rheumatology and immunology

David A. Horwitz, M.D. *Professor and Chief*

Diane Clark Robinson *Administrator*

The Division of Rheumatology and Immunology is known for its programs in patient care, teaching and research, especially for its contributions to the pathogenesis and the clinical manifestations of systemic lupus erythematosus, the prototype of human autoimmune diseases. Drs. William Stohl and David Horwitz have taken advantage of the extraordinary clinical resources of the LAC+USC Medical Center to develop novel biologic agents for the treatment of lupus. Dr. Stohl is directing two phase 2 clinical trials to study the effectiveness of the B lymphocyte growth factor antagonist in SLE and rheumatoid arthritis. Dr. Horwitz has patented a novel approach to harness the patients own immune system for the treatment of SLE and other autoimmune diseases. Drs. J. Dixon Gray and Song Guo Zheng, in his group, are inducing immature immune cells to become immune policemen called regulatory T cells. Clinical studies are being designed to learn if the treated blood cells from a lupus patient can be used as a treatment to induce disease remission. This technology has been licensed by a large pharmaceutical company and represents a partnership between the Keck School of Medicine and private industry to develop novel biologic agents for clinical use.

The Division provides broad clinical activities for Los Angeles County and USC University Hospital. Drs. Francisco Quismorio, Jr. and Rodanthi Kitridou direct a major lupus clinic. Drs. Daniel Arkfeld and Glenn Ehresmann continue to have a strong interest in promising new agents to treat patients with this crippling form of arthritis and work with their orthopedic colleagues to provide comprehensive care for patients with diverse forms of arthritis.

Using the exceptional clinical resources of the LAC+USC Medical Center, Rancho Los Amigos National Rehabilitation Center and USC University Hospital, the Division provides outstanding training for medical students, post-doctoral medical residents and fellows. The rheumatology fellowship emphasizes patient care in a broad range of rheumatic diseases, presentation of clinical conferences, and understanding the role of the immune system in the pathogenesis of autoimmune diseases. This Division's many accomplishments during the past year reflect the skills and creativity of a dedicated faculty.

faculty

Daniel G. Arkfeld, M.D.
Assistant Professor of Clinical Medicine
Associate Director of Rheumatology Education, USC University Hospital
Director of Rheumatology, Center for Arthritis and Joint Implant Surgery

Thomas D. Beardmore, M.D.
Associate Professor of Clinical Medicine
Chief, Rheumatology Program, Rancho Los Amigos Rehabilitation Center
Co-Chief, Arthritis Program

Glenn R. Ehresmann, M.D.
Associate Professor of Clinical Medicine
Director of Rehabilitation Services, USC University Hospital

J. Dixon Gray, Ph.D.
Associate Professor of Research Medicine

David A. Horwitz, M.D.
Professor of Medicine and Molecular Microbiology and Immunology
Chief, Rheumatology and Immunology

Ronald Kaufman, M.D., M.B.A.
Senior Associate Dean for Administration, Keck School of Medicine
Associate Senior Vice President, University of Southern California
Professor of Clinical Medicine

Rodanthi C. Kitridou, M.D., FACP, MACR
Professor of Medicine

Edward E. Morgan, M.D.
Emeritus Associate Professor of Medicine

Francisco P. Quismorio, Jr., M.D.
Professor of Medicine and Pathology
Vice Chief, Rheumatology and Immunology

William Stohl, M.D., Ph.D.
Professor of Medicine

NEW FACULTY

Song Guo Zheng, M.D.
Visiting Assistant Professor of Research

faculty honors

MEMBERSHIP IN DISTINGUISHED SOCIETIES

David A. Horwitz, M.D.
American Society for Clinical Investigation
Southern Society for Clinical Investigation
Western Association of Physicians
Western Society for Clinical Investigation

Ronald L. Kaufman, M.D., M.B.A.
Alpha Omega Alpha

Rodanthi C. Kitridou, M.D., FACP, MACR
Alpha Omega Alpha

MEMBERSHIP IN PROFESSIONAL SOCIETIES

Daniel G. Arkfeld, M.D.
American College of Rheumatology
Arthritis Foundation, Southern California Chapter
Myopain Society
Southern California Rheumatism Association

Thomas D. Beardmore, M.D.
American College of Physicians
American College of Physician Executives
American College of Rheumatology
American Federation for Medical Research
American Medical Association
Arthritis Foundation of Southern California
Arthritis Health Professionals Association
California Medical Association
Los Angeles County Medical Association
Southern California Rheumatology Society

Glenn R. Ehresmann, M.D.
American College of Physicians
American College of Rheumatology
Arthritis Foundation, Southern California Chapter
Arthritis Health Professions Fellowship, Sub-committee

J. Dixon Gray, Ph.D.
American Association of Immunologists

David A. Horwitz, M.D.
American Association for the Advancement of Science
American Association of Immunologists
American College of Physicians
American College of Rheumatology, Master
American Federation for Medical Research
Arthritis Foundation, Southern California Chapter
New York Academy of Sciences
Southern California Rheumatism Society

Ronald L. Kaufman, M.D., M.B.A.
American Academy of Physician Executives
American College of Physicians
American College of Physician Executives
American College of Rheumatology
American Medical Association
American Society of Law and Medicine
Association for Health Services Research
Beta Gamma Sigma, Honor Business Society
California Medical Association
California Society of Internal Medicine
Los Angeles Academy of Medicine
Los Angeles County Medical Association
Southern California Rheumatism Society
Venice Family Clinic, Advisory Board

Rodanthi C. Kitridou, M.D., FACP, MACR
American Behcet's Disease Association
American College of Physicians, Founding Fellow and Master
American College of Rheumatology, Master
Arthritis Foundation
Hellenic American Medical and Dental Society of Southern California
International League Against Rheumatism
Lupus Foundation International
Pan-American League Against Rheumatism
Southern California Rheumatology Society

Francisco P. Quismorio, Jr., M.D.
American Association of Immunologists
American College of Physicians
American College of Rheumatology
Arthritis Foundation, Southern California Chapter
Association of Philippine Physicians in America
Clinical Immunology Society
New York Academy of Sciences
Philippine History Group of Los Angeles
Philippine Medical Society of Southern California
Southern California Rheumatology Society
University of the Philippines Medical Alumni Society in America
UPMASA, Southern California Chapter

William Stohl, M.D., Ph.D.
American Association for the Advancement of Science
American Association of Immunologists
American College of Rheumatology

Song Guo Zheng, M.D.
America Advance Association of Science
American Association of Immunologists
Arthritis National Research Foundation
Chinese Medicine Association
European Association for Cancer Research
Shanghai Anticancer Association

EDITORSHIPS/EDITORIAL BOARDS

David A. Horwitz, M.D.
Arthritis and Rheumatism, Advisory Editor
Lupus, Associate Editor

Francisco P. Quismorio, Jr., M.D.
Dubois' Lupus Erythematosus, Associate Editor
Postgraduate Medicine

William Stohl, Ph.D., M.D.
Lupus News, Editorial/Medical Advisory Board

Song Guo Zheng, M.D.
Journal of Anticancer (China)

MAJOR LECTURES

David A. Horwitz, M.D.

Regulatory T cells generated with IL-2 and TGF-β have long term effects ex vivo. Agean Conference on Autoimmunity, Mykonos, Greece, 10/10/2003.

Regulatory T cells generated with IL-2 and TGF-β have long term effects ex vivo. Kennedy Institute, London, England, 10/16/2003.

Mechanisms responsible for the long term effects of regulatory T cells induced with IL-2 and TGF-β. International Congress of Immunology, Montreal, Canada, 6/20/2004.

Mechanisms responsible for the long term effects of peripheral regulatory T cells induced with IL-2 and TGF-β. International Congress of Immunology, Montreal, Canada, 6/21/2004.

INVITED LECTURES

Daniel G. Arkfeld, M.D.

Pain and arthritis in the elderly. Grand Rounds, Cedars-Sinai Medical Center, Los Angeles, CA, 2/15/2004.

Rheumatoid arthritis in Hispanics living in Los Angeles. Meeting, National Hispanic Medical Association, Washington, DC, 4/3/2004.

Glenn R. Ehresmann, M.D.

Advances in the treatment of rheumatoid arthritis. Educational Conference, West Hollywood Primary Care Physicians, West Hollywood, CA, 9/11/2003.

Osteoporosis. California Association of Nurse Practitioners, Calabasas, CA, 11/12/2003.

The new advances in the prevention and treatment of osteoporosis. The Alliance for Better Bone Health, Burbank, CA, 11/13/2003.

Monoarthritis, issues in diagnosis and management. Update: Regional Physical Medicine Meeting, Southern California Kaiser Permanente, Bakersfield, CA, 11/14/2003.

In-service lecture, Garfield Medical Center, San Gabriel, CA, 4/8/2004.

Osteoarthritis. Lecture for Medical Staff, Anaheim Memorial Medical Center, Anaheim, CA, 5/11/2004.

Rheumatology. In-service Lecture, Monterey Park Hospital, Monterey Park, CA, 5/25/2004.

Advances in arthritis pain management. Educational Conference, Irvine Regional Hospital and Medical Center, Irvine, CA, 6/23/2004.

Manage pain and protect against NSAID-related GI complications. Educational Lecture, Community Clinic, Pico Rivera, CA, 6/24/2004.

David A. Horwitz, M.D.

Natural and induced CD4+CD25+ cells educate CD4+CD25- cells to develop suppressive activity: Role of IL-10 and TGF-β. National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, 12/16/2003.

Effects of cytokines and CD4+CD25+ subsets on CD4+CD25- cells in the generation of renewal of regulatory T cells. National Meeting of American Association of Immunologist, Washington, DC, 2/20/2004.

Prolonged survival of heart allografts by regulatory T cells generated ex-vivo. National Meeting of American Association of Immunologist, Washington, DC, 2/21/2004.

Regulatory T cells in autoimmunity. New York University Advanced Symposium for Rheumatology, New York, NY, 3/12/2004.

Rodanthi C. Kitridou, M.D., FACP, MACR

Pulmonary hemorrhage in systemic lupus. Rheumatology Grand Rounds, Oklahoma Medical Research Foundation, University of Oklahoma, Oklahoma City, OK, 11/12/2003.

Pregnancy in rheumatic diseases, with emphasis on lupus, antiphospholipids, and the neonatal lupus syndrome. Phoenix Rheumatology Association, Phoenix, AZ, 3/25/2004.

OFFICE/COMMITTEE MEMBERSHIPS HELD IN NATIONAL/ REGIONAL PROFESSIONAL & OTHER SOCIETIES

Daniel G. Arkfeld, M.D.
Arthritis Foundation, Southern California Chapter
Medical and Scientific Committee

Thomas D. Beardmore, M.D.
American College of Rheumatology
  Finance Committee
Arthritis Foundation, Southern California Chapter
  Board of Directors
  Executive Committee
  Medical and Scientific Committee, Vice Chair
  Los Angeles Branch, Chair
  Long Range Planning Committee
  Nominations Committee
Arthritis Health Professionals Association, Southern California Chapter, Medical Advisor
Los Angeles County Department of Health, 1986-Present Health Services Management Forum
Southern California Rheumatism Society
  Accommodations Committee
  Fellow Presentation Judging Committee
  Fellow Presentation Selection Committee
  Membership Committee
  Officer Nominating Committee
  Operations Committee
  Professional Education Committee
  Research Committee
  SCAHP Executive Committee
  Vice Chair, Medical and Scientific Affairs

Ronald L. Kaufman, M.D., M.B.A.
American College of Physicians
  Advisory Committee
  Southern California Governor
American College of Rheumatology
  Board of Directors
  Planning Committee
Arthritis Foundation, Southern California Chapter
  Board of Directors
  Governor's Council
  Legislative Advocacy Committee
American Medical Association
  Practice Expense Advisory Committee
  Relative Value Update Committee
California Medical Association
  Academic Practice Forum, Chair
  Council on Legislation
Los Angeles BioMedical Park Team
Los Angeles County Medical Association
  Board of Councilors
  Task Force Medical Students, Residents and Young Physicians, Chair
  Task Force on Public, Private Relationships
Musculoskeletal Education and Research
  Board of Trustees
Southern California Rheumatism Society
  Economics Committee
Venice Family Clinic
  Advisory Board
Visiting Nurses Association of Los Angeles
  Professional Advisory Committee

Rodanthi C. Kitridou, M.D., FACP, MACR
American Behcet's Disease Association
  Medical Advisory Board
American College of Rheumatology
  Abstract Selection Committee, SLE-Clinical Aspects
    Subcommittee, Chair
  Abstract Selection Committee, SLE-Treatment Developments
    Subcommittee, Chair
  Annual Meeting Planning Committee
  Career Development and Women's Health Subcommittee
  Education Committee (Educational Products)
  Meet-the-Professor Sessions, Coordinator
Arthritis Foundation
  Medical and Scientific Committee
  Southern California Chapter
East Los Angeles Lupus Support Group
Hellenic American Medical and Dental Society
  Board of Directors
  Scholarship Committee

Lupus Foundation of America
  Medical Advisory Board, Co-Chair
  Southern California Chapter, Board of Directors

Francisco P. Quismorio, Jr., M.D.
American College of Rheumatology
  Abstract Selection Committee, Chair
  High-Impact Rheumatology CME Program for Primary Care Physicians, Coordinator
Arthritis Foundation, Southern California Chapter
  Medical and Scientific Research Review Projects Committee
Lupus Foundation of America
  Medical Advisory Board
  Medical Scientific Committee

William Stohl, M.D., Ph.D.
American College of Rheumatology
  Abstract Selection Subcommittee, Lymphocyte Activation and Regulation
  Abstract Selection Subcommittee, SLE-Human Etiology and Regulation

NATIONAL INSTITUTES OF HEALTH STUDY SECTIONS/NOTEWORTHY GOVERNMENT ACTIVITIES

Thomas D. Beardmore, M.D.
Social Security Administration Office of Hearings and Appeals
  Department of Health and Human Services, Medical Advisor
State of California
  Board of Medical Licensure and Quality Assurance, Medical Advisor

David A. Horwitz, M.D.
NIAMS
  Phase 1 Clinical Trial of Regulatory T cells in the Treatment of Systemic Lupus Erythematosus
  Study Section, Rheumatic Disease Core Center
Systemic Lupus Erythematosus Initiative Study Sections
  Immunological Sciences Clinical Centers, Ad-hoc reviewer

Ronald L. Kaufman, M.D., M.B.A.
LA Care, Technical Advisory Committee, Vice Chair
State of California
  Office of Statewide Health Planning and Development, California Health Policy and Data Advisory Commission
    Advance Patient Privacy and Care Committee

William Stohl, M.D., Ph.D.
NIAID Special Emphasis Review Panel

AWARDS/HONORS

Rodanthi C. Kitridou, M.D., FACP, MACR
Best Doctors in America
Castle Connoly Directory, Top Doctors in America
Lupus Foundation of America
  Certificates of Appreciation
  Honorary Life Membership Award
  Humanitarian Award
Marquis Who's Who in Medicine and Healthcare

William Stohl, M.D., Ph.D.
Arthritis Foundation, Southern California Chapter, James R. Klinenberg, M.D. Award

SERVICE ON UNIVERSITY, SCHOOL, HOSPITAL AND DEPARTMENTAL COMMITTEES

Daniel G. Arkfeld, M.D.
Keck School of Medicine
  Department of Medicine
    Basic Science Curriculum Committee
    Contracts and Billing Sub-Committee
    Curriculum Committee
    Education Committee
    Preceptorship Program, Director
    Resident Education Committee
  IRB Institutional Research Board Reviewer

Thomas D. Beardmore, M.D.
Keck School of Medicine
  Medical Faculty Assembly
LAC+USC Medical Center
  Quality Assurance, Rancho Los Amigos Representative
Rancho Los Amigos Medical Center
  Credentials Committee,
  Practitioners Well Being Committee

Rodanthi C. Kitridou, M.D., FACP, MACR
Department of Medicine
  Quality Assurance Committee
USC Medical Faculty Women's Association
  Executive Board
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Francisco P. Quismorio, Jr., M.D.
Keck School of Medicine
  Admissions Committee

William Stohl, M.D. Ph.D.
University of Southern California
  Academic Senate, University Research Committee
Keck School of Medicine
  Evaluation of Faculty Promotion, Ad Hoc Committees
  Department of Medicine Appointments & Promotions Committee
  Financial Aid Committee
  M.D./Ph.D. Committee

Thomas Susko, M.D.
Ambulatory Health Clinic
  Operations Committee, Chair
Department of Medicine
  Practice Operations and Development Committee
University Hospital
  Interdisciplinary Dysphagia Team

clinical activities

LAC+USC MEDICAL CENTER

The clinical service consists of an active inpatient and outpatient consultation service, four outpatient clinics per week at the LAC+USC Medical Center. Our physicians provide care for 8,000 outpatient visits and more than 500 inpatients are seen in consultation. We have an active working relationship with the Department of Orthopedics at Rancho Los Amigos National Rehabilitation Center Arthritis Service in the management of arthritis patients needing joint replacement and rehabilitation.

SPECIAL CLINICAL SERVICES

Drs. Arkfeld, Ehresmann, and Kitridou treat over 100 different types of arthritis and rheumatic conditions at the USC Ambulatory Health Care Center. There are more than 5,000 patient visits each year and the numbers have been increasing. The Arthritis Center at USC University Hospital has established a world-renowned reputation for joint replacement with over 400 hip and knee joints replaced annually. As the rheumatologists for the Arthritis Center, we interact directly with the orthopedic surgeons and manage the medical conditions of the patients during the preoperative and postoperative periods. Our physicians develop and present an annual community education for arthritis.

HIGH-IMPACT RHEUMATOLOGY FOR PRIMARY CARE PHYSICIANS

The USC Division of Rheumatology and Immunology, competing with 80 other rheumatology programs nationwide, was awarded a grant from the American College of Rheumatology to conduct a continuing medical course for primary care physicians in the Southern California area. The major objective of the program is to develop higher levels of confidence in diagnosing, managing and communicating with patients suffering from arthritis and other rheumatic diseases.

educational activities

FELLOWS

FIRST YEAR
Christopher Collins, M.D.
Elyse Rubenstein, M.D.
Nina Trinh, M.D.

SECOND YEAR
Morris Kokhab, M.D.
Jenny Oh, M.D.
Shuntaro Shinada, M.D.

CLINICAL ACTIVITIES

The Division of Rheumatology and Immunology is strongly committed to the education of medical students, housestaff and post-graduate fellows. A curriculum has been developed for housestaff and fellows. Our training programs utilize the LAC+USC Medical Center, USC University Hospital and Rancho Los Amigos National Rehabilitation Center (RLANRC). Childrens Hospital of Los Angeles (CHLA), a USC-affiliated institution, serves as an additional resource.

The LAC+USC Medical Center is one of the largest university affiliated general hospitals in the United States. The patients include a wide variety of acutely ill, newly diagnosed rheumatology patients such as those with infectious arthritis, systemic vasculitis, systemic lupus erythematosus, etc. The Division of Rheumatology operates a consultation service and three outpatient arthritis clinics per week and a fourth clinic at the Roybal Comprehensive Health Center.

Rancho Los Amigos National Rehabilitation Center is a major center well known for its expertise in rehabilitation and reconstructive surgery, especially in arthritis. At the USC University Hospital, three faculty rheumatologists staff a 32-bed inpatient rehabilitation unit. These programs provide another dimension to the service and complement the resources of LAC+USC Medical Center. The rheumatology trainee gains in-depth and extensive experience and training in the orthopedic and rehabilitative care of arthritis patients at each facility. In addition, the long-term care of the arthritis patients and the psychosocial aspects of rheumatic diseases are emphasized.

During the second year of fellowship, each trainee spends one month at Childrens Hospital of Los Angeles to gain experience in the diagnosis, management and treatment of pediatric rheumatology cases.

The Division conducts three regularly scheduled conferences: Rheumatology Grand Rounds, Journal Club, and RLANRC Conference. Rheumatology Grand Rounds is a clinical conference held once a week at LAC+USC Medical Center. A patient seen by the trainee is presented and discussed in this conference. Faculty and fellows present one carefully selected journal article in a Journal Club. At RLANRC, each inpatient is presented by the rheumatology trainee in a multidisciplinary patient conference. The rounds are attended by rheumatology staff, orthopedic surgeons, physical therapists, medical psychologists, social workers, occupational therapists, nurses, and other allied health personnel. Decisions are made concerning the optimum care of the patient. Our fellows present and attend a monthly radiology conference for musculoskeletal imaging at LAC+USC Medical Center.

Since the opening of USC University Hospital 13 years ago, our faculty have been responsible for the operation of an inpatient rheumatology service and have become intimately involved with the Department of Orthopedics in the operation of their Center for Arthritis and Joint Implant Surgery. The rheumatology inpatient service hospitalizes patients with rheumatologic or orthopedic problems with a focus on musculoskeletal rehabilitation therapies. For the interested trainee, spending an additional year based predominantly at USC University Hospital can be an invaluable experience.

The research component of the fellowship combines expertise of a team of basic science-oriented faculty and clinical faculty with the exceptional resources in rheumatic diseases available at our teaching hospitals. There are five full-time faculty members who are primarily involved in research. Three of these have received Ph.D. degrees and have demonstrated areas of expertise in immunology and molecular biology. The laboratories occupy 5,000 square feet of space and are located in the Hoffman Basic Science Building, which is across the street from the LAC+USC Medical Center.

research activities

The Division of Rheumatology and Immunology is known for its basic and clinical research on systemic lupus erythematosus (SLE). SLE is a disorder of generalized autoimmunity induced by self-reactive T cells when immune regulation fails. We have taken advantage of the exceptional clinical resources of the LAC+USC Medical Center to study the genetic basis of SLE and to elucidate the cellular mechanisms responsible for immune dysregulation in this disease. Beginning with the efforts of the late Edmund Dubois, this Division is well known for its observations on the clinical and laboratory manifestations of systemic lupus erythematosus (SLE), the prototype of the human autoimmune diseases. Drs. Horwitz, Gray and Stohl have taken advantage of the extraordinary clinical resources of the Keck School of Medicine to study immune regulation in human SLE. These resources include the LAC+USC Medical Center, the largest public hospital in the United States, and the USC International Twin Registry where 160 lupus twins have been identified. Dr. Horwitz and his group have concentrated their efforts on T cells while Dr. William Stohl's current work is focused on B cells. During the past year, information gained from the laboratory bench which either target T cells or B cells has served as the basis for novel treatment strategies.

Drs. Gray and Horwitz have been investigating the role of hormone-like growth factors called "cytokines" in immune regulation. They have shown that the cytokine, transforming growth factor beta (TGF-β) is a critical co-stimulatory factor in the generation of "immunologic policemen." These policemen are T cells that suppress antibody production and cell-mediated immunity, (the functional properties of both T cells and B cells). These workers previously reported decreased lymphocyte production of TGF-β impaired in SLE and they believe that this defect strongly contributes to decreased regulatory T cell function in SLE. Recent studies suggest that regulatory T cell defects in SLE are reversible. Treatment of IL-2 activated SLE lymphocytes to TGF- β restored the ability of CD8+ T cells to decrease autoantibody production. Most recently, using a mouse model of lupus, they have successfully generated regulatory T cells ex-vivo and used these cells to suppress, if not prevent, the development of lupus in vivo. The next step is to restore the ability of T cells from patients with human SLE to suppress antibody production. To accomplish this objective, they plan to obtain large numbers of T cells from lupus patients by apheresis and use the methods described above to induce these cells to develop regulatory activity. After the cells are expanded, they will be infused back to the patient. The patients will then be carefully monitored for suppression of autoimmunity and clinical improvement. If successful, a particular advantage of this novel therapeutic approach is that it would avoid the severe toxic side effects associated with the drugs now used to treat patients with SLE and other chronic, inflammatory autoimmune diseases.

Previously, Dr. Stohl and his colleagues had demonstrated that levels of a potent B cell growth factor called "B Lymphocyte Stimulating Factor (BLyS)" are elevated in a substantial fraction of SLE patients. He and his colleagues are now investigating the role for BLyS overproduction in the development of SLE and are testing the ability of specific antagonists of BLyS to treat patients with SLE.

In addition to generating T cells that down-regulate antibody production, Drs. Horwitz and Gray have successfully induced another subset of T cells to inhibit cell-mediated immunity. They have expanded a minor thymic-derived T cell subset to numbers that have powerful immunosuppressive properties. These cells may not only have the potential to prevent autoimmunity, but also may block the rejection of tissues transplanted from one individual to another. Allogeneic stem cell transplantation has significant potential in the treatment of individuals with hematologic and solid tumors, but this procedure has had limited usefulness because of graft-versus-host disease. The generation of regulatory T cells ex-vivo has the potential to prevent graft-versus-host disease. In addition, kidney, heart and liver transplantation have increasing indications, but require toxic drugs to prevent rejection. The treatment of patients who receive these organ grafts with regulatory T cells has the potential result in long term survival without the use of these toxic drugs.

Novel approaches to treat patients with rheumatoid arthritis. Drs. Dan Arkfeld, Glenn Ehresmann, David Horwitz and Thomas Susko have been investigating new strategies to treat patients with rheumatoid arthritis (RA). This disease affects two million Americans, predominantly women, who suffer from the often crippling effects of this disease. Although the exact cause of RA is not established, most agree it is an autoimmune disease where cells called lymphocytes attack the body instead of eliminating foreign invaders. Lymphocytes called "CD4+ T cells" are involved in the initiation of RA. Macrophages and other cells in synovial joints then invade and destroy joint cartilage. Drs. Arkfeld, Ehresmann and Horwitz have been studying Therafectin (amiprilose hydrochloride) in the management of RA. The studies at USC have revealed that this drug is effective in patients with severe rheumatoid arthritis. The especially encouraging feature of Therafectin is that the drug appears to be much less toxic than most of the remittive drugs now in use for the treatment of RA.

FACULTY RESEARCH AREAS

Daniel G. Arkfeld, M.D.
Rheumatoid Arthritis
Osteoarthritis
Novel Immune Therapies for Immune Disorders

David A. Horwitz, M.D.
Cytokine-Mediated Down-Regulation of B Cell Hyperactivity in SLE
Immunoregulatory Mechanisms in the Rheumatic Diseases
Regulatory T Cell Subsets in SL

William Stohl, M.D., Ph.D.
T Cell Regulation of Polyclonal Immunoglobulin and Autoantibody Production in SLE and Related Rheumatological Diseases
T Cell Helper and Down regulatory Functions Triggered by Microbial Superantigens.

Song Guo Zheng, M.D.
Treatment of Autoimmune Diseases
Prevention of Transplant Organ Rejection

SPECIAL BASIC RESEARCH ACTIVITIES

William Stohl, M.D., Ph.D.

Systemic Lupus Erythematosus and B lymphocyte stimulator (BLyS). Published observations in murine SLE strongly intimate a pathogenic role for excessive production of BLyS, a recently discovered member of the tumor necrosis factor (TNF) ligand superfamily that stimulates B cells in a T cell-independent manner. Published observations from our laboratory indicate that serum BLyS levels are elevated in many human SLE patients. Candidate BLyS antagonists have been developed and are being actively tested in clinical trials. Studies in mouse models of SLE are ongoing to elucidate the mechanisms through which overexpression of BLyS leads to clinical disease.

David A. Horwitz, M.D.

Cytokine-Mediated Down-Regulation of B Cell Hyperactivity in SLE. SLE is a disease of generalized autoimmunity characterized by B cell hyperactivity and the production of many autoantibodies. Our working hypothesis is that SLE patients are deficient producers of the cytokines required for the induction of the regulatory T cells which prevent autoimmunity. The principal goals of this project are to restore the capacity of SLE T cells to down-regulate antibody production, define the cytokine networks involved, and use this information to prepare for clinical trials where we will learn whether normalization of T regulatory cell activity can lead to disease remission. We have learned that Transforming Growth Factor beta (TGF- β) is an important co-stimulatory factor in the generation of CD8+ cells which down-regulate T cell-dependent antibody production, that production of lymphocyte-derived TGF- β is decreased in SLE, and that exposure of SLE PBMC to IL-2 and TGF-β markedly decreased spontaneous polyclonal and autoantibody production. The specific aims of the present proposal are: 1) To determine whether CD4+ T cells activated in the presence of TGF-β also develop the capacity to down-regulate IgG production. If so, we will determine whether they retain their regulatory effects after expansion; 2) To test the hypothesis that IL-10 can be down-regulated by TGF- β, and that decreased amounts of lymphocyte-derived TGF- β in SLE contributes to elevated levels of IL-10; 3) To learn whether T regulatory cells generated ex-vivo and adoptively transferred to NZM2410 mice can delay the onset of SLE. Ultimately, we plan to condition T cells of SLE patients with cytokines ex-vivo to develop down-regulatory activity and learn whether the adoptive transfer of these cells back to the patient will have beneficial therapeutic effects. We intend to establish proof of the concept that regulatory T cells generated ex-vivo using TGF- β and adoptively transferred to patients with SLE can correct a pathogenic immune defect and have beneficial clinical effects on the course of this autoimmune disorder. We have planned to test this hypothesis using two animal models of SLE. In preparation for a Phase 1 clinical study in human SLE, we also plan to determine the optimal composition of regulatory T cells for adoptive transfer, elucidate reversible defects of regulatory cell differentiation in SLE, and learn whether these regulatory T cells can be expanded. Our immediate objective during this project period is to learn how TGF- β induces immature CD4+ and CD8+ lymphocytes to develop suppressive activity. The project has three parts. This information will be very helpful in the design of studies to assess the suppressive effects of these regulatory T cells in vivo.

SPECIAL CLINICAL RESEARCH ACTIVITIES

William Stohl, M.D., Ph.D.

Phase 2 Studies of Lymphostat-B™ (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). The current paradigm of SLE and RA pathogenesis begins with a genetic predisposition leading to the production of pathogenic autoantibodies and autoreactive effector B and T lymphocytes. The rational for developing a BLyS antagonist for treatment of autoimmune disease is supported in the current literature. For example, constitutive overexpression of BLyS in transgenic mice results in the development of autoimmune-like disease characterized by hypergammaglobulinemia, autoantibody production (e.g., anti-dsDNA antibodies, rheumatoid factor antibodies), and kidney involvement. Soluble BLyS receptor (TACI-Fc), as a BLyS antagonist, inhibits proteinuria in, and prolongs the survival of, NZBWF1 mice. TACI-Fc also reduces disease severity in an animal model of RA. Elevated BLyS levels are evident in the serum and synovial fluid of some RA patients and the serum of SLE patients. A positive correlation exists between serum BLyS and serum IgG levels and autoantibody (anti-dsDNA and RF) levels. Taken together, these data provide evidence that BLyS antagonism has potential therapeutic benefit in SLE and RA.

publications

PEER REVIEWED PUBLICATIONS

Metyas S, **Arkfeld DG**, Forrester DM, **Ehresmann GR**: Infliximab treatment and secondary Familial Mediterranean Fever AA Amyloidosis. *J Clin Rheum* 10:134-137, 2004.

Rubinstein E, Metyas S, **Arkfeld DG**, Forrester D, **Ehresmann GR**: Adult onset stills in an elderly patient. *J Amer Geriatrics Soc*, in press, 2004.

Lacson S, **Arkfeld DG**, Metyas SK: Bipolar hip arthroplasty in 101 year-old patient. *J Amer Geriatrics Soc*, submitted, 2004.

Oh J, **Arkfeld DG, Horwitz D**: Development of Crohn's Disease while on etanercept. *J Clin Rheum*, submitted, 2004.

Arkfeld DG, Shinada S, Metyas S, Liebman H: Catastrophic antiphospholipid antibody syndrome treated with rituximab. *Arthritis Rheum*, submitted, 2004.

Horwitz DA, Zheng SG, Gray JD, Wang JH, Ohtsuka K, Yamagiwa S: Regulatory T cells generated ex vivo as an approach for the therapy of autoimmune disease. *Semin Immunol* 16:135-143, 2004.

Horwitz DA, Zheng SG, Wang JH, **Gray JD**: The central role for TGF-β in a network consisting of natural, natural-like and cytokine-dependent CD4+CD25+ cells regulatory T cells. *Nature Review*, submitted, 2004.

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Schaller M, **Stohl W**, Tan SM, Benoit Vm, Hilbert DM, Ditzel HJ: Elevated levels of antiglucose-6-phosphate isomerase (GPI) IgG in serum and synovial fluid from patients with inflammatory arthritis. *Ann Rheum Dis*, submitted, 2004.

TYPE	NUMBER APPEARED	NUMBER IN PRESS	NUMBER SUBMITTED
Peer Reviewed Publications	16	1	5
Books and Book Chapters	0	0	0
Other Publications	0	0	1
Abstracts	14	2	5

federal and agency grants

PRINCIPAL INVESTIGATOR	AGENCY NAME	TITLE OF ACCOUNT OR GRANT	ANNUAL DIRECT $	ANNUAL INDIRECT $	TOTAL $	BEG DATE	END DATE
Horwitz, David A.	Arthritis Foundation - California	Cytokine-Mediated Down Regulation of B Cell Hyperactivity in SLE	$ 40,247	$ 0	$ 40,247	7/1/03	7/1/03
Horwitz, David A.	Treadwell (Nora Eccles) Foundation	Regulatory T Cell Subsets in Systemic Lupus Erythematosus	68,866	0	68,866	7/1/01	7/1/01
Horwitz, David A.	National Institute of Allergy and Infectious Diseases	Immunoregulatory Mechanisms in Rheumatic Disease	218,290	135,340	353,630	9/1/80	9/1/80
Stohl, William	Alliance for Lupus Research	Systemic Lupus Erythematosus	92	7	99	1/1/01	1/1/01
Stohl, William	Arthritis Foundation - California	Murine Model of Sjogren's Syndrome	40,627	0	40,627	7/1/03	7/1/03
Zheng, Song Guo	Arthritis National Research Foundation	Generation of Antigen-Specific T Regulatory Cells in TCR	49,934	0	49,934	6/1/03	6/1/03
		TOTAL:	**$ 418,056**	**$ 135,347**	**$ 553,403**		

other grants

PRINCIPAL INVESTIGATOR	AGENCY NAME	TITLE OF ACCOUNT OR GRANT	ANNUAL DIRECT $	ANNUAL INDIRECT $	TOTAL $	BEG DATE	END DATE
Arkfeld, Daniel	Immunex	TNFR: FC Clinical Trials	$ 4,760	$ 1,190	$ 5,950	3/19/01	Present
Stohl, William	Human Genome Sciences	SLE & RA to Determine B Lymphocyte Stimulation	15,898	3,974	19,872	4/29/02	Present
Stohl, William	Human Genome Sciences	LymphoStat-B Antibody (Monoclonal Anti-BLyS Antibody) in Systemic Lupus Erythematosus	44,106	11,027	55,133	2/1/04	Present
Stohl, William	Human Genome Sciences	LymphoStat-B Antibody (Monoclonal Anti-BLyS Antibody) in Rheumatoid Arthritis	1,400	350	1,750	4/15/04	Present
		TOTAL:	**$ 66,164**	**$ 16,541**	**$ 82,705**		