Rheumatology

Division Photo

First Row: T. Griffin, M. Henrickson, D. Lovell

Second Row: J. Huggins, J. Taylor, T. Ting, E. Morgan DeWitt, S. Thornton, H. Brunner

Third Row: M. Flick, D. Glass, S. Thompson, E. Giannini, A. Grom

Division Data Summary

Research and Training Details	
Number of Faculty	10
Number of Support Personnel	58
Direct Annual Grant Support	$3,993,072
Direct Annual Industry Support	$157,923
Peer Reviewed Publications	16
Clinical Activities and Training	
Number of Clinical Staff	4
Number of Clinical Fellows	6
Inpatient Encounters	3500

Significant Publications

Barnes, M.G., Grom, A.A., Thompson, S.D., Griffin, T.A., Pavlidis, P., Itert, L., Fall, N., Sowders, D.P., Hinze, C.H., Aronow, B.J., Luyrink, L.K., Srivastava, S., Ilowite, N.T., Gottlieb, B.S., Olson, J.C., Sherry, D.D., Glass, D.N., and Colbert, R.A., Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis. Arthritis Rheum, 2009. 60(7): p. 2102-12.

This and the next publication represent the results of over 20 years of dedicated work of a team of investigators within the CCHMC Division of Rheumatology who have combined careful description of the clinical course of many children with JIA and extensive characterization of genetic markers. This study demonstrated JIA subtype differences in the genetic markers expressed on peripheral blood mononuclear white blood cells demonstrating the immunobiologic differences between JIA subtypes.

Griffin, T.A., Barnes, M.G., Ilowite, N.T., Olson, J.C., Sherry, D.D., Gottlieb, B.S., Aronow, B.J., Pavlidis, P., Hinze, C.H., Thornton, S., Thompson, S.D., Grom, A.A., Colbert, R.A., and Glass, D.N., Gene expression

signatures in polyarticular juvenile idiopathic arthritis demonstrate disease heterogeneity and offer a molecular classification of disease subsets. Arthritis Rheum, 2009. 60(7): p. 2113-23.

Even very soon after the development of the disease, subsets of children with Polyarticular JIA (arthritis in more than 4 joints) differ from each other in the gene expression on mononuclear cells in the peripheral blood allowing for a molecular classification of disease and identification of discrete disease processes even within this one JIA subtype.

Zhang, K., Biroschak, J., Glass, D.N., Thompson, S.D., Finkel, T., Passo, M.H., Binstadt, B.A., Filipovich, A., and Grom, A.A., Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. Arthritis Rheum, 2008. 58(9): p. 2892-6.

This manuscript is one of several from this Division focused on understanding the causes of disease for children with the most severe form of JIA – Systemic JIA. This paper showed an association with variations in the gene MUNC 13-4 with the severe complication of systemic JIA called macrophage activation syndrome.

Ruperto, N., Lovell, D.J., Quartier, P., Paz, E., Rubio-Perez, N., Silva, C.A., Abud-Mendoza, C., Burgos-Vargas, R., Gerloni, V., Melo-Gomes, J.A., Saad-Magalhaes, C., Sztajnbok, F., Goldenstein-Schainberg, C., Scheinberg, M., Penades, I.C., Fischbach, M., Orozco, J., Hashkes, P.J., Hom, C., Jung, L., Lepore, L., Oliveira, S., Wallace, C.A., Sigal, L.H., Block, A.J., Covucci, A., Martini, A., and Giannini, E.H., Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet, 2008. 372(9636): p. 383-91.

This manuscript presented results of a large international, double-blind, randomized clinical trial to assess the efficacy and safety of a new class of therapy – i.e., biologic that blocks the stimulation of T-cells in children with severe JIA. Therapy was both efficacious and safe in over 85% of the patients. The clinical trials unit within the Division of Rheumatology directed this entire study.

Suzuki, M., Wiers, K., Brooks, E.B., Greis, K.D., Haines, K., Klein-Gitelman, M.S., Olson, J., Onel, K., O'Neil K, M., Silverman, E.D., Tucker, L., Ying, J., Devarajan, P., and Brunner, H.I., Initial Validation of a Novel Protein Biomarker Panel for Active Pediatric Lupus Nephritis. Pediatr Res, 2009. 65(5):530-6.

This is one of a series of publications from a very productive team of investigators in the CCHMC Divisions of Rheumatology and Nephrology. This manuscript demonstrated proteins found in the urine that can serve as biomarkers in children and adolescents with SLE of the activity of kidney involvement and also can help anticipate the future course of kidney involvement.

Faculty Members

Hermine Brunner, MD, MSc, Associate Professor

Matthew Flick, PhD, Research Instructor

Edward H. Giannini, MSc, DrPH, Professor

David N. Glass, MD, Professor

Thomas Griffin, MD, PhD, Research Assistant Professor

Alexei A. Grom, MD, Research Associate Professor

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

Daniel Joe Lovell, MD, MPH, Professor ; *Interim Division Director*

Susan Thompson, PhD, Associate Professor

Sherry Thornton, PhD, Research Assistant Professor

Clinical Staff Members

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

Trainees

- **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 Phillipines
- **XueMei Tang, MD,** Chongqing Medical University
- **Rina Mina, MD,** PGY-IV, Downstate Medical Center New York
- **Annette Lopez-Martinez, MD,** PGY-IV, University of Puerto Rico Pediatric Hospital

Significant Accomplishments

Clinical and Translational Research Accomplishments

The Division of Rheumatology continues to move forward in a very productive fashion in both clinical and translational research areas. This last year saw the completion of three large international multi-centered Phase III interventional trials that were developed and led by Clinical Trials Unit within the Division of Rheumatology. Results of these trials were published in the *New England Journal of Medicine*, *Lancet* and *Arthritis & Rheumatism*. In addition, these studies led to the approval by the FDA and the European EMEA of two new treatments for children with Juvenile Idiopathic Arthritis (JIA). Each of these treatments represents a powerful and extremely effective treatment option for children with severe JIA. In addition, studies are being developed to provide focused pathogenic driven treatments for children with a form of chronic arthritis for which we have very poor treatments at the current time – Systemic JIA.

Translational laboratory-based investigations in the Division of Rheumatology have been directed towards the goal of understanding the molecular basis of JIA, a heterogeneous disease with several subtypes. Work has focused on defining the basis for genetic risk and identifying distinct molecular profiles related to the various subtypes using gene expression profiling. In the past year genomic JIA datasets, of unprecedented scope, have been completed. The data includes high resolution HLA allele types, single nucleotide polymorphisms (SNP) and copy number variant genotypes for about 1000 patients and 1000 controls and gene expression profiles for a subset of about 200 patients. Genetic association studies have revealed a set of risk factors common with other autoimmune diseases such as Lupus and Crohn's disease as well as risk factors that are unique to JIA and its various subtypes. HLA associations have been defined with greater precision than previously possible. Gene expression studies, using blood samples obtained from patients at onset of disease, have revealed an increased presence and function of various immature cell types including B-cells, monocytes and macrophages. Of importance and supported in each of our datasets, are results suggesting that patients who develop disease at a young age share a common biological basis for disease which is different in patients that develop disease later in life. Together these genomic studies provide evidence for a fundamental shift toward molecular definitions for disease and may lead to a reevaluation of the present clinical criteria for defining subtypes as well as provide insight into disease origins and pathogenesis.

As described above, in the last year research in the CCHMC Division of Rheumatology has resulted in real advances in understanding both the molecular basis of the inflammation but also treatment of JIA- the most common chronic arthritis in children and one of the more common chronic childhood illnesses.

Division Publications

1. Lian L, Wang Y, Flick M, Choi J, Scott EW, Degen J, Lemmon MA, Abrams CS. Loss of pleckstrin defines a novel pathway for PKC-mediated exocytosis. *Blood.* 2009; 113: 3577-84.
2. Harris-Love MO, Shrader JA, Koziol D, Pahlajani N, Jain M, Smith M, Cintas HL, McGarvey CL, James-Newton L, Pokrovnichka A, Moini B, Cabalar I, Lovell DJ, Wesley R, Plotz PH, Miller FW, Hicks JE, Rider LG. Distribution and severity of weakness among patients with polymyositis, dermatomyositis and juvenile dermatomyositis. *Rheumatology (Oxford).* 2009; 48: 134-9.
3. Brunner HI. More may not be better--but is less enough?. *J Rheumatol.* 2009; 36: 7-8.
4. Foeldvari I, Szer IS, Zemel LS, Lovell DJ, Giannini EH, Robbins JL, West CR, Steidle G, Krishnaswami S, Bloom BJ. A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. *J Rheumatol.* 2009; 36: 174-82.
5. Hinks A, Ke X, Barton A, Eyre S, Bowes J, Worthington J, Thompson SD, Langefeld CD, Glass DN, Thomson W. Association of the IL2RA/CD25 gene with juvenile idiopathic arthritis. *Arthritis Rheum.* 2009; 60: 251-7.
6. Mullins ES, Kombrinck KW, Talmage KE, Shaw MA, Witte DP, Ullman JM, Degen SJ, Sun W, Flick MJ, Degen JL. Genetic elimination of prothrombin in adult mice is not compatible with survival and results in spontaneous hemorrhagic events in both heart and brain. *Blood.* 2009; 113: 696-704.

7. Brunner HI, Klein-Gitelman MS, Ying J, Tucker LB, Silverman ED. Corticosteroid use in childhood-onset systemic lupus erythematosus-practice patterns at four pediatric rheumatology centers. *Clin Exp Rheumatol.* 2009; 27: 155-62.
8. Seid M, Opipari L, Huang B, Brunner HI, Lovell DJ. Disease control and health-related quality of life in juvenile idiopathic arthritis. *Arthritis Rheum.* 2009; 61: 393-9.
9. Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, Mieszkalski KL, Ilowite NT, Eberhard A, Levy DM, Kimura Y, von Scheven E, Silverman E, Bowyer SL, Punaro L, Singer NG, Sherry DD, McCurdy D, Klein-Gitelman M, Wallace C, Silver R, Wagner-Weiner L, Higgins GC, Brunner HI, Jung L, Soep JB, Reed A. Premature atherosclerosis in pediatric systemic lupus erythematosus: risk factors for increased carotid intima-media thickness in the atherosclerosis prevention in pediatric lupus erythematosus cohort. *Arthritis Rheum.* 2009; 60: 1496-507.
10. Koneru S, Kocharla L, Higgins GC, Ware A, Passo MH, Farhey YD, Mongey AB, Graham TB, Houk JL, Brunner HI. Adherence to medications in systemic lupus erythematosus. *J Clin Rheumatol.* 2008; 14: 195-201.
11. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhaes C, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M, Penades IC, Fischbach M, Orozco J, Hashkes PJ, Hom C, Jung L, Lepore L, Oliveira S, Wallace CA, Sigal LH, Block AJ, Covucci A, Martini A, Giannini EH. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008; 372: 383-91.
12. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati R, McIlraith MJ, Giannini EH, Martini A. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med.* 2008; 359: 810-20.
13. Carrasco R, Lovell DJ, Giannini EH, Henderson CJ, Huang B, Kramer S, Ranz J, Heubi J, Glass D. Biochemical markers of bone turnover associated with calcium supplementation in children with juvenile rheumatoid arthritis: results of a double-blind, placebo-controlled intervention trial. *Arthritis Rheum.* 2008; 58: 3932-40.
14. Prahalad S, Bohnsack JF, Whiting A, Clifford B, Jorde LB, Guthery SL, Thompson SD, Glass DN, Bamshad MJ. Lack of association of functional CTLA4 polymorphisms with juvenile idiopathic arthritis. *Arthritis Rheum.* 2008; 58: 2147-52.
15. Ting TV, Lovell DJ. Does early sulfasalazine treatment provide long-term benefits to patients with juvenile idiopathic arthritis? *Nat Clin Pract Rheumatol.* 2008; 4: 344-5.
16. Zhang K, Biroschak J, Glass DN, Thompson SD, Finkel T, Passo MH, Binstadt BA, Filipovich A, Grom AA. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. *Arthritis Rheum.* 2008; 58: 2892-6.

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 — $130,219 / $401,754

Mechanisms of Tolerance to Renal Maternal Microchimerism
National Institutes of Health (Children's Hospital and Regional Medical Center-Seattle)
R01 AR 051545 — 09/13/07 - 07/31/10 — $4,540 / $6,520

Early Aggressive Therapy in Juvenile Idiopathic Arthritis (Per Patient)
National Institutes of Health (Children's Hospital and Regional Medical Center-Seattle)
R01 AR 049762 — 09/01/06 - 08/31/11 — $28,846 / $156,750

Biomarkers for Diagnosis, Monitoring, and Prognosis in Pediatric SLE
Lupus Foundation of America (University of Pittsburgh)
10/01/08 - 09/30/09 — $52,311 / $52,311

GLASS, D.

Hematopoietic Cell Transplantation
National Institutes of Health (Fred Hutchinson Cancer Research Center)
U01 AI 069197 — 09/15/08 - 02/28/09 — $210,000 / $210,000

Research Registry For Juvenile Rheumatoid Arthritis
National Institutes of Health

N01 AR 042272	09/30/04 - 09/29/09	$826,858 / $4,255,695

HLA/KIR Region Genetics in Pediatric Arthritis
National Institutes of Health

U01 AI 067150	09/30/05 - 03/31/10	$264,468 / $1,297,617

Hematopoietic Cell Transplantation
National Institutes of Health

U01 AI 069197	09/15/08 - 02/28/09	$210,000 / $315,000

GRIFFIN, T

Pediatric Rheumatology Training Grant
National Institutes of Health

T32 AR 007594	05/01/05 - 04/30/10	$282,840 / $1,464,420

HLA-B27 Misfolding and the UPR in Spondyloarthritis
National Institutes of Health

R01 AR 046177	09/01/06 - 06/30/11	$262,864 / $1,409,806

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	$126,420 / $236,500

Role of Immunoproteasomes in Activated T Cell Apoptosis
National Institutes of Health

R21 AI 073584	09/20/07 - 08/31/09	$147,150 / $275,000

LOVELL, D

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	$87,814 / $719,397

Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomytosis
National Institutes of Health (University of Pittsburgh)

N01 AR 042273	09/01/06 - 09/29/09	$56,674 / $170,022

Cincinnati Multidisciplinary Clinical Research Center
National Institutes of Health

P60 AR 047784	08/18/08 - 07/31/13	$825,653 / $4,210,600
Lovell, D	Administrative Core	66,866
Giannini, E	Methodology Core	105,190
Brunner, H	Project 1	160,309
Lovell, D	Project 2	184,861
Grom, A	Project 3	164,492
Seid, M	Project 4	143,935

Dynamic Outcome Assessment in Multicenter Trials
National Institutes of Health (Duke University)

U01 AR 052186	08/01/08 - 07/31/09	$18,333 / $18,333

THOMPSON, S

Cincinnati Rheumatic Diseases Core Center
National Institutes of Health

P30 AR 047363	09/01/06 - 06/30/11	$388,400 / $2,000,000
Thompson, S	Administrative Core	56,586
Thompson, S	Core 1 - Tissue	43,042
Degen, J	Core 2 - Animal Models of	67,299

	Arthritis/Inflammatory Disease	
Thornton, S	Core 3 - Phenotyping	79,978
Wagner, M	Core 4 - Informatics	41,495
Karp, C	P&F #1	50,000
Thornton, S	P&F #2	50,000

Prevention of Cardiovascular Complications of Pediatric Lupus
National Institutes of Health (Duke University)
N01AR022265 9/30/02 - 8/31/08 $26,873 / $ 134,367

Early Agressive Therapy in JIA
National Institutes of Health (Seattle Children's)
R01AR049762 05/01/08 - 04/30/11 $42,809 / $85,619

Current Year Direct **$3,993,072**

Industry Contracts

Giannini, E

Amgen Inc.	$ 16,369
Genzyme Corporation	$ 19,250

Lovell, D

Pfizer, Inc	$ 42,252
Roche Laboratories, Inc.	$ 80,052

Current Year Direct Receipts **157,923**

Total **$ 4,150,995**