Division Summary

**RESEARCH AND TRAINING DETAILS**

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**CLINICAL ACTIVITIES AND TRAINING**

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<tr>
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<td>Number of Other Students</td>
<td>56</td>
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<td>Inpatient Encounters</td>
<td>390</td>
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<td>Outpatient Encounters</td>
<td>5,031</td>
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Significant Accomplishments

**Clinical Trials Lead to a New Medication for JIA**

Daniel Lovell, MD, MPH, and Division Director Hermine Brunner, MD, MSc, lead the Pediatric Rheumatology Collaborative Study Group (PRCSG), a large research network that coordinates international clinical trials. A recent PRCSG study resulted in the regulatory approval of the interleukin-6 inhibitor, tocilizumab, for the treatment of moderately to severely active JIA by the US Food and Drug Administration as well as the European Medicines Agency. The successful completion of this trial and subsequent regulatory approval markedly increases the types of medications available to achieve inactive disease status and lessens the likelihood of longstanding disability from JIA.

**Progress in detecting mechanisms leading to juvenile arthritis and its complications**

Alexei Grom, MD, in collaboration the Novartis Institutes for Biomedical Research based in Switzerland, and CAGE performed whole-exome sequencing of patients with systemic juvenile arthritis (SJIA). These patients often develop macrophage activation syndrome (MAS), a severe complication of SJIA. De-novo mutations were identified that support the hypothesis that SJIA/MAS is due to alterations in genes affecting cellular assembly, morphology and function as well as cellular stress.

In collaboration with Experimental Hematology, Sherry Thornton, PhD, utilized animal models of arthritis to assess the role hemostatic factors play in the pathogenesis of arthritis. These studies identified plasminogen (and its interaction with other hemostatic factors) as a part of a mechanism explaining why joint inflammation is restricted to only some but not all joints of a patient with arthritis. This research also suggests that interventions at the level of hemostatic factors can be novel drug targets of inflammatory arthritic diseases.
Advances in the Diagnosis of Neuropsychiatric Lupus

Our Lupus Research Team co-developed and validated Pediatric Automated Neurocognitive Assessment Metrics, a PC-based software program, to serve as a screening tool for neuropsychiatric involvement in children with lupus. This research is complementary to Brunner’s innovative MRI-based imaging studies performed together with the Pediatric Neuroimaging Research Center. The investigators demonstrated gray and white matter degenerative changes in children with lupus. Such neurodegeneration is especially pronounced among children with overt cognitive impairment but is also present, albeit to a lesser degree, in children with SLE who have normal cognitive function based on clinical assessment.

Research Highlights

The role hemostatic factors play in the pathogenesis of arthritis
In collaboration with Experimental Hematology, Dr. Thornton utilized animal models of arthritis to assess the role hemostatic factors play in the pathogenesis of arthritis. Differential joint involvement in rheumatoid arthritis has long been appreciated and distinct anatomical location and symmetry/asymmetry of joint disease are important metrics in differential diagnosis of various forms of arthritis. Recent studies indicate plasminogen as a key molecular determinant of inflammatory joint disease that is capable of simultaneously driving or ameliorating arthritis pathogenesis depending on the anatomical location of the joint. Thus, plasminogen (and its interaction with other hemostatic factors) has been identified as a part of a potential mechanism of localization of inflammatory arthritis to specific joints. Furthermore, clinical interventions at the level of hemostatic factors may be a useful strategy in the treatment of some, but not all inflammatory arthritic diseases.

Proof-of-Concept Study Results
The Clinical Trial Unit of the Division led by Drs. Brunner and Lovell served as the coordinating center for a proof-of-concept study that showed early initiation of aggressive therapy of juvenile idiopathic arthritis (JIA) improves the likelihood of achieving clinical inactive disease and clinical remission on medication. This clinical trial was designed by Drs. Giannini and Lovell and innovative statistical analytical techniques were employed by Dr. Huang to accurately delineate the effects of various treatment strategies.

Interdivisional Research findings link Juvenile Fibromyalgia to Adulthood
In interdivisional research with Psychology, Drs. Ting and Kashikar-Zuck recently showed that children and adolescents with Juvenile Fibromyalgia (JFM) have a high likelihood of continued fibromyalgia symptoms into young adulthood with ongoing physical and emotional impairment+, suggesting the condition may be chronic.

Non-Medical Factors Can Reliably Predict HRQOL
Collaboration with researchers of the Division of Psychology provided strong evidence that various non-medical factors can reliably predict health-related quality of life (HRQOL) levels of children with JIA. A finding with particularly high clinical relevance is that child self-efficacy and social support are strongly associated with child-reported HRQOL. This study provides evidence that optimal disease management of JIA can only be brought about by effective drug therapy accompanied by comprehensive medical care and education of the families as well as the affected children.

Pediatric Rheumatology Care and Outcomes Improvement Network improves remission rates
The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is a multi-center quality improvement collaborative with the mission to dramatically improve the outcomes of children with JIA. PR-COIN is coordinated by The Anderson Center for Health Systems Excellence, with leadership from the Division of Rheumatology faculty (Principal Investigator, Dr. Morgan DeWitt. This growing network of 13 sites
has a shared registry that includes over 1,400 patients with JIA who have over 7,000 clinical encounters recorded. This database allows teams to track performance on quality measures of care and guide interventions for improved delivery of care. This past year PR-COIN has shown demonstrable improvement in increasing remission rates in children with JIA on medication by 10% over baseline rates.

Ultrasound in Pediatric Rheumatology
In the past year, Clinical Co-Director, Dr. Tracy Ting, has obtained certification in musculoskeletal ultrasound (MSUS) through the American College of Rheumatology. MSUS has many advantages over other imaging modalities, including its relative cost-effectiveness and its mobility, making it instantly accessible at a patient’s bedside. It is an emerging area of study in pediatric musculoskeletal diseases with wide ranging implications in improving the care of children with arthritis and similar conditions. Because MSUS substantially improves diagnostic and therapeutic capabilities, it opens research opportunities for the Division of Rheumatology and CCHMC.

Significant Publications


This study provides initial evidence there are morphologic changes in the gray and white matter of children with lupus, irrespective of the presence of clinically overt neuropsychiatric lupus. Brain degenerative changes correlate with cognitive ability. This information can be exploited as an imaging biomarker for neuropsychiatric lupus in children.


This study identified there are many determinants of health-related quality of life in children newly diagnosed with juvenile idiopathic arthritis only some of which directly related to the JIA. This suggests, to maximally improve health-related quality of life in these patients, the treatment needs to be multifactorial and not just JIA specific.


This publication provides qualitative data, from the first trial in JIA with clinical inactive disease as the primary outcome as to the frequency and time spent in clinical inactive disease in each of the treatment arms, further establishing the importance of early aggressive therapy in JIA.

Division Publications


32. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA,


Faculty, Staff, and Trainees

Faculty Members

Hermine Brunner, MD, MSc, MBA, Professor
Leadership Division Director

Edward H. Giannini, MSc, DrPH, Adjunct
Leadership Professor Emeritus

Alexei A. Grom, MD, Professor
Leadership Research Director
Michael Henrickson, MD, MPH, Associate Professor  
**Leadership** Telemedicine Program Director

Jennifer Huggins, MD, Associate Professor  
**Leadership** Fellowship and Education Program Director

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  
**Leadership** Quality Improvement Co-Leader & Transitional Service Co-Leader

Halima Moncrieffe, PhD, Instructor

Esi Morgan DeWitt, MD, MSCE, Associate Professor  
**Leadership** Quality Improvement Operations Director

Susan Thompson, PhD, Professor  
**Leadership** Cincinnati Rheumatic Disease Core Center Director

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

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

**Clinical Staff Members**
- Janalee Taylor, MSN, RN, CNS, CNP,  
  **Quality Improvement Co-Leader & Transition Service Co-Leader**

**Trainees**
- Jordan Jones, DO, PGY5, University of Kansas  
- Khalid Abulaban, MD, PGY6, Penn State Hershey Medical Center  
- Patricia Vega-Fernandez, MD, PGY7, University of Texas Health Science Center at San Antonio, Texas  
- Michal Feldon, MD, PGY4, Tel-Aviv University  
- Grant Schulert, MD, PGY5, Children's Hospital at Vanderbilt

**Division Collaboration**

The Division of Rheumatology (Drs. Lovell, Brunner and Giannini) collaborated with Dr. Bin Huang on the analysis of quality of life and biomarker studies in juvenile arthritis. Together with the Rheumatology Clinical Trial Unit, novel trial designs were employed to minimize sample size for a trial of a novel powerful treatment of Familial Mediterranean Fever. (Hermine Brunner, MD, MSc, MBA)

**Biostatistics and Epidemiology**  » Bin Huang, PhD

Together with Dr. Michael Seid, the Division of Rheumatology (Drs. Brunner and Lovell) studied determinants of health-related quality of life in children with juvenile idiopathic arthritis. The first Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is led by Dr. Morgan-DeWitt, working closely with the Anderson Center. (Hermine Brunner, MD, MSc, MBA)

**James M. Anderson Center for Health Systems Excellence**  » Michael Seid, PhD
There is ongoing collaborative research between Dr. Ting and Dr. Kashikar Zuck to develop evidence-based treatments for children with juvenile fibromyalgia syndromes. Dr. Brunner collaborates with Dr. Beebe on assessing cognitive changes of children with lupus. (Hermine Brunner, MD, MSc, MBA)

**Behavioral Medicine and Clinical Psychology** » Susmita Kashikar-Zuck, PhD and Dean Beebe, PhD, ABPP-Cn

Dr. Brunner collaborates with Drs. Bennett and Devarajan on the discovery and validation of biomarkers of lupus nephritis. (Hermine Brunner, MD, MSc, MBA)

**Nephrology and Hypertension** » Michael Bennett, PhD and Prasad Devarajan, MD

Dr. Brunner and Dr. Difrancesco collaboratively investigate imaging functional and structural imaging correlates of neuropsychiatric lupus. (Hermine Brunner, MD, MSc, MBA)

**Radiology** » Mark Difrancesco, PhD

Dr. Brunner and Dr. Witte conduct collaborative research on lupus nephritis and biomarker discovery. (Hermine Brunner, MD, MSc, MBA)

**Pathology and Laboratory Medicine** » David Witte, MD

Dr. Grom works with the team to identify mechanisms leading to macrophage activation syndrome. Dr. Thornton collaborates on research facilitating the assessment of Function in Sorted Dendritic Cells. (Alexei Grom, MD; Sherry L. Thornton, PhD)

**Immunobiology**

Dr. Huggins and Drs. Brady and Frenck studying evidence-based approaches to optimal vaccination strategies for children with lupus. (Jennifer L. Huggins, MD)

**Infectious Diseases** » Rebecca Brady, MD and Robert Frenck, MD

Dr. Lovell and Grom collaborate with Dr. Thompson to determine genetic risk factors and genetic predictors of medication response with juvenile idiopathic arthritis. (Alexei A. Grom, MD; Daniel J. Lovell, MD, MPH)

**Center for Autoimmune Genomics & Etiology** » Susan Thompson, PhD

In collaboration with Dr. Richard Strait, Dr. Thornton studies mechanism of IgG Inhibition in Inflammatory Arthritis. (Sherry L. Thornton, PhD)

**Emergency Medicine** » Richard Strait, MD

Dr. Sherry Thornton explores with Dr. Matthew Flick hemostatic factors contributing to inflammatory arthritis. (Sherry L. Thornton, PhD)

**Experimental Hematology** » Matthew Flick, PhD

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**Grants, Contracts, and Industry Agreements**

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**Childhood Arthritis and Research Alliance**

Arthritis Foundation (Duke University)
5554_CARRA 07/05/13-03/01/14 $500

Childhood Arthritis and Research Alliance Registry
Lupus Foundation (Duke University)

5590_CARRA 07/05/13-09/27/13 $115

Childhood Arthritis and Rheumatology Research Alliance
Arthritis Foundation (Duke University)

5686_CARRA 09/01/12-08/31/15 $800

Innovative Efficacy Measures of Lupus Nephritis Therapies
National Institutes of Health
U01 AR 065098 07/26/13-06/30/16 $148,838

Standardizing and Optimizing Childhood Lupus Nephritis
Arthritis Foundation (The Univ of California, San Francisco)
A120939 03/01/13-02/28/15 $7,654

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 $213,750

HUGGINS, J

ACR REF/Amgen Rheumatology Fellowship Training Award
Rheumatology Research Foundation
07/01/13-06/30/14 $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

MONCRIEFFE, H

AAI Early Career Faculty Travel Grant
American Association of Immunologists
05/02/14-06/01/14 $1,250

MORGAN DEWITT, E

Enhancing PROMIS in Pediatric Pain, Rheumatology, and Rehabilitation Research
National Institutes of Health
U01 AR 057940 09/30/09-07/31/14 $52,716

THOMPSON, S

Cincinnati Rheumatic Disease Core Center
National Institutes of Health
P30 AR 047363 08/25/11-06/30/16 $371,792
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**Exome Sequencing Studies in Juvenile Idiopathic Arthritis**

Arthritis Foundation

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

**Gene Expression In Pediatric Arthritis**

National Institutes of Health

P01 AR 048929 09/01/11-08/31/16 $932,350

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**Current Year Direct** $1,877,466

**Industry Contracts**

**BRUNNER, H**

- Abbott Laboratories $12,569
- Centocor, Inc $13,756
- Eli Lilly and Company $15,417
- GlaxoSmithKline $8,655
- UCB Pharma, Inc $44,380

**HUGGINS, J**

- Genentech, Inc. $8,393

**LOVELL, D**

- Astrazeneca $2,114
- Bristol -Myers Squibb $242,227
- Centocor, Inc $51,937
- Genentech, Inc. $61,668
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**Current Year Direct Receipts**  
$625,860

**Total**  
$2,503,326