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

Number of Faculty	14
Number of Research Fellows	1
Number of Research Students	1
Number of Support Personnel	47
Direct Annual Grant Support	$4,216,305
Direct Annual Industry Support	$338,648
Peer Reviewed Publications	27

Clinical Activities and Training

Number of Clinical Fellows	6
Inpatient Encounters	85
Outpatient Encounters	7,935

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

Alexei A. Grom, MD, Research Associate Professor

Jennifer Huggins, MD, Assistant Professor Clinical

Gerlinde Layh-Schmitt, PD, PhD, Research Assistant Professor

Daniel Joe Lovell, MD, MPH, Professor

Murray H. Passo, MD, Professor Clinical

Susan Thompson, PhD, Associate Professor

Sherry Thornton, 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 Phillipines
- **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 pediataric specific dosing issues and safetyh concerns for a frequently used biologic therapy, inflixximab, 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.

Publications. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, Giannini EH; Pediatric Rheumatology Collaborative Study Group. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 2008 May;58(5):1496-504.

Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, and Giannini EH. 2007. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 56:3096-3106.

Systemic Lupus Erythematosus Research

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

triptorelin to protect from ovarian damage due to chemotherapy for SLE; two multinational studies to discover and test novel biomarkers for SLE renal disease (Alliance for Lupus Research, Department of Defense. This research has identified and validated the usefulness of Neutrophil Gelatinase Associated Lipocalin (NGAL) as specific biomarker of lupus nephritis activity, with initial evidence suggesting that is predictive of the future course of and response to lupus nephritis therapy. Additionally, a lupus nephritis proteomic signature has been delineated and a discrete lupus nephritis panel is being tested at present. In collaboration with the National Rehabilitation Hospital, the CCHMC Lupus Center assessed the usefulness of computer-based cognitive testing to better diagnose cognitive dysfunction with SLE (Lupus Foundation) using the Pediatric Neurocognitive Assessment Metrics (Ped-ANAM). Based on this research the Ped-ANAM could well be the first clinical screening tool for neurocognitive dysfunction of children with SLE, leading to validation studies of the Ped-ANAM that are supported by a P60 Rheumatology Center Grant. Together with the CCHMC Pediatric Neuroimaging Center, The CCHMC Lupus Center performed the first functional magnetic imaging study in children with SLE, supporting that neurocognitive dysfunction in SLE is likely due to white matter disease and that even patient with apparently normal cognition show abnormalities on functional imaging (Arthritis Foundation).). The CCHMC Lupus Center is developing at present clinical trials outcome measures for children with SLE (NIAMS U01). The group has been selected by NIAMS to develop an electronic clinical trial data management system and a National Pediatric Lupus Registry (NIAMS U01). Supported by NIH NIAMS P30 and P60 center grants awarded to the CCHMC Division of Rheumatology as well as a Lupus Foundation grant, measures of patient adherence (compliance) were validated and the impact of SLE-associated cognitive dysfunction on quality of life was explored and risk factors of non-adherence in SLE explored. The results of this study led to a CCHMC Health Service grant to explore interventions to decrease visit and medication adherence using motivational interviewing and text messaging in children and young adults with SLE. Studies initiated within the last year include pharmacogenomic and pharmacodynamic studies to develop the evidence-based dosing regimens of steroids and mycophenolate mofetil for children with SLE. Over past year, nine UC and CCHMC rheumatology as well as nephrology fellows have chosen to conduct their research projects with the CCHMC Lupus Research Group. Similar to the pediatric cancer model, the majority of patients with SLE followed at CCHMC participate in at least 1 of these research studies.

1. S Koneru, M Shishov, A Ware, Y Farhey, AB Mongey, JL Houk, and **HI Brunner.** Effectively Measuring Adherence to Medications For Systemic Lupus Erythematosus In A Clinical Setting**.** Arthritis Rheum 2007, 57: 1000-1006.

2. Mikdashi (Co-Chair), JM Esdaile (Co-Chair), GS Alarcón (Co-Chair), L Crofford, BJ Fessler, L Schanberg, **H Brunner**, V Gall, JR Kalden, MD Lockshin, MH Liang, N Roberts Jr and M Schneider; for the Ad Hoc Committee on Lupus Response Criteria: Cognition Sub-committee: Proposed response criteria for neurocognitive impairment in systemic lupus erythematosus clinical trials. Lupus (2007) 16, 418–425.

3. HI Brunner, NM Ruth, A German, S Nelson, MH Passo, T Roebuck-Spencer, J Ying, D Ris. Initial validation of the pediatric automated neuropsychological assessment metrics for childhood-onset systemic lupus erythematosus. Arthritis Rheum 2007, 57: 1174-1182.

4. M Suzuki, K Wiers, S Nelson, C Rutherford, P Devarjan, **HI Brunner**: Identification of urinary proteomic signature for nephritis in children. Pediatr Nephrol. 2007 Dec; 22(12):2047-2057.

5. M DiFrancesco, S Holland, D Ris C Adler, M DeBello, M Altaye, **HI Brunner**. Functional magnetic resonance imaging of cognitive function in childhood-onset systemic lupus erythematosus: a pilot study. Arthritis Rheum. 2007 Dec;56 (12):4151-63.

6. M Suzuki, KM Wiers, M Klein-Gitelman, KA Haines, J Olson, KB Onel, K O'Neil, MH Passo, NG Singer, L Tucker, J Ying, P Devarajan, **HI Brunner**. Neutrophil Gelatinase Associated Lipocalin as a Biomarker of Disease Activity In Pediatric Lupus Nephritis; Pediatr Nephrol. Pediatr Nephrol. 2008 Mar;23(3):403-12

7. HI Brunner, DD Gladman, D Ibañez, MD Urowitz, ED Silverman: Difference in disease features between childhood-onset and adult systemic lupus erythematosus (SLE). Arthritis Rheum 2008; 58 (2): 556–562.

8. S Koneru, L Kochrala, GC Higgins, A Ware, MH Passo, YD Farhey, AB Mongey, TB Graham, JL Houk, and **HI Brunner**. Adherence to medications in systemic lupus erythematosus. Journal of Clinical Rheumatology; 2008: 14(4):195-201.

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, Ilowite 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.

Prahalad S, Bohnsack JF, Whiting A, Clifford B, Jorde LB, Guthery SL, Thompson SD, Glass DN, Bamshad MJ. 2008 Lack of association of functional *CTLA4* polymorphisms with juvenile idiopathic arthritis. *Arthritis Rheum 2007; 58(7):2147-2152.*

Significant Publications in FY08

Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, Ilowite NT, Brunner HI, Griffin T, Graham TB, Sherry DD, Passo MH, Ramanan AV, Filipovich A, and Grom AA, The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. Arthritis Rheum, 2007. 56(3): p. 965-71.

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

Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, and Giannini EH, A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum, 2007. 56(9): p. 3096-106.

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.

Suzuki M, Wiers KM, Klein-Gitelman MS, Haines KA, Olson J, Onel KB, O'Neil K, Passo MH, Singer NG, Tucker L, Ying J, Devarajan P, and Brunner HI, Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. Pediatr Nephrol, 2008. 23(3): p. 403-12.

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

Turner MJ, Delay ML, Bai S, Klenk E, and Colbert RA, HLA-B27 up-regulation causes accumulation of misfolded heavy chains and correlates with the magnitude of the unfolded protein response in transgenic rats: Implications for the pathogenesis of spondylarthritis-like disease. Arthritis Rheum, 2007. 56(1): p. 215-

23.

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.

Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, and Giannini EH, Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum, 2008. 58(5): p. 1496-504.

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

Dr. Meller serves as Co-Investigator on Susan D. Thompson's Integrative Genomics grant.

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.

Division Publications

1. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. **Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus.** *Arthritis Rheum.* 2008; 58: 556-62.
2. Brunner HI, Ruth NM, German A, Nelson S, Passo MH, Roebuck-Spencer T, Ying J, Ris D. **Initial validation of the Pediatric Automated Neuropsychological Assessment Metrics for childhood-onset systemic lupus erythematosus.** *Arthritis Rheum.* 2007; 57: 1174-82.
3. DiFrancesco MW, Holland SK, Ris MD, Adler CM, Nelson S, DelBello MP, Altaye M, Brunner HI. **Functional magnetic resonance imaging assessment of cognitive function in childhood-onset systemic lupus erythematosus: a pilot study.** *Arthritis Rheum.* 2007; 56: 4151-63.
4. Mikdashi JA, Esdaile JM, Alarcon GS, Crofford L, Fessler BJ, Shanberg L, Brunner H, Gall V, Kalden JR, Lockshin MD, Liang MH, Roberts N, Jr., Schneider M. **Proposed response criteria for neurocognitive impairment in systemic lupus erythematosus clinical trials.** *Lupus.* 2007; 16: 418-25.
5. Hinze CH, Colbert RA. **B-cell depletion in Wegener's granulomatosis.** *Clin Rev Allergy Immunol.* 2008; 34: 372-9.
6. Sahlberg AS, Penttinen MA, Heiskanen KM, Colbert RA, Sistonen L, Granfors K. **Evidence that the p38 MAP kinase pathway is dysregulated in HLA-B27-expressing human monocytic cells: correlation with HLA-B27 misfolding.** *Arthritis Rheum.* 2007; 56: 2652-62.
7. Smith JA, Barnes MD, Hong D, DeLay ML, Inman RD, Colbert RA. **Gene expression analysis of macrophages derived from ankylosing spondylitis patients reveals interferon-gamma dysregulation.** *Arthritis Rheum.* 2008; 58: 1640-9.
8. Smith JA, Turner MJ, DeLay ML, Klenk EI, Sowders DP, Colbert RA. **Endoplasmic reticulum stress and the unfolded protein response are linked to synergistic IFN-beta induction via X-box binding protein 1.** *Eur J Immunol.* 2008; 38: 1194-203.
9. Flick MJ, LaJeunesse CM, Talmage KE, Witte DP, Palumbo JS, Pinkerton MD, Thornton S, Degen JL. **Fibrin(ogen) exacerbates inflammatory joint disease through a mechanism linked to the integrin alphaMbeta2 binding motif.** *J Clin Invest.* 2007; 117: 3224-35.
10. Palumbo JS, Barney KA, Blevins EA, Shaw MA, Mishra A, Flick MJ, Kombrinck KW, Talmage KE, Souri M, Ichinose A, Degen JL. **Factor XIII transglutaminase supports hematogenous tumor cell metastasis through a mechanism dependent on natural killer cell function.** *J Thromb Haemost.* 2008; 6: 812-9.
11. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, Hu Z, Barney KA, Degen JL. **Tumor cell-associated tissue factor and circulating hemostatic factors cooperate to increase metastatic potential through natural killer cell-dependent and-independent mechanisms.** *Blood.* 2007; 110: 133-41.
12. Koneru S, Shishov M, Ware A, Farhey Y, Mongey AB, Graham TB, Passo MH, Houk JL, Higgins GC, Brunner HI. **Effectively measuring adherence to medications for systemic lupus erythematosus in a clinical setting.** *Arthritis Rheum.* 2007; 57: 1000-6.
13. Jayarapu K, Griffin TA. **Differential intra-proteasome interactions involving standard and immunosubunits.** *Biochem Biophys Res Commun.* 2007; 358: 867-72.
14. Hazen MM, Woodward AL, Hofmann I, Degar BA, Grom A, Filipovich AH, Binstadt BA. **Mutations of the hemophagocytic lymphohistiocytosis-associated gene UNC13D in a patient with systemic juvenile idiopathic arthritis.** *Arthritis Rheum.* 2008; 58: 567-70.
15. Pasternak B, Grom A, Yazigi N, Cohen MB. **Suppurative peripheral arthritis in inflammatory bowel disease.** *J Pediatr Gastroenterol Nutr.* 2007; 45: 117-20.
16. Shishov M, Henrickson M, Burgos-Vargas R, Rubio-Perez N, Baca V, Romero-Feregrino R, Solis-Vallejo E, Huang B, Grom AA, Lovell DJ. **Systemic features and early prognostic factors in Hispanic and non-Hispanic children**

from the United States of America and Mexico with systemic juvenile idiopathic arthritis. *Clin Exp Rheumatol.* 2007; 25: 907-14.

17. Khanna D, Lovell DJ, Giannini E, Clements PJ, Merkel PA, Seibold JR, Matucci-Cerinic M, Denton CP, Mayes MD, Steen VD, Varga J, Furst DE. Development of a provisional core set of response measures for clinical trials of systemic sclerosis. *Ann Rheum Dis.* 2008; 67: 703-9.
18. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, Giannini EH. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum.* 2008; 58: 1496-504.
19. Miles L, Bove KE, Lovell D, Wargula JC, Bukulmez H, Shao M, Salisbury S, Bean JA. Predictability of the clinical course of juvenile dermatomyositis based on initial muscle biopsy: a retrospective study of 72 patients. *Arthritis Rheum.* 2007; 57: 1183-91.
20. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, Giannini EH. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 2007; 56: 3096-106.
21. Ruperto N, Ravelli A, Pistorio A, Ferriani V, Calvo I, Ganser G, Brunner J, Dannecker G, Silva CA, Stanevicha V, Cate RT, van Suijlekom-Smit LW, Voygioyka O, Fischbach M, Foeldvari I, Hilario O, Modesto C, Saurenmann RK, Sauvain MJ, Scheibel I, Sommelet D, Tambic-Bukovac L, Barcellona R, Brik R, Ehl S, Jovanovic M, Rovensky J, Bagnasco F, Lovell DJ, Martini A. The provisional Paediatric Rheumatology International Trials Organisation/American College of Rheumatology/European League Against Rheumatism Disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. *Arthritis Rheum.* 2008; 59: 4-13.
22. Huber AM, Dugan EM, Lachenbruch PA, Feldman BM, Perez MD, Zemel LS, Lindsley CB, Rennebohm RM, Wallace CA, Passo MH, Reed AM, Bowyer SL, Ballinger SH, Miller FW, Rider LG. The Cutaneous Assessment Tool: development and reliability in juvenile idiopathic inflammatory myopathy. *Rheumatology (Oxford).* 2007; 46: 1606-11.
23. Huber AM, Dugan EM, Lachenbruch PA, Feldman BM, Perez MD, Zemel LS, Lindsley CB, Rennebohm RM, Wallace CA, Passo MH, Reed AM, Bowyer SL, Ballinger SH, Miller FW, Rider LG. Preliminary validation and clinical meaning of the Cutaneous Assessment Tool in juvenile dermatomyositis. *Arthritis Rheum.* 2008; 59: 214-21.
24. Suzuki M, Ross GF, Wiers K, Nelson S, Bennett M, Passo MH, Devarajan P, Brunner HI. Identification of a urinary proteomic signature for lupus nephritis in children. *Pediatr Nephrol.* 2007; 22: 2047-57.
25. Suzuki M, Wiers KM, Klein-Gitelman MS, Haines KA, Olson J, Onel KB, O'Neil K, Passo MH, Singer NG, Tucker L, Ying J, Devarajan P, Brunner HI. Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. *Pediatr Nephrol.* 2008; 23: 403-12.
26. Zeft A, Shear ES, Thompson SD, Glass DN, Prahalad S. Familial autoimmunity: maternal parent-of-origin effect in juvenile idiopathic arthritis. *Clin Rheumatol.* 2008; 27: 241-4.
27. Fall N, Barnes M, Thornton S, Luyrink L, Olson J, Ilowite NT, Gottlieb BS, Griffin T, Sherry DD, Thompson S, 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: 3793-804.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

Brunner, H

Triptorelin for Ovary Protection in Childhood Lupus
Food and Drug Administration
FD-R-002369-03 — 09/30/03 - 09/29/08 — $300,000 / $900,000

Efficacy Measures for Pediatric Lupus Studies
National Institutes of Health
U01 AR 055054 — 08/17/07 - 07/31/10 — $134,120 / $401,754

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 / $144,230

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 Dermatomytosis
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

National Institutes of Health (Duke University)
R01 AR 051307 07/01/03 - 06/30/08 $6,316 / $25,394

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	53,973
Thompson, S	Core 1	52,099
Degen, J	Core 2	53,570
Thornton, S	Core 3	76,244
Wagner, M	Core 4	53,834
Karp, C	P&F #1	50,000
Thornton, S	P&F #2	48,700

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