focus of the laboratory research efforts of the Division for many years has been to better understand the role of genes and their expression patterns in the subtypes of JIA. The genetic features of JIA are complex and it is clear that some susceptibility polymorphisms are unique to JIA or its subtypes while other polymorphisms influence the risk to a number of autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease...
and multiple sclerosis). Thus, progress in other autoimmune disease results in the identification of candidate genes is being leveraged for testing in JIA. At the same time, the unique features of JIA require new well-powered genetic association analyses. Genome-wide single nucleotide polymorphism (SNP) association analysis comparing oligoarticular and polyarticular JIA, high-resolution HLA genotyping, and subtype specific measurements of gene expression represent three large-scale discovery-based approaches being used in our laboratory. These approaches have accelerated the understanding of the genetic traits contributing to JIA and the molecular profiles that are potentially relevant to diagnosis, outcome and therapeutic response. Genome-wide association analysis has resulted in the identification of a genetic variant near Krüppel-like factor 13 (KLF13) which is thus far uniquely associated with oligoarticular JIA. We have confirmed this finding in an independent European cohort. KLF13 is a member of a family of transcription factors and a positive regulator of CCL5 (commonly known as RANTES). This is of interest since CCL5 is a ligand for CCR5 which is commonly expressed on T cells in inflamed JIA joints. In addition, genetic association with JIA has been confirmed for variation in the genes PTPN22, PTPN2, IL7R, IL2Ra and STAT4, all of which have reported associations in other autoimmune diseases. Merging the data from the genome-wide SNP studies and high resolution HLA typing will lead to a new understanding in JIA of the HLA region at the haplotype level.

In complementary gene expression studies, several unique or overlapping patterns have been identified in peripheral blood samples from patients with JIA compared with controls. Analyzing these expression patterns indicated involvement of the IL-10 signaling pathway for all subtypes of JIA studied (ERA, oligoarticular, polyarticular, systemic). Other pathways identified provide support for the concept that systemic JIA is an autoinflammatory disease while the remaining JIA subtypes are autoimmune diseases. Further analysis of the differentially expressed genes relative to disease subtype suggests that the current JIA classification scheme may not be optimal. Through the discovery of genetic associations and the associated pathways important mechanistic information with respect to JIA subtypes and the similarities of JIA to other autoimmune diseases will be established.

Fall N, Barnes M, Thornton S, Luyrink L, Olson J, llowite NT, Gottlieb, BS, Griffin, TB, Sherry, DD, Thompson, SD, Glass, DN, Colbert, RA, Grom, AA. Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals molecular heterogeneity that may predict macrophage activation syndrome. Arthritis Rheum 2007;56(11):3793-804.


Significant Publications in FY08


First publication to identify biomarkers for macrophage activation syndrome in systemic JIA patients and to identify high risk sub-population of patients.


Large randomized placebo controlled trial that identified pediatric specific dosing and safety concerns for infliximab. This publication significantly changed clinical practice guidelines for use of infliximab in children with JRA.


Identified a highly sensitive biomarker for active disease in the kidney in children with SLE.

This publication demonstrated a mechanism for the relationship between B27 and inflammation. This provided additional support for a novel hypothesis for spondyloarthritis proposed by Dr. Colbert.


Longest continuous exposure to Etanercept in published literature. Contains subjects from the original Phase 3 study. Demonstrated continued benefit and lack of any additional safety concerns.

**Division Highlights**

The Division of Rheumatology strives to be a national and international leader in patient care, research, and education in pediatric rheumatic diseases. As one of the largest pediatric rheumatology divisions in North America, providers logged over 7,000 patient encounters last year. While the majority of this activity occurs in Treatment Center 14 at CCHMC, there is a considerable outreach effort. Dr. Thomas A. Griffin has been responsible for a clinic at Toledo Children’s Hospital, where over 300 patients were seen in 2008. Dr. Griffin also travels to St. Vincent Children’s Hospital north of Indianapolis, IN, where he provides care for close to 50 children. The Division has an active Fellowship Training Program that is supported by an NIH T32 grant, and there are currently 6 fellows at various stages of training.

Research in the Division spans clinical, translational, and laboratory-based based investigation. It is the home of the Pediatric Rheumatology Collaborative Study Group (PRCSG) and an active participant in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) network. Eight Clinical Research Coordinators recruit and enroll patients in clinical and translational protocols focused on therapeutics, outcomes, health care delivery, the discovery and use of biomarkers, and a better understanding of genetic susceptibility and pathogenesis. There is also a considerable laboratory-based research effort that includes animal models of rheumatic diseases, with programs in genetics, arthritis pathogenesis, and T cell biology.

The Division is actively involved in quality improvement projects, with efforts spearheaded by Dr. Murray Passo and Janalee Taylor, MSN, RN, CNP. The focus has been on children with juvenile idiopathic arthritis (JIA) with expanding efforts to include systemic lupus erythematosus (SLE).

The Division of Rheumatology was one of first CCHMC divisions to pilot the Epic outpatient electronic medical record system.

### Division Collaboration

**Collaboration with Division of Immunology**

**Collaborating Faculty: Fred Finkelman, MD**

Dr. Finkelman serves on the Scientific Advisory Committee for the Division and serves as mentor for several research faculty.

**Collaboration with Division of Developmental Biology**

**Collaborating Faculty: Jay Degen, PhD**

Dr. Degen collaborates with Matthew J. Flick to investigate the role of the coagulation protein fibrinogen in inflammatory arthritis.

**Collaboration with Division of Behavioral Medicine & Clinical Psychology**

**Collaborating Faculty: Susmita Kashikar-Zuck, PhD**

Drs. Lovell and Ting participate as investigators on two NIH-funded projects in patients with fibromyalgia-longitudinal observation study and interventional trial.

**Collaboration with Biomedical Informatics**

**Collaborating Faculty: Michael Wagner, PhD**

Dr. Wagner is the Core Director of the P30 Informatics Core and serves as a Co-Investigator on Susan D. Thompson's Integrative Genomics grant.

**Collaboration with Biomedical Informatics**

**Collaborating Faculty: Jarek Meller, PhD**
Collaboration with Biomedical Informatics

**Collaborating Faculty: Jarek Meller, PhD and Michael Wagner, PhD**

Drs. Meller and Wagner collaborate with Susan D. Thompson to develop new methods for combining different levels of genomic data to provide new insight into JIA. These datasets include genome-wide SNP and Copy number data, global gene expression data and high resolution HLA typing data.

Collaboration with Human Genetics

**Collaborating Faculty: William Nichols, PhD**

Dr. Nichols serves as a co-investigator for investigations of JIA as a complex genetic trait with added expertise for fine mapping needs.

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**Division Publications**


Grants, Contracts, and Industry Agreements

Grant and Contract Awards

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<th>Brunner, H</th>
<th>Triptorelin for Ovary Protection in Childhood Lupus</th>
<th>Food and Drug Administration</th>
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<th>09/30/03 - 09/29/08</th>
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<td>Efficacy Measures for Pediatric Lupus Studies</td>
<td>National Institutes of Health</td>
<td>U01 AR 055054</td>
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<td>National Institutes of Health (Children's Hospital and Regional Medical Center-Seattle)</td>
<td>R01 AR 049762</td>
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Colbert, R.

**Gene Expression In Pediatric Arthritis**
National Institutes of Health
P01 AR 048929 08/22/03 - 07/31/08 $949,059 / $5,234,051

Colbert, R  Administrative Core  481,529
Thompson, S  Core A  94,268
Pestian, J  Core B  64,614
Glass, D  Project 1  100,521
Colbert, R  Project 3  89,695
Grom, A  Project 4  118,432

**Pediatric Rheumatology Training Grant**
National Institutes of Health
T32 AR 007594 05/01/05 - 04/30/10 $282,840 / $1,464,420

**Mechanism and Consequences of HLA-B27 Misfolding**
National Institutes of Health
R01 AR 046177 09/01/06 - 06/30/11 $270,561 / $1,409,806

Glass, D.

**Arthritis Foundation Gene Expression**
Arthritis Foundation 08/22/03 - 07/31/08 $250,000 / $1,290,000

**Research Registry for Juvenile Rheumatoid Arthritis**
National Institutes of Health
N01 AR 042272 09/30/04 - 09/29/09 $837,572 / $4,255,695

**HLA/KIR Region Genetics in Pediatric Arthritis**
National Institutes of Health
U01 AI 067150 09/30/05 - 03/31/10 $266,844 / $1,297,495

Griffin, T

**Role of Type I Interferons in a Self-Sustaining Murine Model of Mytosis**
National Institutes of Health
R21 AR 055702 09/14/07 - 08/31/09 $107,500 / $236,500

**Role of Immunoproteasomes in Activated T Cell Apoptosis**
National Institutes of Health
R21 AI 073584 09/20/07 - 08/31/09 $125,000 / $275,000

Lovell, D

**Kids on the Run; Distance Learning for Tomorrow's Rheumatologist**
American College of Rheumatology Research and Education Foundation 07/01/07 - 06/30/08 $15,000 / $15,000

**Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyosity**
National Institutes of Health (University of Pittsburgh)
N01 AR 042273 09/01/06 - 09/29/09 $56,674 / $170,022

**IL-1 Trap for Treatment of Familial Mediterranean Fever**
Food and Drug Administration (The Cleveland Clinic Lerner College of Medicine) 09/29/07 - 09/28/10 $83,041 / $183,059

**Early Aggressive Therapy in Juvenile Idiopathic Arthritis**
National Institutes of Health (Children's Hospital and Regional Medical Center-Seattle)
R01 AR 049762 09/01/06 - 08/31/11 $114,532 / $719,397

Thompson, S

**Nitric Oxide In Pediatric Statin-Treated SLE**
Cincinnati Rheumatic Diseases Core Center
National Institutes of Health
P30 AR 047363 09/01/06 - 06/30/11 $388,400 / $2,000,000

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**Current Year Direct** $4,216,305

**Industry Contracts**

- Giannini, E
  - Amgen Inc. $ 166,265
  - Genzyme Corporation $ 100,068

- Lovell, D
  - Regeneron Pharmaceuticals, Inc. $ 3,463
  - Roche Laboratories, Inc. $ 68,852

**Current Year Direct Receipts** $338,648

**Total** $4,554,953