

## ARTHRITIS CENTER/RHEUMATOLOGY ANNUAL REPORT 2008-2009

### Current Faculty:

Robert W. Simms, M.D., Professor of Medicine; Section Chief, Rheumatology  
Saralynn Allaire, R.N. Sc.D., Research Professor of Medicine  
Kristin Baker, M.D., Research Assistant Professor  
Hyon Choi, M.D., Ph.D., Professor of Medicine  
David T. Felson, M.D., M.P.H., Professor of Medicine and Public Health; Section Head, Clinical Epidemiology Research and Training Unit  
Alessandra Farina, M.D., Ph.D., Instructor of Medicine  
Raphael Kieval, M.D., Clinical Assistant Professor of Medicine  
Eugene Kissin M.D., Assistant Professor of Medicine  
Robert Lafyatis, M.D., Professor of Medicine  
Michael LaValley, Ph.D., Associate Professor of Epidemiology and Biostatistics  
Caryn Libbey, M.D., Clinical Associate Professor of Medicine  
Peter A. Merkel, M.D., M.P.H. Professor of Medicine; Vasculitis Center Director  
Paul Monach, M.D., Ph.D., Assistant Professor of Medicine  
Tuhina Neogi, M.D., M.P.H., Assistant Professor of Medicine  
Jingbo Niu, Ph.D., Research Assistant Professor  
Burt Sack, M.D., Clinical Professor of Medicine  
Martha Skinner, M.D., Professor of Medicine  
Steven Vlad, M.D., M.P.H., Instructor of Medicine  
Michael York, M.D., Assistant Professor of Medicine  
Yuqing Zhang, Ph.D., Professor of Medicine

### Key Administrative Staff:

Fredric Majnoun, M.S., Rheumatology Section  
Catherine Brennan, Rheumatology Section  
Mary Lou Kemp, Rheumatology Section  
Lisa Massa, Clinical Epidemiology Research and Training Unit  
Nilsa Carrasquillo, Clinical Epidemiology Research and Training Unit  
Jackie Chapski, Vasculitis Center

The Arthritis Center includes nine full-time M.D. faculty, four full-time Ph.D. faculty and four part-time clinical faculty. The past academic year the Center added two new faculty: Dr. Alessandra Farina (Instructor of Medicine) and Dr. Hyon Choi (Professor of Medicine). During the past academic year, there were seven rheumatology fellows. We also have on staff nine clinical trial coordinators. Planned or additional recent faculty include Drs. Maria Trojanowska, Professor of Medicine and Arthritis Center Director (anticipated start date 10/09), Dr. Andrea Boujor, Research Assistant Professor

(anticipated start date 10/09) and Dr. Amy Wasserman, Assistant Professor of Medicine (start date 8/09).

#### Major Accomplishments:

Recruiting efforts over the past year have led to important faculty additions: these include Drs. Choi, Wasserman, Trojanowska, Boujor, and Farina. Significant growth as a result of these key faculty recruits is anticipated in both laboratory research efforts and funding as well as in clinical research, funding and clinical care. Recent additional highlights include: successful challenge grant awardees Choi, Monach, VCRC grant renewal (Dr. Merkel), and plenary session national meeting presentation (Dr. Farina).

Center faculty members have continued to achieve widespread national recognition for both their research programs and their clinical expertise. They serve on nationally and internationally influential committees for the American College of Rheumatology, the National Institutes of Health, the Arthritis Foundation, the Scleroderma Foundation, the International Scleroderma Network, and the Scleroderma Clinical Trials Consortium and on advisory boards for a number of biotechnology and pharmaceutical companies. They have continued to play pivotal and leading roles in studies of scleroderma, osteoarthritis and vasculitis. Over 13 publications in high impact journals were authored by Center Faculty.

#### Teaching:

Medical school: Headed by Dr. Eugene Kissin as Course Director, the faculty of the Arthritis Center teaches the musculoskeletal component of the Disease and Therapy course. An important feature of this course is bringing patients into small group sessions to bridge didactic work with clinical contact. In addition to approximately 19 hours of formal lectures in the Biology of Disease course, the Center contributed over 600 hours of teaching time in the outpatient department and inpatient services for medical students, residents and fellows. Our faculty has been active in continuing medical education and has given many Department of Medicine Grand Rounds, Rheumatology Grand Rounds, both intra and extra-mural, and invited lectures at national meetings including the American College of Rheumatology.

Residents: Our rheumatology rotation teaches a large number of medical residents from Primary Care, General Internal Medicine, Dermatology, Rehabilitation Medicine and Orthopedics. Residents gain exposure to outpatient medicine in rheumatology, which is not achieved unless they rotate through the specialty.

Fellows: The Fellowship Program, headed by Dr. Simms with Dr. Monach as Associate Program Director, continues to be funded by an NIH T32 grant with Dr. Felson as PI. Fellows in the program continue to be successful in their research productivity: this past academic year, 4 presented papers at recent national or international meetings (Drs.

Grayson, Tomasson, Misra and Sweeney . Graduates from the Program also continue to obtain excellent positions following their fellowship training. Within the past two years two Fellowship Program graduates obtained faculty positions: Dr. Will Harvey at Tufts and Dr. Bart Wise at UC Davis. Our fellowship program had a large number of outstanding candidates this year and our two positions for July 2010 were filled with two highly ranked applicants in the rheumatology match.

#### Laboratory and Clinical Research Programs:

The laboratory research efforts of the Center relate to basic biologic mechanisms in the especially focused on the pathogenesis of scleroderma and autoimmune mechanisms in systemic lupus.. There is a concordant research effort in clinical investigation of these disorders, including the testing of novel therapies. Faculty within the Clinical Epidemiology Section of the Arthritis Center continue to carry out ground-breaking research efforts in understanding osteoarthritis, the most common type of arthritis.

The Scleroderma Laboratory Research Program, directed by Dr. Robert Lafyatis, Professor of Medicine, includes Dr. Michael York (Assistant Professor) and Dr. Alessandra Farina (Instructor, pending). The focus of this group has been on understanding the interactions between the three key pathogenic events in systemic sclerosis: autoimmunity, fibrosis and vascular biology. The traditional base of research in the group is in fibrosis and matrix biology and on understanding the pathogenesis of fibrosis in the tight skin (Tsk) mouse. The group has made several key observations over the past year, most notably observations about the role of Wnt regulation in Tsk mice and systemic sclerosis, and CCN3 regulation of elastogenesis. A second axis of scleroderma research in the laboratory is being spearheaded by Dr. York, Dr. Lafyatis and Dr. Farina, and two Rheumatology research fellows, Dr. John McCahan and Dr. Fabienne Denhez, working closely with Dr. Marshak-Rothstein (Professor of Immunology). The goal of these closely-related projects is to further explore innate immunity in scleroderma. Dr. York has obtained important results showing effects of  $\alpha$ -satellite DNA and TLR agonists on IFN-regulated genes in leukocytes. These studies promise to clarify whether autoantibodies targeting centromere proteins act as immune adjuvants in scleroderma patients. This work is part of a broader effort to understand the effects of autoantibody immune complexes in scleroderma. Dr. Farina and Dr. York are carrying out pivotal work on understanding the roles on TLRs on fibroblasts and endothelial cells.

Dr. McCahan and Dr. Marshak-Rothstein are developing several new models of autoimmunity, one of which promises to become an exciting model for systemic sclerosis. Work in vascular disease has also seen significant progress over the past years due to a strong collaboration between the laboratories of Drs. Lafyatis and Farber (BUMC) and Dr. Whitfield (Dartmouth Medical Center). These groups identified several intriguing microarray biomarkers of pulmonary hypertension in scleroderma patients. Our success over the last year has been manifest by important publications ranging from basic science to translational medicine to clinical trials, successful funding through NIH U01 and R01 grants (Dr. Lafyatis, PI), grants for biomarker studies from Actelion and BiogenIdec (Dr. Lafyatis), grants for studies on innate immunity in systemic sclerosis from

the Scleroderma Foundation and the American College of Rheumatology (Dr. York) and grants for Dr. Marshak-Rothstein for closely collaborative work on animal models of scleroderma from the NIH (R01) and the Scleroderma Research Foundation. These highly collaborative research efforts continue to position the Section well to make further advances in understanding this devastating disease.

Dr. Skinner is the Director of Special Projects in the Amyloid Treatment and Research Program at Boston University School of Medicine. Dr. David Seldin succeeded her as overall Program Director in July 2007. The Program is internationally recognized as a program of excellence in research on amyloidosis and in patient care. The focus is on basic and translational research for the systemic forms of amyloidosis using a multidisciplinary approach with investigators in molecular biology, mass spectrometry, immunology, biochemistry, cell biology and pathology. The research and clinical program is supported by grants from NIH, FDA, HRSA, and private foundations. The Program recently completed a 5 year Program Project Grant from the National Heart Lung Blood Institute of the NIH. Major basic research progress was accomplished in the past year. A web data base (ALBase) of more than 3000 light chain gene sequences (more than 200 of them are amyloidogenic light chains from patients seen at Boston Medical Center) has been set up for use by investigators worldwide. The clinical Amyloid Program has continued to grow, and conducts multidisciplinary 3-day evaluations on approximately 500 patients/year and treats approximately 50 patients/year with high-dose chemotherapy and stem cell transplantation in the Stem Cell Transplant Suite in the Moakley Building. An international trial for the treatment of familial transthyretin type amyloidosis (PI Dr. John Berk, Amyloid Program Clinical Director) is progressing well

In the area of vasculitis, the Boston University Vasculitis Center continues to be one of the world's leading centers for care and research for this spectrum of diseases. Peter A. Merkel, MD, MPH, Director of the Boston University Vasculitis Center, Director of Clinical Trials for the Section of Rheumatology, and Professor of Medicine, is the Principal Investigator of the Vasculitis Clinical Research Consortium, an international research collaboration that conducts clinical trials, cohort studies, translational research, and clinical research training. Dr. Merkel received a \$6.25 million NIH grant for support of the VCRC for the next 5 years and the Consortium has greater than \$7 million in additional funding from NIH, FDA, and industry sources. Dr. Merkel also leads international outcome studies in vasculitis, is a key investigator in various clinical trials in vasculitis and scleroderma, and is conducting genetic and translational biologic studies of vasculitis. Dr. Merkel's work is supported by several grants from various institutes at the National Institute of Health (NIAMS, NCCR, and NIAID). Paul A. Monach, MD, PhD, Assistant Professor of Medicine, is another core member of the Vasculitis Center. Dr. Monach's background in immunology has positioned him well to lead on work on biomarkers in vasculitis, supported by a grant from the Arthritis Foundation. Dr. Monach's clinical focus is also on vasculitis. Drs. Kissin, Neogi, and Simms all also participate in the work of the Vasculitis Center and the Arthritis Center.

The Boston University Vasculitis Center is the largest clinical program in vasculitis in the Northeast United States with a continually enlarging practice stemming from regional, national, and international referrals.

*Key Boston University collaborations of the Boston University Vasculitis Center:*

- Whitaker Cardiovascular Institute (Dr. Jane Freedman)
- Genetics Program (Dr. Lindsay Farrer)
- Bioinformatics Program (Dr. Avrum Spira)

*Key national/international collaborations of the Boston University Vasculitis Center:*

- Cambridge University
- Cleveland Clinic
- Johns Hopkins University
- Mayo Clinic
- McMaster University
- Oxford University
- University of Alabama at Birmingham
- University of Lübeck
- University of Michigan
- University of Paris
- University of Toronto

A key component of the Arthritis Center is the Clinical Epidemiology Unit, a section within the Department of Medicine. Many Clinical Epidemiology Unit faculty have secondary appointments in Rheumatology and engage primarily in arthritis-related clinical research, enhancing the overall function of the Arthritis Center.

The Clinical Epidemiology Unit is headed by Dr. David Felson, Professor of Medicine and Epidemiology. He directs an NIH Center Grant, encompassing multiple clinical research projects within Arthritis. Other faculty include Dr. Saralynn Allaire, Associate Director of the Clinical Epidemiology Unit and a leading investigator in work disability in arthritis; Dr. Yuqing Zhang, a leading quantitative epidemiologist in arthritis with an interest in internet-based studies; Dr. Michael LaValley, a biostatistician whose focus has been on clinical trials methodology and meta-analysis in rheumatology; Dr. Jingbo Niu, an epidemiologist with extensive expertise in data management and analysis; Dr. Tuhina Neogi, a rheumatologist whose research is focused on osteoarthritis and vasculitis; Dr. Bin Zhang, a biostatistician whose focus has been on clinical trials and other new statistical methodology; Dr. Kristin Baker, an exercise physiologist and nutritionist who has successfully completed exercise trials and is currently investigating nutritional aspects of osteoarthritis; Dr. Steven Vlad, a rheumatologist with research interest in pharmacoepidemiology; and Dr. Julie Keysor, a physical therapist whose research concerns functional limitation and disability associated with osteoarthritis. Dr. Felson's main interest focus on osteoarthritis epidemiology, including identifying persons at high risk of disease in whom disease can be prevented. He is a Principal Investigator of a large multicenter observational study of persons at high risk of OA, the Multicenter Osteoarthritis Study (MOST) and the Principal Investigator of a sub-study of the Framingham Heart Study, the Framingham Osteoarthritis Study. The Clinical Epidemiology Unit investigators have also been responsible for standardizing outcome measurement in rheumatoid arthritis clinical trials, a process that is ongoing. In addition to the P60 NIH Center Grant, the clinical epidemiology unit is funded through two R01 grants, two K23 grants, six Arthritis Foundation grants, 7 American College of Rheumatology Research and Education Foundation grants, and 2 T32 grants.

Among recent scientific accomplishments in the clinical epidemiology group have been the following:

1. Newer techniques to quantify cartilage on MRI, such as volume and thickness, are relatively insensitive to the changes occurring in the cartilage during the early stages of osteoarthritis, with semiquantitative assessments being superior at detecting these focal lesions. This has implications for methods used to study early osteoarthritis (Drs. Felson and Reichenbach)
2. The finding that central bone marrow lesions, related to anterior cruciate ligament injuries, are associated with cartilage loss suggests a role for enthesopathy in the development of osteoarthritis. (Drs. Felson and Hernandez-Molina)
3. Leg-length inequality is associated with occurrence and worsening of knee osteoarthritis, suggesting a simple preventative measure may be a shoe lift to minimize leg-length inequalities. (Drs. Felson and Harvey)

4. Epidemiologic studies until now have focused on the causes of new onset disease, but many chronic diseases disable people by causing acute episodes of pain and suffering. We are now using novel approaches to studying risk factors for pain among subjects with knee osteoarthritis, including within-person knee-matched case-control study and self-matched case-control design nested in longitudinal studies. Recently a new statistical method to analyze correlated ordinal data under self-matched study design has been developed. (Dr. Y. Zhang)
5. The demonstration that radiographic osteoarthritis is indeed strongly associated with knee symptoms even at the earliest stages of disease, a finding that is contrary to the common perception that knee symptoms have very little to do with structural abnormalities on x-rays. (Dr. Neogi)
6. The finding that serum uric acid, a key risk factor for gout, is independently associated with atherosclerotic plaque, suggesting a pathophysiologic role for uric acid in development of cardiovascular disease and that uric acid itself is likely another risk factor for heart disease among persons with gout. (Dr. Neogi)
7. Triggers for gout attacks, as determined from a novel internet-based case-crossover study, include all types of alcohol, even at low-to-moderate intakes, purine intake, low-dose aspirin, hospitalizations, infections, and hot humid weather, while drinking water can reduce the risk for recurrent gout attacks (Drs. Zhang and Neogi)

#### Clinical Trials:

The clinical trial effort of the Section of Rheumatology continues to grow and there are many active clinical trials in scleroderma and vasculitis. Dr. Robert Simms, Section Head and Professor of Medicine, is the regional PI for a pivotal NIH-funded, national multicenter trial of autologous stem cell transplantation versus intravenous cyclophosphamide for poor prognosis diffuse scleroderma. This pivotal trial is proceeding to actively enroll patients both regionally and nationally and involves a *major national collaborative effort* with nationally recognized scleroderma centers, including those at Duke University, University of Texas at Houston, University of Wisconsin, University of Michigan at Ann Arbor, and at U.C.L.A. The Program will also be a center in mycophenylate vs. cyclophosphamide in interstitial lung disease associated with scleroderma, a trial of anti-CTGF and interferon gamma and dasatanib. Additional trials of the Scleroderma Program include those involving an innovative topical therapy for Raynaud's phenomenon, mycophenylate mofetil (an anti-rejection therapy for transplantation) and imatinib for diffuse scleroderma. Additional *collaborative efforts* of the Scleroderma Program include the Genomewide Association Study in Systemic Sclerosis study headed by Dr. Maureen Mayes at the University of Texas, a national collaborative effort to identify gene expression signatures which characterize systemic sclerosis.

The Scleroderma Program is also one five national sites conducting a trial of a novel antifibrotic therapy, anti-interleukin 13 for pulmonary fibrosis associated with scleroderma. Additional studies of anti-interferon type receptor and a novel B cell

antagonist are planned for the near future. Ongoing work also includes a trial of oral treprostinil for therapy of digital ulcers associated with scleroderma. Dr. Simms currently serves on the steering committee for this innovative trial. The Program is also conducting several therapeutic trials of vasodilators for pulmonary hypertension, a common and severe complication of scleroderma. Scleroderma Program faculty including Drs. Lafyatis, Simms, Farber, Kissin and York are actively conducting prospective translational longitudinal studies to link biomarkers of scleroderma to clinical outcomes such as the development of pulmonary hypertension, worsening skin disease, pulmonary fibrosis and renal crisis. Program faculty including Drs. Simms, Merkel and Lafyatis are also working to develop improved outcomes of disease activity and involvement.

#### Clinical activities:

The Clinical Program in rheumatology is a major referral center for autoimmune and rheumatic diseases. Patients with scleroderma and vasculitis are seen from throughout the Northeast and in substantial numbers from throughout the United States and even abroad. The Scleroderma Program and Vasculitis Program are recognized foci of excellence in clinical care and clinical research throughout the region, nationally and internationally. Center faculty serve as identified expert clinicians broadly in the field of rheumatology as well within their research interest area. Dr. Kissin, Assistant Professor of Medicine, assumed the role of Clinical Director as the expanding clinical program continues to meet the needs of patients and referring physicians. He has emerged as a national leader in the use and teaching of musculoskeletal ultrasound, which has also become central to the fellowship training program curriculum.. Total clinical volume has continued to grow with over 8000 annual outpatient visits in addition to several hundred inpatient consultations each year. Many of the referred patients have complex medical problems and their referral to the institution contributes substantially to the reputation of the Medical Center and further enhances clinical collaborative efforts with colleagues in multiple specialties, including in Cardiology, Pulmonary Diseases, Radiology and other medical specialties.

The Arthritis Center remains a key player in research, clinical activity, clinical investigation, and education programs nationally and internationally. We anticipate continued growth on all these fronts.

#### High Impact Publications:

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