

Division of Pediatric Rheumatology

DIVISION PROFILE	
Number of Faculty	12
Number of Fellows	
Clinical Fellows	5
Research Fellows	4
Number of Graduate Students	1
Number of Support Personnel	40
Annual Total Grant Support (direct)	\$4,677,114
Annual Total Industry Contracts (direct)	\$153,260
Number of Peer Reviewed Publications	18
Patient Encounters	
Outpatient	3,731
Inpatient	269

FACULTY LISTING

- David N. Glass, MD**, Professor of Pediatrics, Division Director William S. Rowe Division of Rheumatology
Hermine I. Brunner, MD, MSc, Research Assistant Professor of Pediatrics
Robert A. Colbert, MD, PhD, Associate Professor of Pediatrics, Associate Director William S. Rowe Division of Rheumatology; Associate Director of the MD/PhD Program University of Cincinnati
Edward H. Giannini, MSc, Dr. PH, Research Professor of Pediatrics, Co-Director of the Clinical Trials Unit
T. Brent Graham, MD, Assistant Professor of Pediatrics
Thomas A. Griffin, MD, PhD, Assistant Professor of Pediatrics
Alexei Grom, MD, PhD, Assistant Professor of Pediatrics
Joseph E. Levinson, MD, Professor Emeritus of Pediatrics
Daniel J. Lovell, MD, PMH, Professor of Pediatrics, Associate Director William S. Rowe Division of Rheumatology; Joseph E. Levinson Chair in Pediatric Rheumatology; Co-Director of the Clinical Trials Unit
Murray H. Passo, MD, Professor of Pediatrics, Director of the Division of Rheumatology Clinical and Training Programs
Susan Thompson, PhD, Research Associate Professor of Pediatrics
Sherry Thornton, PhD, Research Assistant Professor of Pediatrics

OVERVIEW

The division is coming to the end of its first cycle of focused clinical care initiatives, this first cycle has resulted in significant advances including the call center, adding additional nursing help in clinic and planning and beginning to execute a redesign of our clinic space, administrative offices and dry laboratory research areas. The structure of the new clinic allows for the integration of clinical, clinical research, translational research directly into clinical activities. A retreat which proved pivotal in planning activities for the next 5 years was held May 26. The retreat was structured around nominal group techniques and conducted by two faculty members Drs. Edward Giannini and Hermine Brunner. A major focus of interest that evolved during the discussion was the need to introduce electronic medical records, continue to expand and integrate the patient Registry into our informatics infrastructure and on the research side to give priority to the study of new biologics. It is anticipated that these changes will continue to

Outreach

Patient encounters for the Rheumatology Division also occurred at the following outreach clinics in FY 2004:

Outreach Clinic	Inpatient	Outpatient
Toledo Children's Hospital	12	456
Dayton Children's Medical Center	2	257

The above encounters were not included in the overall numbers that were listed in the division summary.

improve the quality of care delivered in the division and through the introduction of new biologics have the potential to impact the quality of life of all children throughout the United States with juvenile arthritis.

Another area of concern has been access to care. The environment at CCHMC is well provided for in terms of the professional team delivering high quality care in pediatric rheumatology, this is not so for big areas. Our training program has its goal of producing two graduates a year as an important part of the national effort directed at improving the availability of pediatric rheumatologists. Some States have insufficient pediatric rheumatology subspecialty care, Kentucky is one such. To improve access in the past we have focused our outreach efforts in Toledo and Dayton both within Ohio but attracting patients from Indiana and Michigan. The next step is to provide support for patients from Kentucky and to this end a clinic will be established initially in Florence at the CCHMC satellite. It is anticipated that this will act as a Center for patients, some of whom, would not have ventured as far as or been referred to Cincinnati itself.



Left to Right: (1st row) B. Graham, S. Thompson, H. Brunner, D. Glass, E. Giannini, (2nd row) T. Griffin, A. Grom, S. Thornton, M. Passo

HIGHLIGHTS

Systemic onset JRA and NK cell function, Dr. Alexei A. Grom.

Systemic Onset Juvenile Rheumatoid Arthritis and an associated condition known as Macrophage Activation Syndrome are severe and often devastating illnesses. The pathological mechanisms are not known but Dr. Alexei Grom has focused his research approach on NK and cytotoxic cell function in this disease. The rationale for this approach has been based on the strong clinical similarities between MAS and the better understood autosomal recessive disorder familial hemophagocytic lymphohistiocytosis, in which the uncontrolled proliferation of T cells and macrophages has been recently associated with decreased NK cell and cytotoxic cell functions secondary to mutations in the gene encoding perforin. Recent observations suggest as in FHLH, MAS patients also have profoundly depressed NK function. Moreover, a large subgroup of systemic JRA patient has very similar immunologic abnormalities. Combined with the evidence of the immunoregulatory role of NK cells in many immune responses, this suggests that NK dysfunction is relevant to the pathogenesis of MAS. New directions have thus been established for research in this poorly understood disease.

Future of Biologics in Pediatric Rheumatology, Dr. Daniel J. Lovell.

Biologics have revolutionized the treatment of many rheumatic diseases for both children and adults. These new biologic therapies result in profound improvement in the manifestations of a wide variety of rheumatic diseases and have been demonstrated in rheumatoid arthritis to stop the progression of the joint damage. So what does the future hold for biologics?

New biologic therapies continue to be developed at a very rapid rate. Some target in novel ways the inflammatory response while others provide more user-friendly or safe approaches to blocking known mechanisms of inflammation. These new biologics will continue to need to be tested in children to determine the proper dose, as well as the efficacy and safety in childhood rheumatic diseases. To do this properly will require multi-centered clinical trials.

An exciting area is the expansion of the use of biologic therapies into other rheumatic diseases. The trials to date in children have been focused on the most severe form of juvenile rheumatoid arthritis. Trials are in planning to address other subtypes of JRA, such as systemic JRA as well as complications of JRA such as the chronic, potentially blinding inflammatory eye disease called uveitis. In addition, other rheumatic diseases, such as lupus, dermatomyositis, spondyloarthropathies, sarcoidosis, Neonatal Onset Multisystem Inflammatory Disease (NOMID) and vasculitis in children have a great potential to be aided by biologic therapy. At this time no trials have been performed in children with these other rheumatic diseases looking at biologic therapies.

Identifying the most effective combinations of biologic therapies with traditional drug therapies has not been well studied. Because of the profound effectiveness of these treatments in controlling the disease, investigators are now thinking about induction of remission both on and off medications as a very real and possible outcome. However, no studies have been done to assess the practicality of this approach.

Biologic therapy is a relatively new approach to the treatment of rheumatic diseases and as such long-term safety has not been fully addressed. Large, longitudinally followed cohorts of patients will need to be studied to better assess the long-term safety of biologic therapy in children. In addition, the biologic therapies are costly and an important question is: what indicates that a patient can safely discontinue the therapy without risk (or minimal risk) of disease flare?

All of the above areas are important to understand thoroughly, and if understood thoroughly, will have profound effects on our treatment of children with rheumatic diseases and an improvement in these children's short-term and long-term outcome.

The Pediatric Rheumatology Division of Cincinnati Children's Hospital has been intimately involved in the design and execution of all of the biologic therapy trials in children with rheumatic diseases. Given the critical work to be done, our continued involvement in this area will remain a large part of our clinical research agenda for many years.

Clinical Improvement, Dr. Murray H. Passo and Janalee Taylor

The Division of Rheumatology has been a participant in the Pursuing Perfection Program for 3 years. Teams have been focused on improving outcomes for children with Juvenile Rheumatoid Arthritis (JRA), as well as the assessment and improvement of key drivers contributing to outcome. Specific drivers include function, pain, and quality of life assessed using functional measures of outcome. Function was measured by use of Childhood Health Assessment Questionnaire (CHAQ) and the Pediatric Quality of Life Questionnaire.

TRAINING

Natasha Ruth, MD	PL-IV	University South Carolina School of Medicine, Charleston, SC
Michael Shishov, MD	PL-IV	New York University Medical Center, New York, NY
Ruy Carrasco, MD	PL-V	University of New Mexico School of Medicine, Albuquerque, NM
Judith Smith, MD	PL-V	University of Chicago, Chicago, IL
Mina Chaudhari, MD	PL-VI	St. George's, Grenada
Dawn Sowders, PhD		Miami University, Miami, OH
Krupakar Jayarapu, PhD		Indian Institute of Science, India

CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract Awards	Annual Direct/Project Period Direct
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Brunner, H

Long-term Outcomes and Gonadal Function in Childhood Onset Systemic Erythematosus

Lupus Foundation

10/01/02 – 09/30/04 \$25,000/\$50,000

Prevention of Cardiovascular Pediatric Systemic Lupus Erythematosus

National Institutes of Health (Duke University subcontract)

N01 AR 02265 09/30/02 – 09/29/06 \$24,111/\$50,875

Guidelines for Steroids in Children with Lupus

National Institutes of Health

R03 AR 049860 05/08/03 – 04/30/06 \$50,000/\$150,000

Triptorelin for Ovary Protection in Childhood Lupus

Food and Drug Administration

FD-R-002369 09/30/03 – 09/29/06 \$300,000/\$900,000

Colbert, R

Mechanism and Consequences of HLA-B27 Misfolding

National Institutes of Health

R01 AR 46177 08/24/00 – 07/31/05 \$141,000/\$667,200

Pediatric Rheumatology Training Grant

National Institutes of Health

T32 AR 07594 05/01/00 – 04/30/05 \$203,480/\$696,023

HLA-B27 Misfolding in Spondyloarthritis Pathogenesis

National Institutes of Health

R01 AR 48372 09/28/01 – 08/31/06 \$250,000/\$1,250,000

Glass, D

NIAMS Multidisciplinary Clinical Research Center

National Institutes of Health

P60 AR 47784 09/01/01 - 6/30/06 \$600,322/\$3,218,871

Glass, D	\$32,262	Administrative Core
Giannini, E	\$125,680	Methodology Core
Kashikar-Zuck,S	\$129,008	Project 2
Dardzinski, B	\$141,936	Project 3
Glass, D	\$171,436	Project 4

Research Registry for Juvenile Rheumatoid Arthritis

National Institutes of Health

N01 AR 42218 09/30/99 – 09/20/04 \$612,352/\$2,899,279

Development of Sophisticated I.S. for the STC

Butler Foundation

07/01/01 – 6/30/04 \$60,000/\$186,303

Arthritis Foundation Gene Expression

Arthritis Foundation

08/22/03 – 07/31/08 \$285,319/\$1,200,000

Gene Expression in Pediatric Arthritis

National Institutes of Health

P01 AR 048929 08/22/03 – 07/31/08 \$1,061,470/\$5,234,051

Glass, D	\$522,738	Administrative Core
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Glass, D	\$100,269	Project 1
Colbert, R	\$84,939	Project 3
Grom, A	\$109,127	Project 4
Thompson, S	\$88,923	Core A
Pestian, J	\$155,474	Core B
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Griffin, T		
Assembly, Structure and Function of Proteasome Subsets		
Arthritis Foundation	07/01/99 – 06/30/04	\$52,000/\$320,000
Propeptide Mediation of Immuno Proteasome Assembly		
National Institutes of Health K08 AR 049733	04/15/03 – 03/31/07	\$110,750/\$443,000
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Grom, A		
Pathogenic Mechanisms of the Vasculopathy		
National Institutes of Health R21 AR 050828	09/30/03 – 5/31/05	\$100,000/\$200,000
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Lovell, D		
Clinical Trials in Pediatric Rheumatology		
National Institutes of Health K24 AR 02154	04/01/00 – 3/31/05	\$109,780/\$525,692
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Thompson, S		
Cincinnati Rheumatic Diseases Core Center		
National Institutes of Health P30 AR 473.63	03/15/01 – 02/28/06	\$400,000/\$2,039,000
Thompson, S	\$67,585	Administrative Core
Thompson, S	\$42,891	Core #1
Dardzinski, B	\$55,018	Core #2
Thornton, S	\$88,923	Core #4
Pestian, J	\$44,778	Core #5
Griffin, T	\$50,000	Pilot Study #3
Hildeman, D	\$50,000	Pilot Study #4
Prevention of Cardiovascular Complications OD Pediatric SLE		
National Institutes of Health (Duke University subcontract) N01 AR 22265	08/01/02 – 07/31/07	\$31,311/\$149,392
Genomic Landscape in Large Scale Integrated JRA Studies		
National Institutes of Health R01 AR 050688	09/15/03 – 08/31/07	\$194,000/\$752,000
Nitric Oxide in Pediatric Statin-Treated SLE		
National Institutes of Health (Duke University subcontract) R01 AR 051307	07/01/03 – 06/30/07	\$6,219/\$25,394
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Thornton, S		
The Role of Fibrinogen/Angiotensin-Related Protein in Autoimmune Arthritis		
Arthritis Foundation	07/01/02 – 06/30/05	\$60,000/\$202,500
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Current Year Direct		\$4,677,114

Industry Contracts

Giannini, E		
Immunex Corporation		\$136,657
Lovell, D		
Immunex Corporation		\$16,603
Current Year Direct Receipts		\$153,260
TOTAL		\$4,830,374

Funded Collaborative Efforts

Brunner, H		
Outcomes and Cost Effectiveness Evaluation of Entanercept in Children with Juvenile Rheumatoid Arthritis		
Arthritis Foundation		
PI: Kotagal	07/01/03 – 06/30/04	15%
Thornton, S		
Arthritic Disease and the Hemostatic System		
National Institutes of Health		
PI: Degen, J	02/12/04 – 12/31/08	23%

PUBLICATIONS

1. **Brunner HI**, Jones OY, **Lovell DJ**, Johnson AM, Alexander P, Klein-Gitelman MS. Lupus headaches in childhood-onset systemic lupus erythematosus: relationship to disease activity as measured by the systemic lupus erythematosus disease activity index (SLEDAI) and disease damage. *Lupus* 2003;12(8):600-6.
2. **Brunner HI**, Maker D, Grundland B, Young NL, Blanchette V, Stain AM, Feldman BM. Preference-based measurement of health-related quality of life (HRQL) in children with chronic musculoskeletal disorders (MSKDs). *Med Decis Making* 2003;23(4):314-22.
3. **Brunner HI**, **Giannini EH**. Health-related quality of life in children with rheumatic diseases. *Curr Opin Rheumatol* 2003;15(5):602-12.
4. De Albuquerque DA, Saxena V, Adams DE, Boivin GP, **Brunner HI**, Witte DP, Singh RR. An ACE inhibitor reduces Th2 cytokines and TGF-beta1 and TGF-beta2 isoforms in murine lupus nephritis. *Kidney Int* 2004;65(3):846-59.
5. **Colbert RA**. The immunobiology of HLA-B27: variations on a theme. *Curr Mol Med* 2004;4(1):21-30.
6. Ogilvie EM, Fife MS, Thompson SD, Twine N, Tsoras M, Moroldo M, Fisher SA, Lewis CM, Prieur AM, **Glass DN**, Woo P. The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. *Arthritis Rheum* 2003;48(11):3202-6.
7. Rosen P, Hopkin RJ, **Glass DN**, **Graham TB**. Another patient with chromosome 18 deletion syndrome and juvenile rheumatoid arthritis. *J Rheumatol* 2004;31(5):998-1000.
8. Kight AC, Dardzinski BJ, Laor T, **Graham TB**. Magnetic resonance imaging evaluation of the effects of juvenile rheumatoid arthritis on distal femoral weight-bearing cartilage. *Arthritis Rheum* 2004;50(3):901-5.
9. Jayarapu K, **Griffin TA**. Protein-protein interactions among human 20S proteasome subunits and proteasassemblin. *Biochem Biophys Res Commun* 2004;314(2):523-8.
10. **Grom AA**. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr Opin Rheumatol* 2003;15(5):587-90.

11. **Grom AA**. Natural killer cell dysfunction: A common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? *Arthritis Rheum* 2004;50(3):689-98.
12. **Lovell D**. Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. *Paediatr Drugs* 2004;6(3):137-46.
13. Ruperto N, Ravelli A, Murray KJ, **Lovell DJ**, Andersson-Gare B, Feldman BM, Garay S, Kuis W, Machado C, Pachman L, Prieur AM, Rider LG, Silverman E, Tsitsami E, Woo P, **Giannini EH**, Martini A. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology (Oxford)* 2003;42(12):1452-9.
14. Huber AM, Feldman BM, Rennebohm RM, Hicks JE, Lindsley CB, Perez MD, Zemel LS, Wallace CA, Ballinger SH, **Passo MH**, Reed AM, Summers RM, White PH, Katona IM, Miller FW, Lachenbruch PA, Rider LG. Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile idiopathic inflammatory myopathies. *Arthritis Rheum* 2004;50(5):1595-603.
15. Rennebohm RM, Jones K, Huber AM, Ballinger SH, Bowyer SL, Feldman BM, Hicks J, Katona IM, Lindsley CB, Miller FW, **Passo MH**, Perez MD, Reed AM, Wallace CA, White PH, Zemel LS, Lachenbruch PA, Hayes JR, Rider LG. Normal scores for nine maneuvers of the Childhood Myositis Assessment Scale. *Arthritis Rheum* 2004;51(3):365-70.
16. Moroldo MB, Chaudhari M, Shear E, **Thompson SD, Glass DN, Giannini EH**. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. *Arthritis Rheum* 2004;50(6):1928-34.
17. Rosen P, **Thompson S, Glass D**. Non-HLA gene polymorphisms in juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 2003;21(5):650-6.
18. Katakura S, Jennings K, Watanabe S, Adachi E, **Thornton S**, Gao G, Wilson JM, Burstein H, Trapnell B, Hirsch R. Recombinant adeno-associated virus preferentially transduces human, compared to mouse, synovium: implications for arthritis therapy. *Mod Rheumatol* 2004;14(1):18-24.