

Division of Rheumatology



George C. Tsokos, MD,
Chief

● *Overview*

The Division of Rheumatology at Beth Israel Deaconess Medical Center includes strong clinical, educational and research programs. The goals of the Division are to provide outstanding care to patients suffering from rheumatic diseases, exceptional teaching to medical students, medical residents, interns and trainees enrolled in the rheumatology fellowship program, and to conduct cutting-edge clinical, translational and basic research.

● *Clinical Activities*

The Rheumatology Division maintains an active outpatient clinical practice and an inpatient consultation service for patients with rheumatic diseases and other musculoskeletal problems. The outpatient practice evaluates and treats approximately 1800 new and more than 9000 established patients each year. This is a unique integrated practice environment that also includes a clinical trials unit and a rheumatology nurse specialist who provides patients with medication teaching and monitoring. All of the full-time members of the Division provide care based on a model in which each physician is responsible for personalized continuity of care for their patients. The individualized service provided to patients and referring physicians by the administrative and physician staff is in large part responsible for the growth and expansion of the outpatient clinical practice. The Division is a major referral center for patients with refractory rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, and polychondritis.

The Lupus Center provides the highest-quality, comprehensive healthcare for patients with SLE by rheumatologists with particular expertise

in the treatment of this disease. Collaboration and coordinated care with colleagues in other specialties, including the Renal Division, encourages optimal and efficient care.

Under the leadership of Dr. Fadi Badlisi, the Division, in collaboration with the Department of Orthopedics, operates the Musculoskeletal Medicine Unit in the Shapiro Clinical Center. This unit is a unique outpatient service that provides care for patients with acute and subacute regional pain syndromes and soft tissue disorders such as neck pain, back pain, tendonitis and bursitis. Other non-operative orthopedic and musculoskeletal conditions are seen in a setting that provides rapid access and diagnostic and treatment services.

● *Quality Improvement*

Under the leadership of Dr. Robert Shmerling, a number of quality improvement projects are monitored in the Division, including documentation of procedures, regular ophthalmologic examinations among patients taking anti-malarial medications, appropriate laboratory monitoring of patients taking methotrexate, screening for tuberculosis prior to infliximab therapy, improving patient telephone access, and improved documentation of reproductive counseling prior to the initiation of methotrexate or cyclophosphamide therapy.

● *Educational Programs*

The Division participates in the Harvard Medical School fellowship program with Brigham and Women's Hospital. The program provides a three year fellowship, the first year of which is devoted to clinical training and the last two years of which are devoted to research. During

the first year, the fellows provide coverage for an active inpatient consultation service. Formal teaching rounds are conducted at least twice a week with attending physicians from the Division. In addition, fellows are responsible for daily work rounds on all patients on the service. Throughout the three-year training period, fellows participate in a continuity outpatient rheumatology practice. Multiple clinical sites are used for this experience, including the West Campus rheumatology practice and the Musculoskeletal Medicine Unit at the Shapiro Center. This site provides unique exposure to soft tissue rheumatic disorders, sports medicine, rheumatologic procedures, as well as non-operative orthopedic trauma.

Dr. George Tsokos and Dr. Cox Terhorst, the Chief of the Division of Immunology, will direct an newly awarded T32 Training Program on Systemic Autoimmunity. Through this program, fellows in rheumatology, nephrology, dermatology and other subspecialties, as well as in basic sciences, will be mentored to become independent investigators in the field of lupus or other systemic autoimmune diseases.

Under the leadership of Drs. Gwen Kane-Wanger and Vasileios Kyttaris, the Division's weekly Rheumatology Grand Rounds invites local and national experts to present updates on clinical and research topics of interest. Dr. Ingrid Avalos is leading monthly meetings of members of the Lupus Center to discuss difficult and interesting patients with SLE.

The Division sponsors a Monthly Lupus Lecture Series and an annual one-day Lupus Symposium. Distinguished speakers from around the country and the world are invited to present their findings at these events. Basic and clinical researchers, students and fellows from various Boston institutions attend these events. Dr. Tsokos is the Chair of an Annual School on Systemic Autoimmune Diseases under the aegis of the Clinical Immunology Society.

Dr. Tsokos established and serves as the director of the FOCIS (Federation of Clinical Immunology Societies) Center of Excellence. The goal of the center is to promote educational and collaborative activities among 20 clinical/basic immunologists at BIDMC.

● *Research Activities*

<i>Research Funding • AY'07</i>	
Federal Direct	609,535
Federal Indirect	431,925
Other Direct	630,216
Other Indirect	79,115

The Division has an active and expansive basic, translational and clinical research program in the field of rheumatic diseases with special emphasis on the study of SLE. The laboratory is located at the Center for Life Sciences building.

The Tsokos laboratory is interested in studies of immune cell signaling and gene transcription in human SLE, as well as in mechanisms of tissue injury. By exploring the molecular origin of the multiple immune cell abnormalities in SLE, the studies identify novel biomarkers for the diagnosis of the disease and therapeutic targets.



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● Dr. Ingrid Avalos with a patient.

Drs. Tsokos and Yuang-Taung Juang conduct studies to characterize aberrant immune cell signaling processes in SLE T cells. SLE T cells have been found to express increased T cell receptor (TCR)-mediated early signaling response. Lipid rafts are aggregated on the surface membrane of T cells, while the TCR is rewired

with the FcR chain assuming the function of the CD3 chain. Additional signaling molecules are present in the lipid rafts, including Syk and the adhesion molecule CD44, which signals through pERM. In a collaborative effort with Dr. Costenbader of Brigham and Women's Hospital and funds from the Alliance for Lupus Research, Dr. Tsokos studies the expression of CD44 isoforms as possible disease biomarkers.

Drs. Tsokos, Juang and Kyttaris conduct studies to define the molecular origin of decreased production of interleukin-2 (IL-2) in human SLE T cells. It has been established that decreased transcriptional activity of IL-2 leads to decreased production of IL-2 by SLE T cells. They have found that the suppressor CREM is expressed in increased amounts in SLE T cells and binds to the IL-2 promoter. After binding, CREM recruits HDAC1, which deacetylates histones and confers a "closed" chromatin structure. CREM activation and binding to the IL-2 promoter were found to be caused by increased CaMKIV expression in SLE T cells. In parallel studies, they found that SLE T cells express increased amounts of PP2Ac, which dephosphorylates CREB and thus deprives the IL-2 promoter of a putative transcriptional enhancer. Dr. Kyttaris, recipient of a K23 award from NIAMS, studies the molecular basis for the inability of SLE T cells to produce IL-2 while they express excessive amounts of CD40L.

Dr. Tsokos, in collaboration with Dr. Ahearn of the University of Pittsburgh, is conducting

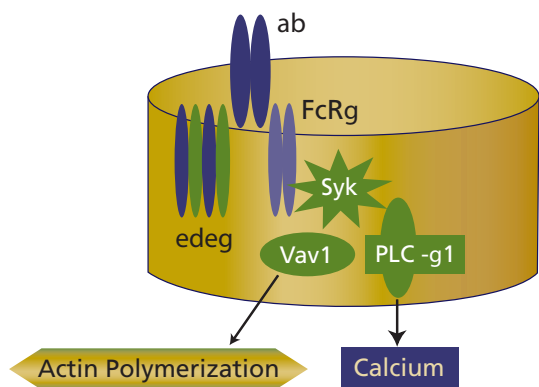
studies to develop T cell-based biomarkers for SLE. Aggregated lipid rafts on the surface membrane of SLE T cells represent a disease-specific and highly sensitive phenomenon. Expression of aggregated lipid rafts and molecules that are included in the rafts, such as FcR, Syk, CD44 and complement components, are being studied with the goal of using them as disease biomarkers.

Drs. Tsokos, Juang and Guomin Deng conduct studies to define mechanisms whereby natural autoantibodies activate complement and cause tissue injury. We have demonstrated, using a mouse model of mesenteric ischemia/reperfusion (I/R), that autoantibodies, such as anti-DNA, cardiolipin, histones and RNP, infused in mice resistant to I/R, Rag1^{-/-}, do not cause any tissue injury unless the mice undergo I/R. In collaboration with Dr. Holers of the University of Colorado, we have shown that these antibodies bind to neoantigens expressed on IR-stressed tissues, activate complement and execute pathology. The goal of these studies is to decipher mechanisms of tissue injury and develop approaches to limit damage.

Patients with SLE have an increased risk of cardiovascular disease. There is limited evidence suggesting that patients with SLE have an abnormal response to aspirin. Dr. Avalos, with funding from the American College of Rheumatology, studies mechanisms that lead to aspirin resistance in patients with systemic autoimmune diseases. These are believed to involve inappropriate production of thromboxane through the upregulation of cyclooxygenase-2. This clinical study is expected to generate information that will lead to better measures to limit cardiovascular disease in patients with SLE.

● Awards and Honors

Dr. Tsokos served as past-president of the Clinical Immunology Society, serves as Compliance Officer of the Federation of Clinical Immunology Societies, is a permanent member of the Hypersensitivity, Allergy and Immune-mediated Diseases Study Section of the National Institutes of Health, and chair of the Alliance for Lupus Research Study Section. In addition, he serves as consulting editor of the *Journal of Clinical Investigation*, Associate Editor-in-Chief of *Clinical Immunology* and Editor of *Autoimmunity*. Dr. Tsokos was elected fellow of the American Association for the Advancement of Sciences and he received the Mary Kirkland Lupus Scholar Award. Dr. Shmerling is the President of the New England Rheumatism Society. Dr. Vaishali Moulton received a 3-year fellowship award from the



● Lipid Raft in SLE T Cells

Arthritis Foundation. Dr. Martin-Villa, a visiting Professor in the Division, received a stipend award from the Real Colegio Complutense de Harvard. Dr. Jose Crispin, Rheumatology Fellow, received a stipend award from the Fundacion Mexico en Harvard. Dr. Katsue Sunahori, Rheumatology Fellow, received a scholarship from the Japanese College of Rheumatology.

● *Selected Publications*

Li Y, Harada T, Juang YT, Kyttaris VC, Wang Y, Zidanic M, Tung K, Tsokos GC. Anti-CD3/TCR autoantibodies induce p-ERM and trigger T cell polarization, adhesion and migration into inflamed SLE kidney. *J Immunol* 2007; 178:1938-1947.

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Gibson HM, Hedgcock C, Aufiero BM, Wilson AJ, Tsokos GC, Wong HK. Regulation of the human CTLA-4 promoter is dependent on NFAT1. *J Immunol* 2007; 179:3831-3840.

Juang YT, Sumibcay L, Tolnay M, Wang Y, Kyttaris VC, Tsokos GC. Elf-1 binds to the FcR promoter and suppresses its activity. *J Immunol* 2007; 179:4884-4889.

Moulton VR, Juang YT, Kyttaris VC, Tsokos GC. The RNA stabilizing protein HuR regulates the expression of CD3 in human T cells. *J Biol Chem* 2008; 283:20037-44.

Cohen AA, Bayliss G, Crispin J, Kane-Wanger GF, Van Beek CA, Kyttaris VC, Avalos I, Yu CY, Tsokos GC, Stillman IE. T cells and *in situ* cryoglobulin deposition in the pathogenesis of lupus nephritis. *Clin Immunol* 2008; 128:1-7.

Juang YT, Wang Y, Jiang G, Peng HB, Ergin S, Finnell F, Kyttaris VC, Tsokos GC. PP2A dephosphorylates Elf-1 and determines the expression of CD3 and FcR in human systemic lupus erythematosus T cells. *J Immunol*, 2008; 181:3658-64.

Crispin J, Kyttaris VC, Juang YT, Tsokos GC. Systemic lupus erythematosus: New molecular targets. *Ann Rheum Dis* 2008; 66:65-69.

● *Faculty*

Ingrid Avalos, MD	Vasileios Kyttaris, MD
Fadi Badlisi, MD	Peter Lapchack, PhD
Guomin Deng, MD, PhD	Paul Romain, MD
Arturo Diaz, MD	Robert Shmerling, MD
Sukran Ergin, MD	Francine Ton-Nghiem, MD, MMSc
Lisa Fitzgerald, MD	David Trentham, MD
Yuang-Taung Juang, MD, PhD	George Tsokos, MD
Gwen Kane-Wanger, MD	



Crispin J, Kyttaris VC, Juang YT, Tsokos GC. Signaling and gene transcription aberrations dictate systemic lupus erythematosus T cell phenotype. *Trends Immunol* 2008; 29:110-115.

Tsokos GC. Calcium signaling in SLE lymphocytes and its therapeutic exploitation. *Arthritis Rheum* 2008; 58:1216-1219.

Lee YC, Shmerling RH. The Benefit of non-pharmacologic therapy as the primary treatment of patients with symptomatic osteoarthritis. *Curr Rheumatol Rep* Simon L, ed 2008; 10:5-10.

- Dr. Shmerling reviews X-rays with Dr. Noss, rheumatology fellow.