

10TH NATIONAL CONFERENCE
THE CHANGING FACE OF INFLAMMATION: STRATEGIES FOR THE NEW MILLENNIUM

September 24-28, 2000, The Homestead, Hot Springs, VA



Dr. Michael Weinblatt,
Plenary Lecturer

**Dr. Michael Weinblatt to be featured as
Plenary Speaker**

Michael E. Weinblatt, M.D., President-Elect of the American College of Rheumatology (ACR), has been invited to present the Plenary Lecture on the opening day of the upcoming IRA 10th National Conference. Dr. Weinblatt's lecture, "Treatment of Rheumatoid Arthritis in the New Millennium," will highlight the clinician's perspective of strengths and limitations of currently available antiarthritic therapeutic agents and set the stage for the remainder of the meeting, which focuses on our current understanding of inflammatory mechanisms, their involvement in a variety of human diseases, and strategies for intervention. Dr. Weinblatt is Director of Clinical Rheumatology at the Brigham

and Women's Hospital and Professor of Medicine at Harvard Medical School, where his major research interest is therapeutic interventions in rheumatoid arthritis. He has published over 160 papers, invited chapters, reviews and abstracts in the field of rheumatology, primarily rheumatoid arthritis therapeutics. He has directed a research program that has extensively studied multiple synthetic products including methotrexate, cyclosporin and leflunomide, and biologic response modifiers including anti-CD4 therapy, TNF neutralizers including etanercept, lenercept and D2E7, the IL-1 receptor antagonist and IL-4 and IL-10. He is co-editor of the textbook, *Treatment of Rheumatic Diseases*, and is a member of the subspecialty board in rheumatology for the American Board of Internal Medicine (ABIM).

Guest Society to Sponsor Symposium

For the first time, a guest society, the International Society for Rheumatic Therapy, will sponsor a symposium at the biennial Conference. The ISRT Symposium, "Recent Therapeutic Experiences with New Generation Drugs for Inflammatory Diseases," will open the Conference on Sunday afternoon and will provide the clinician's perspective on the relative benefits

and limitations of recently introduced antiinflammatory drugs. Presentations are expected to include cyclooxygenase-2 inhibitors, TNF neutralizers and other recently introduced drugs. The combination of this symposium and Dr. Weinblatt's Sunday evening Plenary Lecture is intended to provide insight into current and anticipated clinical needs, and to establish a clinical foundation on which all of the other sessions of the Conference can build.

Main Scientific Symposia

The five symposia planned for the next four days of the Conference are intended to provide an overview of current research in the topical area as well as details of particular strategies for therapeutically useful intervention. The symposia are organized by experts in each topic and will include invited lectures as well as up to three short presentations from submitted abstracts:

Molecular Signaling, organized and chaired by Dr. Alem Truneh (SmithKline Beecham) and Dr. Sankar Ghosh (Yale University). Signal transduction mechanisms provide the interface through which cells respond to changes in their external environment. Signaling involved in inflammatory responses and in the regulation of cells involved in inflammatory and immune reactions represent potential sites for therapeutic intervention. Presentations are planned on novel TNF/TNFR homologs in inflammatory processes (Dr. Alem Truneh / SmithKline Beecham), NF- κ B: a pleiotropic mediator of inflammatory responses (Dr. Sankar Ghosh / Yale University), STAT and IRF proteins in host defense (Dr. David E. Levy / New York University), turning T-cells on and off (Dr. Arthur Weiss / UCSF), and signaling and cell death in lymphocytes (Dr. Richard Flavell / Yale University).

Inflammation and Oncogenesis, organized and chaired by Dr. Sreekant Murthy (Hahnemann University Medical School). Chronic inflammation is a commonly observed feature of many cancers. For example, the risk of colorectal cancer is

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high among patients with ulcerative colitis and long-standing Crohn's disease. Similarly, the incidence of cancer is increased in all other gastrointestinal tissues as a result of chronic inflammation, whether it is induced by bacterial or viral pathogens or idiopathic inflammatory diseases. Speakers will review the clinical aspects and mechanisms of carcinogenesis in chronic inflammatory diseases. While the use of COX-2 inhibitors in the chemoprevention of certain cancers is well recognized, other emerging antiinflammatory agents, that reduce the risk of carcinogenesis in chronic inflammatory conditions, will be discussed.

Matrix Metalloproteinases and Adamalysins, organized and chaired by Dr. Gillian Murphy (University of East Anglia) and Dr. David Becherer

(Glaxo Research Institute). In addition to their roles in matrix remodeling and degradation, the MMPs are showing previously hidden talents in immunology and related areas. New members of the ADAMs family are being regularly discovered and this family of enzymes has become all the rage in fields from development to death!

Orphan Receptors: Novel Target Identification and Validation, organized and chaired by Dr. Jilly Evans (Merck & Co.) and Dr. Lee F. Kolakowski, Jr. (UTHSC at San Antonio). Genomics research has identified a number of expressed genes for proteins with characteristics of known receptors but with no recognized ligand. The search for the natural ligands and functional roles of these orphan receptors is now

revealing new approaches to antiinflammatory therapies. This symposium will include presentations by Dr. Kevin Lynch (University of Virginia), Dr. Jim Liu (Merck & Co.), Dr. Robert Ames (SmithKline Beecham) and others actively involved in unraveling the mysteries of orphan receptor function.

New Drugs for Inflammatory, Allergic and Immunologic Diseases, organized and chaired by Dr. Richard Griffiths (Pfizer) and Dr. Kevin Koch (Array BioPharma). The translation of preclinical results into new drugs is the ultimate and difficult-to-achieve outcome sought in pharmaceutical research. This symposium will include presentations on pharmaceutical agents currently beginning or about to begin clinical trials. The selection of compounds to be included is ongoing and is expected to be finalized in June 2000, providing the most up-to-date information possible on these new and exciting compounds.

Editor's Corner



l to r: Lian Liauw, Joan Chapdelaine, Kathy Gans-Brangs, Debbie Wolff, and Marcia Bliven

For the past seven years, since the premier issue of the *IRA Newsletter*, I have acted as sole editor, chief writer and recruiter of articles for this publication. This will be my final issue as editor, as I have announced my intention to retire from Pfizer on May 1, 2000.

The first seeds were planted early in 1990 when, inspired by Greg Harper's BIRAs newsletter, I casually mentioned to Neil Ackerman, then President of the IRA, my interest in starting a newsletter to increase communication among the members of our organization. He then proceeded to announce this to the

world, thereby obligating me to act on my casual remark! And so the first issue debuted in September 1992, in time for the IRA 6th International Conference.

The publishing of the *Newsletter* has definitely been a labor of love, the outlet for a secret avocation and previously unfulfilled ambition. However, as with any product that proceeds to market, it is never just the work of one person, but the support of many that has brought the *Newsletter* to you: all those contributing authors who answered the call and took time from an already busy schedule to write the IRA meeting summaries, especially Mike Parnham, who prepared a detailed summary of every IRA International Conference and IAIS Meeting within days of its occurrence; Dick Carlson, who always had his ear to the ground and became the primary source of the latest sightings of career movements for the "People on the Move" column; Pfizer and my department directors, initially Niall Doherty, and currently Steve Gilman, for willing financial support of the printing and mailing of every issue, and the Pfizer graphics department, especially Carole Drong, for her unquestioning cooperation, can-do attitude, and exceptional design skills; and lastly, Ivan Otterness, who first introduced me to the IRA, and without whose mentoring and support this undertaking would not have become a reality, who encouraged my initiatives, and time and again lent a willing ear and a critical eye to a novice editor. I am also deeply indebted to all those contributors who have responded to my quarterly pleas for copy, and to the IRA Officers and Board members who enthusiastically supported my efforts. Although this may be the last printed issue for the time being, it is the intention of the Board to continue the *Newsletter* on the IRA website in the near future (check it out for the June 1999 issue).

I am grateful for the friendships, and the associations and alliances formed through my more than 16 years of involvement with the IRA, spanning eight Boards and sets of Officers. My work with Conference Coordination began with the 2nd International Conference in 1984. But it was never really work; I enjoyed every minute of being a part of the activities and forming lasting friendships with a very special group. I'll especially remember the fun (and sometimes stressful!) times together that Lian Liauw, Kathy Gans-Brangs, Debbie Wolff, Joan Chapdelaine and I shared behind eight Conference registration desks over the years. I wouldn't have missed it for the world! In fact, Debbie enjoys it so much that even though her career has taken her out of the inflammation area, she continues to return every two years to share that week with us! I would invite and encourage YOU to take advantage of the opportunity to become involved and experience the same rewards.

I look forward to keeping in touch with friends and colleagues and IRA activities through future issues of the *Newsletter*. And I'll see you at the 10th National Conference in September!

-Marcia L. Bliven

Workshops

The workshops are presentations of selected submitted abstracts on topics that compliment the symposia presentations. The workshops will be chaired by experts in the topical areas and will coordinate programs of short presentations followed by group discussion within their workshop. The tentative workshop titles are listed below, but others may be added if supported by the submitted abstracts. Please check the website (www.inflammationresearch.org) for the updated plans.

- New Approaches to Acute and Chronic Inflammatory Diseases
- New Drugs: Rational Design, Pharmacodynamics and Pharmacokinetics
- Inflammatory Cell Signaling
- Tissue Remodeling
- Biomarkers for Inflammatory Diseases

Poster Sessions

All submitted abstracts will be considered for oral presentation or poster session and will be reviewed by the topic chairpersons. For the first time, several abstracts will be selected for oral presentation during the morning symposia, after the invited speaker lectures. Others will be selected for workshop presentations. Two poster sessions will provide opportunities for all scientists to discuss experimental design, methods, results and conclusions from research reported in submitted abstracts.



Dr. James Louie, after-dinner speaker

Dr. James Louie to be after-dinner speaker at Conference Banquet

Dr. James Louie will once again be the after-dinner speaker at the closing banquet of the 10th National Conference. His lecture on Renin and his arthritis was received with such enthusiasm and interest in 1998 that he

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was invited to join us for a return engagement to present another lecture, entitled "Art and Inflammatory Disease." This new presentation will highlight other artists and their arthritic afflictions, including Rubens and gout, Dufy and the treatment of RA, Klee and his lack of treatment for scleroderma, and Grandma Moses and her home remedies for OA. He will illustrate the point that different arthritic conditions have different pathogenetic mechanisms, and that the most effective therapies come from the best knowledge of disease mechanisms.

Dr. Louie has lectured on several artists, including Renoir, Rubens, Dufy, Klee, Toulouse Lautrec, and Grandma Moses in venues in Europe, Australia, South America and Asia, as well as the United States.

Dr. Louie is a Fellow of both the American College of Rheumatology and the American College of Physicians. Among his many professional activities are committee service for the ACR, the Arthritis and Lupus



The Homestead chosen as venue

Foundations, as well as reviewing manuscripts for several national rheumatology journals. He has been honored with awards for teaching and achievements in education, and is listed in "Best Doctors in America: Pacific Region."

The Homestead Chosen as Venue

The Homestead, a premier resort located in the mountains of western Virginia, will be the venue for the Conference. Beginning back in November 1998, the IRA Board decided to seek an upscale site to mark our 10th biennial Conference and celebrate the upcoming millennial year in style. The dates of the Conference, September 24-28, 2000, will be an especially lovely time of year in the Virginia mountains.

The hotel literature offers a preview of what you can expect in this spectacular resort. *"Since 1766, guests have come here to gaze at the glorious mountain beauty, to relax in the luxurious, yet comfortable, retreat that is The Homestead. Now, restored to its former splendor, The Homestead awaits your group, with a combination of state-of-the-art meeting facilities, exquisite accommodations and an unmatched array of activities. In short, The Homestead is the ideal setting for a meeting that will be both productive and pleasurable."*

Recognized world wide for superb meeting facilities and service, The Homestead has every major meeting award to its credit. The Homestead is on Conde Nast's 1998 Gold List of the world's top hotels, resorts, and spas. There are more than 500 luxuriously appointed rooms and suites, superb dining, a wealth of activities (including golf, fishing,

swimming, horseback riding, tennis, shooting sports, biking and hiking trails, canoeing, bowling, and a spa salon!), in addition to traditional Southern hospitality in a gracious atmosphere.

So mark **September 24-28, 2000** on your calendars and start making your plans to be in Hot Springs to attend the 10th National Conference of the Inflammation Research Association!

Contact Registrar Joan Chapdelaine for more information (Tel: 570-585-2211, Fax: 570-585-2383, *Email: joan.chapdelaine@pils.com), and visit the IRA website (www.inflammationresearch.org) and The Homestead website (www.thehomestead.com).

*Note new Email address for Conference Registrar!



INVITATION FOR PROPOSALS FOR "NEW DRUGS" SYMPOSIUM

Dear Colleague:

The finale of the 10th National Conference of the Inflammation Research Association in Hot Springs, VA, September 24-28, 2000, will once again be devoted to "New Drugs for Inflammatory, Allergic, and Immunologic Diseases." This symposium has been a much anticipated event at past Conferences and with this letter we begin the process of soliciting proposals for presentations at the next meeting.

You may recall that the intent of the Symposium is to feature debut presentations of new drugs currently beginning or about to begin clinical trials. Each talk is to appeal to a broad audience of biochemists, pharmacologists, medicinal chemists and clinicians. The talks will include background of the therapeutic

approach, information on the discovery and design of the agent, *in vitro* and *in vivo* characterization, some structure-activity information, support for the role of the drug in the management of disease and early clinical data. The organizing committee would like to select four to five presentations from those submitted. The Symposium will be held on the final morning of the Conference and is intended to be a major feature of the meeting. The Symposium's 1998 edition, featuring presentations on an ICE inhibitor, a PDE4 inhibitor, a selective COX-2 inhibitor, an inhibitor of LFA1/ICAM-1 interactions and an anti-CD4 antibody, was well attended and considered to be a highlight of the Conference.

If you have a new drug that you feel meets the criteria for the Symposium as outlined above, please call or email one of us at the address listed below. Feel free to forward this letter to your colleagues, especially to those who may be involved in advanced studies on therapeutic agents targeting inflammatory aspects of diseases not traditionally grouped within the realm of inflammation.

Thank you in advance for your assistance in making this Symposium and the 10th National Conference a success.

Sincerely,

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IAIS – 10 YEARS AND GOING STRONG!

The International Association of Inflammation Societies (IAIS) owes its origins to a round table discussion during an Inflammation Research Association (IRA) meeting held in White Haven, PA, in 1988, when the need for greater communication and collaboration between the many inflammation societies around the world was shared by representatives from the IRA, the British Inflammation Research Association (BIRAs), the European Inflammation Society (EIS/EWI) and the Groupe de le Recherche et d'Etude des Mediateurs de l'Inflammation (GREMI). The broad and dynamic field of inflammation research was flourishing globally, and there was a need to share progress and new developments in the molecular basis of the many diseases with inflammatory components, as well as the discovery and clinical development of new therapies. It was also felt that the few Congresses that focussed on inflammation research at that time were often designed for profit, and the high registration fees often precluded the participation of young investigators and academic investigators with limited funding.

Representatives from the participating societies agreed to arrange a series of meetings to establish the benefits for such a Society, to be named the IAIS, and so a Steering Committee was established. This committee, whose members would later become the officers of the Society, consisted of Alan Lewis (IRA) as President, Kay Brune (EIS/EWI) as Treasurer and Rodger McMillan (BIRAs) as Secretary. The first meeting was a small, but very successful, satellite that was organized by Wim van den Berg (Nijmegen, The Netherlands) in Noordwijk, The Netherlands, at the time of the 1990 IUPHAR Congress in Amsterdam. On this occasion, the need to encourage other inflammation societies to join the IAIS was discussed, as well as a proposal to review a Charter for the Society that would formalize the organization and focus on the following aims:

- Assist inflammation scientists to initiate and organize societies in regions of the world where they are not currently available.



Bringing the IAIS into concept: Alan Lewis (first President of IAIS), Mike DiMartino, Hamish Humphray and John Westwick in White Haven, 1988



IAIS President, Alan Lewis, convening INFLAMMATION '93 in Vienna



IAIS business meeting at White Haven, 1994



Toronto IAIS Satellite, 1994

- Foster cooperation with affiliated societies for the purpose of organizing international scientific meetings and teaching courses for scientists that emphasize inflammation research. These would seek to encourage maximal participation of graduate students and post-doctoral scientists by minimizing registration and housing costs wherever possible.

- Initiate and organize IAIS satellite meetings in conjunction with international meetings, such as IUPHAR, and workshops within international meetings with the assistance of local inflammation societies.

- Develop interrelationships with outside societies.

This was followed by the first of the major Congresses, entitled INFLAMMATION '93 and held in Vienna, Austria. The successful debut of this series of Congresses, which have been subsequently held every two years, was due to the tremendous efforts of Kay Brune (Erlangen, Germany), who orchestrated a dynamic and enjoyable Conference with a broad participation from over 40 countries. The Conference was also able to generate a modest profit in order to seed the next Conference planned for Brighton, U.K., in 1995. In 1994, the Canadian Inflammation Society (CIS) arranged another IUPHAR satellite, this time in Toronto, to maintain the momentum for the Society. Waldemar Pruzanski and Peter Vadas, from the CIS, and Doug Morgan, representing the IRA, were responsible for this successful satellite.

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Kay Brune becomes the 2nd President of IAIS at Brighton, 1995



IAIS business meeting in Brighton, 1995



Morris Ziff, Alan Lewis, and Helen Muir, first Ciba-Geigy Prize winner, in Vienna, 1993

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The success of INFLAMMATION '95 was further proof that there was an appetite for such multi-disciplinary meetings that included academic, clinical and industrial scientists from around the world. This meeting was followed by INFLAMMATION '97, organized by the Japanese Inflammation Society (JIS) in Tokyo, and INFLAMMATION '99, organized by GREMI in Paris. It is very encouraging that these very successful meetings have now become the premier international meetings that focus on inflammation research. The IAIS will continue the series of meetings in Edinburgh, September 22-26, 2001 (BIRAs), Vancouver, August 3-6, 2003 (IRA), and Sydney in 2005 (Society for Cytokine, Inflammation and Leukocytes [SCIL] Research). The Organization has developed as the originators of the idea hoped and has exceeded their expectations. We are confident that, with the continued focus on globalization of the healthcare industry and medicine, and the continued exciting discoveries in our understanding of the mechanisms associated with inflammatory diseases, the IAIS will continue to thrive with the involvement of scientists from around the world.

- Alan J. Lewis
Signal Pharmaceuticals



Congratulations to Rodger McMillan for organizing the successful Brighton meeting INFLAMMATION '95



IAIS steering committee in Tokyo, 1997



The passing of the President's Olympic hat to Rodger McMillan at Tokyo, 1997



IAIS business meeting in Paris at INFLAMMATION '99

MEETING REPORT

SECOND IRA WEST COAST SYMPOSIUM: GENE REGULATION IN INFLAMMATION AND BONE EROSION

September 23-24, 1999

La Jolla, CA

The second Inflammation Research Association West Coast Symposium was held on September 23-24, 1999, at the Hilton La Jolla Torrey Pines in La Jolla, California. This year's one and one-half day symposium, "Gene Regulation in Inflammation and Bone Erosion," was organized by Tony Manning of Signal Pharmaceuticals and Marie Chabot-Fletcher of SmithKline Beecham Pharmaceuticals, and attended by approximately 90 participants. The meeting began on Thursday evening with a reception and keynote address by **Dr. Tony Hunter** of the Salk Institute. Dr. Hunter's talk, entitled "Transcytoplasmic Signaling by Phosphorylation," focused on cellular signaling mediated by tyrosine kinases.

Symposium participants reconvened on Friday morning to hear the session's first speaker, **Dr. Renu Heller** of Roche Biosciences, who spoke on "Gene Expression Studies in Multiple Sclerosis." Dr. Heller began by giving an overview of gene chip gene expression technologies and their usefulness in profiling human diseases. She then continued with a discussion of gene expression in MS, and the use of gene chip technologies to analyze the genes expressed in MS tissue. Cluster analysis of the data showed that not only does myelin degradation occur during the course of this disease, but that myelin synthesis is also compromised. Among the genes shown to be up-regulated in the MS tissues were MHC class I and II, immunoglobulin and complement components, selectin (P) and integrin (B4), as well as a number of macrophage specific molecules.

Dr. Martin Lotz of the Scripps Institute followed Dr. Heller with a talk entitled "Interleukin Signaling in



Speaker Tony Manning (Signal), IRA President Lisa Marshall (SKB) and IRA Past President (1986-1988) Alan Lewis (Signal)

Extracellular Matrix Degradation." Dr. Lotz stated that cartilage degradation is a hallmark of both rheumatoid arthritis (RA) and osteoarthritis (OA). However, the processes underlying cartilage degradation differ in the two diseases. In RA, cartilage degradation is an extrinsic process involving an aberrant immune response and a dialogue between the synovium lining the joint and the cartilage itself. In contrast, OA is characterized by an age and time dependent decompensation of repair mechanisms leading to degradation of the matrix. Potential targets in these processes include extracellular stimuli such as the cytokines IL-1, IL-18, TNF, and IL-17. In addition, matrix degradation fragments, mechanical stress, intracellular signaling pathways, and various effector molecules may play a role. Potential effector molecules

include the matrix metalloproteinases, cysteine/serine proteases, lysosomal enzymes, oxygen radicals and nitric oxide.

Dr. Gary Firestein (UCSD), whose talk was entitled "Defective Tumor Suppressor Genes in Arthritis," pointed out that RA synoviocytes are inherently invasive and went on to discuss p53 tumor suppressor genes in RA. Many p53 mutations are seen in RA patients and are specific for synovial tissue and located in known tumor hot spots. p53 expression in RA, particularly long standing RA, is increased. Transformation is seen later in the disease. Dr. Firestein then turned his attention to a discussion of NF- κ B activation in RA. NF- κ B and the I κ B kinases can be activated in RA synoviocytes. IKK β (IKK2) inactivation by a K>M mutant prevented NF- κ B activation in synoviocytes. An adenoviral construct of IKK β injected into the joint was reported to result in increased I κ B phosphorylation and NF- κ B/DNA binding as measured by EMSA in the rat synovium. Also seen was a large increase in paw swelling and moderate synovitis. Dominant negative IKK β adenoviral constructs administered to adjuvant arthritis rats reduced paw swelling, suggesting that the activation of IKK β and NF- κ B plays a key role in mediating the joint inflammation seen in these models.

Dr. Roger Davis' (University of Massachusetts Medical Center) presentation was entitled "Signal Transduction by Stress Activated MAP Kinases." Dr. Davis' focus

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Keynote Speaker Tony Hunter

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was on the c-Jun NH₂-terminal kinase (JNK) pathway, wherein JNK activation leads to the phosphorylation of c-Jun and a subsequent increase in gene expression. Various Jnk knockouts were constructed to study the roles of these isoforms. Mice deficient in Jnk1, Jnk2, Jnk3, and Jnk1/Jnk3 or Jnk2/Jnk3 double mutants all survived normally. The Jnk3 KO displaying a defect in neuronal apoptosis while the Jnk1 and Jnk2 knockouts, on the other hand, show defects in T-cell functions. Dr. Davis reported that the Jnk2 KO had defects in Type 1 cytokine expression and a failure to respond to IL-12. In contrast to the other Jnk knockouts, the Jnk1/Jnk2 double knockout was reported to be embryonic lethal with severe dysregulation of apoptosis in the developing brain. Dr. Davis then focused his attention on the important role of scaffolding and anchor proteins in MAP kinase signaling pathways. Scaffold proteins can bind several signaling molecules to create multi-enzyme complexes. Examples of these proteins are the Ste5p and Pbs2p proteins in yeast which are important in regulating mating and osmoregulation, respectively. Recently, MAP-kinase scaffold proteins were identified in mammals. JNK-interacting protein 1 (JIP-1) and JNK-activating protein (JAP-1) have been shown to selectively interact with multiple components of the JNK signaling pathway. As such, these proteins are likely to play an important role in restricting the subcellular location of MAP-kinase signaling pathways, targeting MAP kinases to specific substrates, or linking these pathways to specific cellular events as do their yeast counterparts.

The MAP kinase discussion continued with **Dr. Sanjay Kumar's** presentation "p38 MAP Kinase as a Target for Bone and Joint Disease." Dr. Kumar (SmithKline Beecham) presented evidence that p38 inhibitors block cytokine production both *in vivo* and *in vitro*. However, not all cytokines are affected. The mechanism of this inhibition was shown to be due to the very selective inhibition of p38 through interaction of the drug with the ATP binding pocket of the kinase. This inhibition blocks the phosphorylation of MAPKAP kinase 2. Interestingly, MAPKAP K2 knockout mice display a phenotype similar to that of CSAID treatment. *In vivo*, p38 inhibitors were shown to reduce serum IL-6 levels and reduce paw volume in the rat adjuvant arthritis model in a manner comparable to indomethacin. Furthermore, the compounds were shown to restore normal joint architecture. Dr. Kumar reported that in



Co-chair Marie Chabot-Fletcher introduces a speaker

the ovariectomized model of osteopenia p38 inhibitors protect from bone loss due to a decrease in bone resorption. This decrease leads to a net maintenance of bone density in this model.

Dr. Brydon Bennett of Signal Pharmaceuticals spoke on "JNK Inhibitors for Inflammation and Autoimmunity." Dr. Bennett discussed recent data generated with SP600125, an ATP competitive and selective inhibitor of JNK (100-200 nM *in vitro*). *In vitro* studies have shown that SP600125 inhibits IL-12 production (5-10 μM) in PMA+PHA activated T-cells. The mechanism was shown to involve a decrease in c-jun phosphorylation with no changes in p-ERK, p-p38 or IκBα degradation. The compound was shown to block endotoxin-induced TNF production in mice when administered either orally or by iv. In RA synoviocytes, where JNK2 is the predominant JNK family member expressed, SP600125 was shown to block the IL-1 induced phosphorylation of c-jun and the expression of MMP-1. Furthermore, Dr. Bennett reported that the JNK inhibitor also reduces paw swelling, arthritis severity and joint destruction in the rat adjuvant arthritis model when administered at 30 mg/kg s.c.

Dr. Robert Abraham, Duke University, began the afternoon with a presentation entitled "Regulation of Cytokine Inducible Gene Expression by mTOR." The bacterial metabolite rapamycin is thought to inhibit biochemical events required for the progression of IL-2 stimulated T cells from G1 to S-phase of the cell cycle. Rapamycin binds to its intracellular receptor FKBP12 (immunophilin). This complex then mediates its effects through its interaction with mTOR, the mammalian target of rapamycin. mTOR contains an extended N-terminal domain which is needed for function. The protein also contains an FRB domain to which the immunophilin-drug complex binds. The molecule also contains a PI3-kinase related catalytic domain which is a protein serine/threonine kinase. mTOR activation has been linked to the activation of the p70S6 kinase and a subsequent increase in protein synthesis. Activation of mTOR is also thought to lead to the phosphorylation of PHAS/4E-BP1, a key regulator of translation initiation. Upon phosphorylation, PHAS-I no longer binds to eIF-4E, allowing the latter to interact with the remaining members of the initiation factor complex, which leads ultimately to an increase in eIF-4F-dependent translation initiation. As such, rapamycin, through its interaction with mTOR, is able to inhibit the



Tony Hunter leaving the meeting in his vintage VW bug

phosphorylation of PHAS-I, inhibit eIF-4E-dependent protein synthesis and prevent cells from entering S-phase.

Dr. Inder Verma of the Salk Institute presented an eloquent review of the discovery of NF-κB some 10-15 years ago, and the remarkable advances which have been made in understanding the regulation of this important transcription factor, including how work on the IκB kinase knockouts have helped us understand the roles of these kinases. Dr. Verma also presented some interesting data on the double IKK1/IKK2 knockout mouse. The double knockout is embryonic lethal at day 9 and displays neural tube defects. The NF-κB activity in the fibroblasts of these animals is completely absent in response to TNF and IL-1 stimulation.

The discussion around NF-κB signaling was continued by **Dr. Merl Hoekstra** of Signal Pharmaceuticals who discussed IKK3. Unlike the other IκB kinases IKK1 and IKK2, Dr. Hoekstra reported that IKK3 mRNA is induced in response to inflammatory cytokines. The kinase is not a component of the signalsome as are the other two isoforms, and serine 36 is not phosphorylated. IKK3 was reported to induce NF-κB activity, but is able to block IL-1 signal transduction. An E>S mutation in the activation loop of the kinase was shown to prevent this blockage of IL-1 signal transduction. Interestingly, IKK3 has no effect on TNF signaling. Dr. Hoekstra also provided an overview of ubiquitination as a common theme in signal transduction.

The symposium concluded with a talk on TGF-β signaling. **Dr. Jeff Wrana**, The Hospital for Sick Children, Toronto, discussed "TGF-β Family Signal Transduction." The TGF-β family of proteins signal across cell membranes through complexes of transmembrane receptor serine/threonine kinases which, in turn, activate the Smad signaling pathway. Phosphorylation of the receptor regulated Smads (R-Smads) allows their interaction with the downstream Smad4 and migration of the heteromeric complex to the nucleus where it regulates transcriptional responses. Recently, the recruitment of Smad2 to the TGF-β complex has been shown to be regulated by SARA (Smad Anchor for Receptor Activation). Dr. Wrana reported that SARA co-precipitates with Smad2 in the absence of signal. However, its association with Smad2

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10TH NATIONAL CONFERENCE PRELIMINARY AGENDA

	Sunday 9-24	Monday 9-25	Tuesday 9-26	Wednesday 9-27	Thursday 9-28
Morning	Registration 10:00 AM	Symposium 8:30 AM-Noon <i>Molecular Signaling</i> Oral Abstracts	Symposium 8:30 AM-Noon <i>Matrix Metalloproteinases & Adamalysins</i> Oral Abstracts	Symposium 8:30 AM-Noon <i>Orphan Receptors: Novel Target Identification and Validation</i> Oral Abstracts	Symposium 8:30 AM-Noon <i>New Drugs for Inflammatory, Allergic and Immunologic Diseases</i>
Afternoon	ISRT Symposium 4:00-6:00 PM <i>Recent Therapeutic Experiences with the New Generation Drugs for Inflammatory Diseases</i>	Van Arman Workshop Presentations 1:30-3:00 PM Poster Session I 3:00-5:00 PM	FREE AFTERNOON	Poster Session II 3:00-5:00 PM	ADJOURN
Evening	Plenary Lecture 8:30 PM <i>Treatment of Rheumatoid Arthritis in the New Millennium</i> Welcome Reception 9:30 PM	IRA Dinner 5:30-7:00 PM Special Symposium 7:00-9:30 PM <i>Inflammation and Oncogenesis</i>	Workshops 7:00-9:00 PM	Cocktail Reception 6:00 PM Banquet 7:00 PM After-dinner Lecture <i>Art and Inflammatory Disease</i> Awards	

Check the IRA website (www.inflammationresearch.org) for updated information.

KEY DEADLINES

Abstract Submission
Early Registration
Hotel Reservation
Written Cancellation (for refund)

April 1, 2000
June 1, 2000
ASAP
September 1, 2000

7TH BIENNIAL C. GORDON VAN ARMAN SCHOLARSHIP COMPETITION

The Inflammation Research Association will be sponsoring a competition at the 10th National Conference on September 24-28, 2000, in Hot Springs, VA, to encourage exploratory and applied research in inflammation among graduate students and postdoctoral fellows. Thirteen graduate students and first year post-doctoral fellows entered the sixth biennial competition for the C. Gordon Van Arman Awards at the 9th International Conference at Hershey, PA, on November 1-5, 1998.

The awards have been named to recognize the example of C. Gordon Van Arman who, during his long and distinguished research career as an industrial scientist, published over 100 scientific papers. The development of the drugs diphenoxylate, disopyramide, sulindac, and diflunisal can be directly attributed to his work. In 1970, Dr. Van Arman with Edward L. Takesue, Marvin E. Rosenthale and Mary Lee Graeme founded the Inflammation Research Association as an informal forum for bench scientists to exchange research ideas in inflammatory diseases. By establishing this award, we support our continuing commitment to high quality inflammation research in young scientists.

The Scholarship Committee selects the award winners based on a poster presentation to the committee (50%),



1998 Van Arman Scholarship Award winners (l to r) Nathalie Rioux, Paula Phipps, Tim Brazelton, Joyce van Meurs, and Stephen Getting (missing, Kurt Weiss)

a mini-paper (25%), and an oral presentation (25%). All finalists will be reimbursed for travel expenses, will be provided with room and board, and will have the opportunity to compete for prizes of \$1500 (1st), \$750 (2nd), \$500 (3rd), and \$300 (honorable mention). Awards are presented at the Conference Banquet.

The winners at the 9th International Conference were:

1st place:
Nathalie Rioux, Laval University, Laval, Canada

2nd place:
Stephen Getting, William Harvey Institute, London, UK

3rd place:
Kurt Weiss, University of Pittsburgh, Pittsburgh, PA

Honorable Mentions:
Timothy R. Brazelton, Stanford Medical School, Palo Alto, CA; Paula Phipps, St. Bart's and Royal London School of Medicine, London, UK; Joyce van Meurs, University Hospital Nijmegen, Nijmegen, The Netherlands

The Van Arman Award participants add a refreshing and scholarly dimension to the Conference and we look forward to future award competitions. Registration materials are available. For information please contact Dr. Richard Harris, the Chairperson for the Scholarship Committee.

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AMERSHAM PHARMACIA BIOTECH POSTER COMPETITION

The Most Therapeutic Potential

Amersham Pharmacia Biotech is sponsoring a competition with cash prizes for the three best posters at the IRA 10th National Conference.

The first poster competition was held at the 9th International Conference, where three representatives of the Inflammation Research Association Board formed the judging panel to select those posters describing work with "the most therapeutic potential." Cathy Phipp Howat of Amersham presented the monetary prizes at the closing banquet on November 4, 1998.

The first prize of \$1000 was presented to Y-J Hei, B.C. Beeler, S. Chen, J. Lupisella, J. Reczek and K.M. Tramposch from Bristol-Myers Squibb for their poster "Mouse Collagen-Induced Arthritis (CIA) Induces Over-Expression of Matrix Metalloproteinases (MMPs): Suppression by a Retinoic Acid Receptor Antagonist."

The second prize of \$500 was awarded to F. Nantel, D. Denis, A. Northey, R. Gordon, M. Cirino, K. Metters and C.C. Chan from Merck-Frosst for their poster presentation "Regulation of Prostaglandin-H Synthetase-2 (COX-2) in Carrageenan-Promoted Inflammation."



Winners of the poster competition at the 9th International Conference in Hershey, 1998

The third prize of \$250 was shared by two groups: M.R. Allen, L. Svensson, M. Roach, C.A. Gabel and J.D. McNeish from Pfizer for their poster "Evaluation of p38-a MAP Kinase-Deficient Embryonic Stem Cells"; and J.S. Mudgett, L. Guh-Siesel, N.A. Chartrain, L. Yang and M. Shen from Merck and UMDNJ for their poster "Targeted Inactivation of the p38 Gene Results in Midgestation Embryonic Lethality."

Amersham Pharmacia Biotech, which has a commitment to enabling molecular medicine, will continue to sponsor this competition at the 10th

National Conference. To participate in the competition, eligible contestants should return the abstract form included in the Registration Materials of the 10th National Conference. Abstracts accepted by the IRA for display as scientific posters at the meeting will be automatically entered into the competition.

The deadline for abstract submission is **April 1, 2000**. Three representatives of the IRA Board will form the judging panel, and will be selected and announced at the start of the 10th National Conference. They will award a 1st, 2nd, and 3rd prize to the posters which, in their opinion, describe work which has "the most therapeutic potential." The decision of the judges is final. The judges will announce three prizes at the Conference Banquet on September 27, 2000. Cash awards have been increased for 2000:

1st prize	\$1500
2nd prize	\$750
3rd prize	\$350

Prize winners will be awarded a certificate at the Banquet. To claim their award, prize winners must complete the form on the back of the certificate and fax/mail to Amersham Pharmacia Biotech at the address indicated on the form.

INFLAMMATORY BOWEL DISEASE, MOLECULAR MECHANISMS AND POTENTIAL THERAPEUTICS

Thursday, October 14, 1999

New York, New York

The second IRA meeting of the academic year, held at the New York Academy of Sciences, was organized by Amy Roshak of SmithKline Beecham and Sreekant Murthy of Hahnemann University. Amy Roshak introduced the program with a brief outline of significant advances in the understanding of the etiopathology of human ulcerative colitis and Crohn's disease, collectively known as inflammatory bowel diseases (IBD). She noted that these advances have paved the way for novel critical therapeutic cytokine targets, which would be the focus of presentations.

The first speaker, **Gary R. Lichtenstein, M.D.** (University of Pennsylvania School of Medicine, Philadelphia), spoke on "Inflammatory Bowel Diseases-Clinical Perspectives and Therapeutic Options." He described many exciting recent research developments in understanding these idiopathic multifactorial diseases and how these developments have dramatically increased research and medications to treat IBD. He outlined the primary goals of medical therapy for IBD: inducing remission; improving quality of life, maintaining adequate nutritional status, suppressing inflammation in the intestine, and reducing the number of disease flare-ups (maintaining remission). The ideal medication would be effective, safe, simple to administer, affordable and tailored to each person's needs.

Dr. Lichtenstein described how aminosalicylates and its congeners have evolved and are maintaining remission of IBD. Corticosteroids (prednisone, methylprednisolone, hydrocortisone, etc.) are the mainstay for acute flare-ups; however, 20 to 30 percent of IBD patients will not respond to corticosteroids and some have steroid-dependent disease. It is difficult to taper off steroids without experiencing flare-ups. Steroids do not maintain remission in both forms of IBD, and long-term use of steroids results in significant side effects like osteoporosis. Strategies to reduce side effects include carefully tapering steroids using every-other-day dosing, and rectal application of rapidly metabolizable corticosteroids, like budesonide, which has not yet been approved by the FDA and is not available in the U.S.

In IBD, antibiotics are used as primary therapy and to treat infections. Metronidazole (Flagyl®) is used as a primary therapy for active Crohn's disease that affects the colon. It delays the recurrence of Crohn's for the first two to three years after ileal resection. In more than 50% of individuals, metronidazole can be very effective in managing perineal Crohn's. Ciprofloxacin (Cipro®) and clarithromycin (Biaxin®) are showing promising results in active Crohn's disease.

The use of immunosuppressant agents, such as azathioprine (Imuran®) and 6-mercaptopurine (6-MP, Purinethol®), has emerged as a tool in treating both active and inactive IBD. They block activation of the immune system and are considered appropriate for

those who do not respond to other treatments. Imuran and 6-MP have slow onset of action (three to six months for full effect); however, they reduce relapses in Crohn's patients in remission. The role of azathioprine and 6-MP in ulcerative colitis is emerging.

Cyclosporine A (Sandimmune®, Neoral®) at very high doses shows some efficacy in patients with active Crohn's disease who are on steroids. Cyclosporine has been more successful as a "bridge" therapy in treating severe ulcerative colitis, especially for those who face surgery despite high doses of intravenous steroids.

Methotrexate has been used to effectively treat rheumatoid arthritis and could reduce or eliminate steroid use while inducing remission in some Crohn's patients. However, methotrexate is not effective in ulcerative colitis.

In August 1998, the FDA approved Infliximab (Remicade), a chimeric (75 percent human, 25 percent mouse protein) monoclonal antibody which blocks the production of tumor necrosis factor-alpha (TNFα). In a short-term study, Infliximab, given as a single two-hour intravenous infusion to more than 100 steroid resistant Crohn's patients with moderate to severe disease, showed significant improvement in two-thirds of patients, while one-third achieved remission. A second study, that involved nearly 100 patients with fistulas (single or multiple), showed that in two-thirds of these patients, most of the fistulae closed, and, in more than half, all of the fistulae were closed after three infusions over a six-week period. Preliminary data suggest that the beneficial effect of Infliximab persists when the medication is reinfused every two months. The effectiveness and possible side effects of Infliximab following long-term use are unclear. Therefore, possibility of allergic reactions to repeated infusions, and even the appearance of malignancies, is being evaluated. Treatment should be reserved for patients who do not respond to conventional therapies.

Dr. Lichtenstein reported on two new medications under investigation for the treatment of IBD, Tacrolimus (FK506) and Mycophenolate mofetil. Tacrolimus has been used successfully to treat steroid refractory patients suffering from acute attacks of IBD. Mycophenolate mofetil, in combination with corticosteroids, has been shown to be effective for active Crohn's that has not responded to other therapies.

Antisense oligonucleotide, ISIS 2302, has shown some benefit in a small study of 20 Crohn's patients who were steroid-dependent. This agent targets intercellular adhesion molecule-1 (ICAM-1) by blocking its production. This therapy is currently under further analysis and investigation.

Other treatments involving cytokines are being assessed. Cytokine targets under study include interleukin-10 and interleukin-11 in people with active Crohn's disease. Similarly, trials will begin with

antibodies targeted against interleukin-12 in Crohn's patients who need steroids and are not responding to other forms of treatment.

Currently, the Bowman-Birk Protease Inhibitor is undergoing clinical trials in ulcerative colitis. This agent has been shown to prevent cancer in animals. Other agents that have been shown to afford some benefit include heparin, short-chain fatty acids, omega-3 fatty acids and nicotine patches.

Dr. Lichtenstein concluded that there is no standard regimen for managing all persons with IBD. The symptoms, course of disease, and prognosis vary considerably among people with IBD. Management depends upon an accurate diagnosis. This typically requires endoscopic, radiologic, and pathologic (analysis of tissues) observations. A successful treatment strategy employs not only the medical therapies discussed in this review, but careful attention to detail and use of common sense. Surgical consultants experienced in the management of IBD are vital to proper management. At the present time, surgical resection of the colon is the only cure for ulcerative colitis, although in the majority of Crohn's patients the disease recurs after resection.

Sreekant Murthy, Ph.D. (MCP Hahnemann University, Philadelphia) first discussed how difficult it is to produce an ideal model of IBD and outlined several criteria for selecting an animal model for preclinical trials. He then described the spontaneous, immunological, bacterial, chemical, transgenic and mutant models of experimental colitis, and outlined some of the advantages and disadvantages of using these animal models for preclinical trials. He then mapped out how a dextran sulfate model of mouse colitis histologically and immunohistologically resembles chronic human ulcerative colitis and human colitis-associated colon cancer, and listed various pharmacological classes of agents that have been tested in this model. He described the CD45TbhiCD4+ model and how that model has facilitated drug discovery, and also discussed several transgenic and gene knockout models such as HLA-B-27, beta-2 macroglobulin transgenic rats, IL-2, IL-10 and TCR knockout mice, and the lessons that can be learned from those models in terms of pathogenesis of disease. He cautioned that many animal models have the tendency to respond to anti-inflammatory therapy. Thus, investigators must be careful in interpreting the results by making sure that such results can be reproduced in a second model. He also emphasized that investigators must take extra precautions in making sure that the species, strains, substrains and uniformity in the mode of induction of disease is reproducible in their laboratory. Otherwise, these variables could adversely affect therapeutic outcome.

Scott Plevy, M.D. (Mount Sinai School of Medicine, New York) discussed the role played by TH1 and TH2

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cells in the pathogenesis of IBD, and how the imbalance in the distribution of these cells in the lamina propria contributes to disease process. He then proceeded to describe the regulated expression of IL-12 in antigen presenting cells and the prominent role that has been established for IL-12 in the pathogenesis of intracellular infections and chronic inflammatory disorders. The thrust of his presentation focused on host defense mechanisms triggered by microbial lipoproteins through Toll-like receptors (TLR). IL-12 plays a key role in the cell-mediated immunity against many infectious pathogens, but the mechanisms of this immunity still remain undefined. He presented evidence to demonstrate that a purified 19 lipoprotein isolated from *M. tuberculosis* induces IL-12 production by using the IL-12 p40 promoter. The induction of the IL-12 p40 promoter is dependent on C/EBP and NF- κ B sites and occurs through TLR2, since a TLR-2 dominant negative mutant can block it. Dr. Plevy briefly discussed the role that bacterial pathogens play in the etiology of IBD. He demonstrated involvement of MAP kinase pathways in the induction of IL-12 and IL-10 gene expression by bacterial products, and described how this work furthers our understanding of the role that IL-12 plays in the bacteria or bacterial byproducts-induced pathogenesis of IBD, thereby suggesting that IL-12 can be used as a therapeutic target to treat human IBD.

Gary Wu, M.D. (University of Pennsylvania School of Medicine, Philadelphia) spoke on "Inhibitors of NF- κ B as Novel Therapeutic Targets for the Treatment of Inflammatory Bowel Disease." Homo- and heterodimeric complexes of the NF- κ B/Rel family of transcription factors regulate many immune response genes such as IL-8, including NF- κ B 1 (p50), NF- κ B 2 (p52), RelA (p65), RelB, and c-Rel. Given the critical role that NF- κ B plays in the activation of many immune response genes, it is perhaps predictable that activation of this family of transcription factors is also observed in chronic intestinal inflammation associated with IBD. Multiple studies have now shown that NF- κ B is activated in intestinal inflammation. Nuclear extracts isolated from lamina propria biopsy specimens of patients with Crohn's disease show higher levels of p65, increased DNA binding activity, presence of activated NF- κ B in macrophages and epithelial cells in the inflamed mucosa of patients with IBD *in situ*. Importantly, *in vivo* studies with high-dose systemic and local steroid treatment led to the inhibition of NF- κ B activation in Crohn's disease that correlated with the clinical improvement of patients.

Thus, methods that either increase the expression of, or inhibit the degradation of I κ B proteins and mechanisms that inhibit the activation of NF- κ B would be very valuable in this regard. An antisense oligonucleotide for the p65 subunit of NF- κ B has been shown as a potent inhibitor of inflammatory cytokine gene expression in lamina propria macrophages *in vitro* and of gross intestinal inflammation in two rodent models of IBD *in vivo*.

The two drugs currently shown to be effective in the treatment of IBD in humans, sulfasalazine and the

related 5-aminosalicylic acids, have been shown to inhibit activation of NF- κ B. Sulfasalazine inhibited phosphorylation of I κ B- α through a mechanism yet to be defined. Dr. Wu showed that proteasome inhibitors, that prevent the proteolysis of phosphorylated I κ B- α , decrease both iNOS and VCAM-1 expression and attenuate the onset of chronic colitis in an animal model.

Finally, he discussed his most recent work in characterizing the ability of nuclear hormone receptors to act as anti-inflammatory agents. Peroxisome proliferator-activated receptor γ (PPAR γ) is a member of the nuclear hormone receptor superfamily whose ligands include several prostanoids, including 15-deoxy- Δ prostaglandin J₂ (15d-PGJ₂), polyunsaturated fatty acids, a variety of non-steroidal anti-inflammatory drugs (NSAIDS), and a new class of oral antidiabetic agents, the thiazolidinediones (TZDs). Heterodimerization of PPAR γ with the retinoid X receptor (RXR) in the presence of ligand leads to DNA-binding to a hexameric direct repeat and the subsequent activation of gene transcription. PPAR γ ligands are best characterized as regulators of adipocyte differentiation and glucose homeostasis.

Emerging evidence suggests that ligands for PPAR γ have potent anti-inflammatory activity in several cell types *in vitro* such as monocytes, macrophages, and neuronal cells. Dr. Wu's laboratory has shown that these ligands can also inhibit the activation of cytokine gene expression in intestinal epithelial cell lines consistent with the high level expression of the PPAR γ receptor in these cell lines and in the colonic epithelium. Most importantly, they have also shown that TZD ligands can dramatically reduce colonic inflammation in the DSS model of murine colitis. The highly significant anti-inflammatory effect observed *in vivo* provides the single best indication that PPAR γ ligands may have clinical efficacy in patients with IBD, a chronic debilitating disease that affects millions of people worldwide.

Kathy Myers (Isis Pharmaceuticals) closed the meeting with a presentation on the "Use of Antisense Oligonucleotides for the Treatment of Inflammatory Bowel Diseases." She first outlined the Isis antisense drug discovery process and the development of a new class of drugs based on antisense oligonucleotides. She also described Isis' programs to modify the properties of those oligo drug candidates using the most commonly used phosphorothioate and 2'-sugar modifications. She briefly described how once oligos bind the target mRNA, they can inhibit the expression of encoded protein by RNase H and translational arrest. She also focused on ISIS 2302, an antisense inhibitor of ICAM-1 that is undergoing a Phase II trial for Crohn's disease. She showed that in animal studies, Isis' ICAM-1 inhibitor demonstrated significant activity in murine models of cardiac allograft rejection, ulcerative colitis and endotoxin-induced lung inflammation. In Phase I studies, the drug was well tolerated in normal volunteers at all doses expected to have therapeutic activity. A well-controlled 20-patient Phase II trial of

ISIS 2302 in the treatment of Crohn's disease showed a statistically significant lowering of steroid requirements in ISIS 2302-treated patients. In addition, by the end of the one-month treatment period, ISIS 2302 produced disease remission (Crohn's Disease Activity Index <150) in 47% of patients treated with the drug. The mean duration of remission was prolonged; at the end of the 6-month trial five of the seven ISIS 2302-treated remitters were still in remission following a single course of treatment. In addition, at the end of six months, corticosteroid treatment was completely discontinued in 33% (5 of 15) of the ISIS 2302 treated patients and in no placebo patients. Based upon these favorable results, a 300 patient pivotal trial was initiated and recently completed enrollment.

Overall, the conference was well attended and the audience had ample time to interact with speakers.

- Sreekant Murthy
Hahnemann University

FIRST ANNOUNCEMENT

5th WORLD CONGRESS ON INFLAMMATION



Organized by the
British Inflammation Research Association (BIRAs)
under the auspices of the
International Association of Inflammation Societies (IAIS)

**Edinburgh, Scotland
22-26 September 2001**

KEY DATES

1 December 2000

Call for abstracts and preliminary program

1 May 2001

Deadline for abstract submission

1 June 2001

Deadline for advance registration and advance hotel booking



For information contact:

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PHARMACOGENETICS IN DRUG DISCOVERY AND DEVELOPMENT

Introduction

There is dramatic variation in the way individuals respond to drugs both in terms of efficacy and side effects. Among the most commonly prescribed drugs there is astonishing variability in response rates, with around 30% of patients deriving no therapeutic benefit. It is now realized that the overriding factors leading to this variability are genetic in origin. Genetic variation among individuals and between ethnic groups has a profound impact on how drugs are metabolized, while polymorphisms in drug targets (e.g., membrane receptors, ion channels, etc.) or other genes involved in the drug response pathway are critical in regulating drug responsiveness. This high frequency of non-responders is particularly worrying given the high incidence of adverse events associated with the use of prescription medications. In the U.S., around two million people are hospitalized per year as a result of adverse drug events (Lazarou et al, 1998). The overall incidence of serious adverse events of around 6.7% does not include common side effects, such as dizziness or nausea, that do not result in hospitalization but do lead to poor compliance. The inescapable conclusion from these data is that, under current treatment regimens, many patients are routinely exposed to the risk of serious adverse events without any potential benefit.

It is becoming clear that improvements in the knowledge of the molecular basis of both disease and drug responsiveness, coupled with high throughput genetic analysis will lead to a change in the way medicines are discovered and prescribed. This, in turn, will result in an improvement in risk/benefit and cost/benefit for commonly prescribed drugs of the future.

Genotyping for Polymorphic ADME Genes - Eliminating a Source of Risk

Pharmacogenetics has to-date largely focused on the importance of polymorphic ADME genes, particularly drug metabolizing enzymes, in regulating pharmacological responsiveness to drugs. The vast majority of drugs are metabolized by the cytochrome P450 oxidation system in the liver. The most important polymorphic drug metabolizing enzyme discovered to date is cytochrome P450 2D6 (CYP2D6), an enzyme involved in the metabolism of 25% of marketed drugs. Inheritance of two copies of a defective CYP2D6 gene leads to a poor metabolizer phenotype, a condition observed in 5 to 10% of Caucasians that leads to aberrant metabolism that has a clinical impact under a number of circumstances. CYP2D6 poor metabolizers are unable to activate certain prodrugs and cannot convert codeine to morphine or metabolize the antimalarial proguanil to cycloguanil. Malarial breakthrough has been shown to be a significant problem in these individuals. A more common problem

seen in CYP2D6 poor metabolizers is adverse events linked to aberrant metabolism. Drugs that target the cardiovascular system or CNS are commonly found to be CYP2D6 substrates. Both tricyclic antidepressants and selective serotonin reuptake inhibitors are metabolized extensively by CYP2D6, and variable metabolism can lead to side effects. Blurred vision, constipation and ECG changes have been observed in poor metabolizers taking nortryptiline, while Prozac levels accumulate dramatically in this subpopulation of patients. The anti-arrhythmic lidocaine can cause heart failure in CYP2D6 poor metabolizers.

Inheritance of multiple copies of the CYP2D6 gene leads to the ultra-fast metabolizer phenotype, seen in 1 to 6% of Caucasians, which is associated with lack of efficacy of drugs that are substrates for CYP2D6.

Other important polymorphic CYP enzymes include CYP2C19, which metabolizes compounds such as warfarin and omeprazole, and CYP2C9 which metabolizes NSAIDs.

Polymorphisms in Drug Targets and Pharmacological Responsiveness

It is now appreciated that polymorphisms in genes are common and have a significant impact on the function

of the gene product with clear implications for both disease susceptibility and drug responsiveness. A recent study that surveyed 106 cardiovascular and CNS candidate genes found, on average, five single nucleotide polymorphisms (SNPs) in the coding region of each gene, one of which is predicted to change the structure of the protein (Cargill et al, 1999). Other studies have confirmed that polymorphisms are more common than previously appreciated, and the consensus is that a SNP occurs at a reasonable frequency about every 350 base pairs. SNPs also occur in the promoter region of genes and can have a profound impact on the level of expression of the protein. A recent publication has illustrated how this type of polymorphism may have a significant impact on drug responsiveness in asthma (Drazen et al, 1999). In this study, clinical responses to a 5-lipoxygenase inhibitor (ABT-761) were stratified according to the number of tandem Sp1-binding repeats in the 5-lipoxygenase gene (ALOX5). Those patients expressing the mutant form of ALOX5 derived no therapeutic benefit from ABT-761. This mutant has been shown to reduce the level of gene expression in reporter assays, and so it is thought that these patients do not express significant pulmonary lipoxygenase activity. What this study shows is that a disease can be stratified by mechanism; in this case, a leukotriene-

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IVAN OTTERNESS, IRA PAST PRESIDENT, TO RETIRE FROM PFIZER



Ivan Otterness

Ivan Otterness, 5th IRA President (1984 to 1986), has announced his intention to retire from Pfizer on May 1, 2000, after more than 28 years in the inflammation group. He was involved in the development of the drugs piroxicam, CP-17,193, fenetilole, pirtianol, and tenidap, as well as other drugs currently in development, and has published more than 100 papers on topics related to drug discovery and mechanisms of arthritic disease. In recent years, he developed models of arthritis in the hamster, and has utilized this to study interaction of disease, therapy, physical activity and cartilage breakdown. More recent work has been on markers of OA and the potential for monitoring disease and the effects of drug treatment. To this end, he designed an assay of type II collagen degradation, which has shown potential for monitoring drug efficacy in humans.

Prior to Ivan's term of office, the IRA President was appointed by the previous President. During his tenure, Ivan established a governing board, instituted an annual meeting with elections of officers, established the position of secretary (Lian Liauw was the first secretary), wrote the first Bylaws, and incorporated the society as a non-profit organization. In 1988, Richard Carlson and Ivan established the first C. Gordon Van Arman Scholarship Competition and Awards. His first retirement activity will be to join former IAIS President Kay Brune at the University of Erlangen in Germany for several months of study.

We wish him a long, healthy and productive retirement!

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mediated form of asthma can be differentiated from a form where other pathways may play a dominant role in mediating pathology.

While the discovery of more genetic risk factors is essential for the pharmacogenetic positioning of drugs in the clinic, there are a number of preclinical examples of genetic diversity in drug targets leading to variability in pharmacological responsiveness. In fact, functional polymorphisms have been shown to occur in most classes of drug target. Over 50% of current drugs target G-protein coupled receptors and even a cursory perusal of the recent literature reveals a plethora of studies highlighting the impact of genetic diversity in this class of molecular target. Receptors where variants have been detected showing aberrant binding of endogenous ligand and/or synthetic agonist/antagonist include serotonin receptors, dopamine receptors, opioid receptors, chemokine receptors and β 2-adrenoceptors. Furthermore, the polymorphisms in β 2-adrenoceptors have a significant clinical impact. An Ile164Thr polymorphism in the transmembrane domain of the β 2-adrenoceptor leads to decreased adrenaline binding and is associated with poor outcome in patients with congestive heart failure (Liggett et al, 1998) while an Arg16Gly polymorphism near the N-terminus is associated with weak bronchodilator responses to albuterol (Lima et al, 1999).

Is Routine Genotyping in Clinical Practice on the Horizon?

It is increasingly being realized that stratifying patient populations for increased risk of complications prior to prescription of certain medicines or prior to certain surgical procedures will improve both risk/benefits and cost/benefits. Genotyping procedures that are available now and could deliver significant healthcare benefits include:

- Genotyping for CYP2D6 metabolic status prior to prescription of antidepressants (both tricyclics and SSRI's) and psychotropic agents.
- Genotyping for Factor V Leiden prior to prescription of oral contraceptives and HRT therapy to reduce risk of thromboembolic complications
- Genotyping for thiopurinemethyltransferase deficiency prior to prescription of azathioprine and other purines to prevent the risk of rare, but life-threatening, side effects
- Genotyping for Factor VIIQ353R to reduce risk of bleeding complications during surgery

Despite the value of applying such genotyping procedures to clinical practice, this message has not yet filtered through to general practitioners. The accessibility of genotyping services and the added cost of performing such procedures also hamper the diffusion of pharmacogenetics through clinical practice.

A dramatic reduction in the unit cost of SNP analysis combined with greater awareness among patient groups is likely to facilitate the more general utilization of pharmacogenetics. The main driver for its more general introduction is the increasing concern about the risk of adverse events linked to aberrant metabolism, which may be brought to a head by litigation or pre-emptive legislation.

Pharmacogenetics – The Way Forward in Drug Discovery

While the genetic stratification of a number of common diseases into subpopulations will inevitably occur in the long-term, there are a number of ways that pharmacogenetics can be applied to the drug discovery and development process that will add value in the near future. Knowledge of the genetic diversity in drug targets can be used to determine if one allelic form of the molecular target is a genetic risk factor for disease. This will validate this drug target and increase confidence that it is a central role in the pathogenesis of disease. This form of validation will allow prioritization of the plethora of molecular targets emerging from genomic databases and facilitate the selection of molecular targets most likely to be linked to a critical disease pathway. In order for the pharmaceutical industry to reduce the rate of attrition and associated costs in drug development, it is essential for them to select genetically validated targets, since 50% of drug candidates fail in Phase III, often due to lack of efficacy.

Since variants in drug targets often impact on pharmacological responsiveness, knowledge of their genetic diversity should condition drug candidate selection. Depending on the circumstances, it may be important to choose drug candidates that interact equally well with all the drug target allelic variants in the patient population to maximize efficacy response rates. Alternatively, if one allelic variant predisposes to disease, it may be desirable to design compounds selective for that allele to limit the risk of side effects. In any event, knowledge of the number and frequency of allelic variants in drug targets throughout the patient population allows the selection of higher quality drug candidates. This would represent a significant advance on the current practice of optimizing drug candidates on a cloned receptor which, by definition, represents only one of a number of variants and may not even be the most common form.

The application of pharmacogenetic technologies can also be of value when the drug candidates are advanced into clinical development. If there is a suspicion that the drug candidate is a substrate for a polymorphic drug metabolizing enzyme, Phase I studies could be carried out in individuals genetically deficient in that enzyme to determine the pharmacokinetic liabilities of that compound. Finding out pharmacokinetic problems early is much better than waiting for problems to



Roy Pettipher

emerge in late clinical trials or even after approval, when vast sums of money have been spent. In Phase II and III trials, placebo and different dose groups should be balanced to represent the frequencies of the allelic variants to avoid variable clinical responses and the selection of an inappropriate dosage. It is also important to collect DNA samples from Phase III trials so that patient populations can be stratified for the degree of therapeutic efficacy and/or incidence of adverse events based on variants in the drug target or disease-susceptibility genes.

Pharmacogenetics is at the early adopter stage of the technology diffusion curve, but is set to change how medicines are discovered and how they are prescribed. The most visionary pharmaceutical companies are beginning to apply pharmacogenetics. The very least that should be done is to collect DNA samples from Phase III trials to capitalize on the emerging knowledge of the genetic basis of disease.

- Roy Pettipher
Oxagen Ltd

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CANADIAN ARTHRITIS NETWORK: A NEW APPROACH

It's virtually a new approach to tackling the crippling battle of arthritis.

Thanks to a \$14.5-million grant from Canada's federal government, 120 leading Canadian scientists and clinicians from over 44 different institutions across Canada have teamed up to create the Canadian Arthritis Network. Together, they're working to improve the quality of life for people with arthritis.

"Our investigators are working on projects that extend from bench to bedside," says Dr. Tony Cruz, program director of the Canadian Arthritis Network. The virtual organization supports research projects, such as the development of new diagnostic and therapeutic technologies, while also providing new services in partnership with industry and government.

One of 15 federal Networks of Centres of Excellence, the Canadian Arthritis Network was created in 1998 and is currently the only disease-specific network. The organization funds arthritis research and provides services in patent development, commercialization and product development.

A significant milestone was achieved last fall when the Canadian Arthritis Network launched its Web site. "The Internet allows investigative teams to collaborate with each other despite any geographical distances and it has enabled us to develop a virtual training mentoring program," explains Dr. Tineke Meijers, the network's executive director and past recipient of a Gordon Van Arman Award from the Inflammation Research Association.

In addition to supporting its members, the Canadian Arthritis Network is working with the Canadian Arthritis Society to ensure people have information about the latest developments in arthritis research through the Internet. "Our Web site allows Canadians and people from around the world to log on and see what projects some of Canada's top researchers and



scientists are tackling in the battle against arthritis," says Meijers. People with arthritis can click-on to an electronic journal called "A-Plus" to keep them informed of current scientific advances.

Cheryl Koehn is chair of the Network's consumer advisory board, a committee made up of people with arthritis from a wide range of professional and leadership backgrounds. Koehn explains "the Web site allows for a new level of public transparency." In addition to using the Web to communicate with the public, Koehn emphasizes the consumer advisory board actively participates at the decision-making table with researchers, informing management about the perceptions, issues and priorities of the arthritis community.

The Network's Web site is also helpful for companies involved, or looking for ways to get involved, in arthritis research. Pharmaceutical and assistive device manufacturers can find high-tech services on the site, such as nation-wide clinical trials networks for testing new therapies.

To date, two biotech companies have been developed from technologies based at the Network and several other products are in the pipeline. "The commercialization potential for the Canadian Arthritis Network is enormous," says Dr. Robin Poole, associate program director for the Network and chief contributor to one of the Network's first products, diagnostic assays to detect proteoglycan and collagen cleavage in human articular cartilage.

For more information about the Canadian Arthritis Network's comprehensive services in clinical trials, disease management, genetics, animal models, screening systems, information transfer and personnel training, visit www.arthritis.ca, an umbrella page for Canadian arthritis-related organizations.

- Christina Marshall
Canadian Arthritis Network

cont'd from page 6 SECOND IRA WEST COAST SYMPOSIUM: GENE REGULATION IN INFLAMMATION AND BONE EROSION

decreases with increasing Smad2 phosphorylation. Concomitant with the decrease in Smad2/SARA association is an increase in the formation of Smad2/Smad4 complexes and their nuclear localization. As such, SARA may scaffold Smad2 with the TGF- β receptor. Dr. Wrana also discussed Smurf1, a new member of the Hect family of E3 ubiquitin ligases. Smurf1 mediates the degradation of Smad1, a Smad involved in the transmission of BMP (bone morphogenic protein, a TGF- β family member) signals. As such, Smurf1 antagonizes BMP signaling in Xenopus.

The second West Coast symposium was highly

successful, thanks to the top-notch speakers, interested participants, the Inflammation Research Association and our corporate sponsors, Signal Pharmaceuticals, SmithKline Beecham Pharmaceuticals, Pfizer Central Research, Roche Biosciences, Merck Research Laboratories, and Inflazyme Pharmaceuticals Ltd. We hope to see everyone again at the next West Coast meeting.

- Marie Chabot-Fletcher
SmithKline Beecham

Company News People on the Move

Neil Ackerman, President of the IRA from 1990-1992, is currently Senior Vice President, R&D and Scientific Affairs, for Cygnus, Inc. He has been working on a non-invasive glucose monitoring device for patients with diabetes. On December 6, 1999, an FDA Advisory Panel unanimously recommended approval of this device.

Marcia Bliven, IRA Board member, *Newsletter* editor, and past Secretary, will retire on May 1, 2000, after more than 36 years with Pfizer. For 24 of those years, she and Ivan Otterness have collaborated on work with drugs for rheumatoid and osteoarthritis. Since 1984, Marcia has helped organize the IRA International Conferences and, since 1992, has edited the *IRA Newsletter*.

Kay Brune, a past President of the European Inflammation Society (EIS) and the International Association of Inflammation Societies (IAIS), reports the completion of a new institute building at the University of Erlangen in Germany. The new facility is well equipped to support molecular pharmacology and gene manipulation, and has such scientific amenities as photon laser scanning microscopes and animal nuclear magnetic resonance tomography. Prof. Brune notes the promotions of members of his department. **Dr. Gerd Geisslinger** has become Chairman of the Department of Clinical Pharmacology at the University of Frankfurt, and **Dr. Swandulla** has become Chairman of the Department of Molecular Physiology at the University of Bonn.

On December 1, 1999, **Chris Evans** moved from the University of Pittsburgh to Harvard Medical School to take up an endowed chair in the Department of Orthopedic Surgery, where he is establishing a Center for Molecular Orthopedics. This group will focus predominately, but not exclusively, on developing gene treatments for arthritis and related rheumatic and orthopedic conditions.

Sergio Ferreira has been named as the first President of the newly formed Brazilian Society of Inflammation (SBIN). Sergio has been active in IAIS activities for several years. The IRA welcomes this new society as they join their sister societies from around the world in IAIS membership!

Congratulations to **Leo Joosten**, a long-time member of Wim van den Berg's group in Nijmegen, The Netherlands, who was recently awarded his Ph.D. for his work "Targeting of Cytokines in Experimental Arthritis." Leo has supported the IRA for many years with his attendance and participation at the biennial International Conferences. We look forward to raising a toast to him at the 10th National Conference in Hot Springs! Other members of Wim's lab who were recently awarded their doctorates were **Reinout Stoop**, who is a postdoctoral fellow with Kati Mikecz at Rush-Presbyterian and St. Luke Medical Center in Chicago, and **Erik Lubberts**, who (along with Leo) will remain in Wim's lab as a postdoctoral fellow.

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Company News / People on the Move

Alan Main, IRA past Vice President, has left Novartis to become President and CEO of Coelacanth Corporation in the Princeton, NJ area. They use high performance chemistry to generate very novel compound sets for screening by major pharmaceutical and biotech companies. The compounds are made in 50-100 mg amounts using very scalable solution chemistry, meet the Lipinsky "Rule of Five" and are all 100% QC'd for purity. Alan can be reached at 609-448-8200, x2021 or by email at <alan_main@coelacorp.com>.

Ivan Otterness, President of the IRA from 1986-88, has announced his intention to retire from Pfizer on May 1, 2000, after more than 28 years of service (see article on p. 11). As his first retirement project, he will be joining Kay Brune in Erlangen, Germany, for a four month period of research and writing. After May 1, Ivan's friends and colleagues can find him at <otterx@earthlink.net>.

The inaugural meeting of the **Hungarian Inflammation Society** will take place on May 14-15, 2000. **Mike Parnham** (Pliva), representing the IAIS, will deliver a presentation on the goals and aims of the international organization and will welcome the new society into IAIS membership.

Roy Pettipher, previously a research scientist in the inflammation group at Pfizer in Groton, has returned to the U.K. to pursue a new career as Director of Business Development for Oxagen. Oxagen is the UK's leading genomics company which is harnessing the power of family genetics to discover the genetic basis of common diseases, including coronary artery disease (partnered with AstraZeneca), women's health and chronic inflammatory disease. Understanding the genetic basis of these diseases is leading to the identification of novel genetically validated drug targets and diagnostic markers that will form the essential basis for future pharmacogenetic studies. Oxagen's inflammation group has ongoing programs in asthma, inflammatory bowel disease, psoriasis and autoimmune thyroid disease.

IRA Officers:

President	Lisa Marshall
Vice-President	Richard Dyer
Secretary	Stephen Stimpson
Treasurer	Dennis Roland

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For further information:

<http://www.inflammationresearch.org>

MEETING ANNOUNCEMENTS

March 16, 2000

IRA "Chemokine Function and Role in Disease"

Contact: Richard Dyer – Email: richard.dyer@wl.com

New York, NY

April 12, 2000

BIRAs "Apoptosis in Inflammation"

Contact: Dr. Dean Willis – Tel: 0171 419 3755 – email: dean.willis@ucl.ac.uk

London, UK

April 27-29, 2000

3rd Symposium of the International Cartilage Repair Society (ICRS) "Cartilage and Cartilage Repair in the New Millennium"

Contact: ICRS Secretariat – Fax: +41 31 934 10 16 – Website: www.cartilage.org

Gothenburg, Sweden

May 3-6, 2000

International Congress: "Advances in Immunology and Allergy on the Threshold of the XXI Century"

Contact: Congress Secretariat – Tel: (+7 095) 336-5000, (+7 095) 429-9620

Fax: (+7 095) 336-5000 – Email: immuneh@ibch.siobc.ras.ru

Eilat, Israel

May 18, 2000

IRA "Tissue Repair and Remodelling in Arthritis" and Annual Business Meeting

Contact: Richard Dyer – Email: richard.dyer@wl.com

New York, NY

May 25-26, 2000

IRA "Chemokines – Recent Discoveries and New Understandings"

Contact: Richard Dyer – Email: richard.dyer@wl.com

Boston, MA

June 4-8, 2000

11th International Conference "Advances in Prostaglandin and Leukotriene Research: Basic Science and New Clinical Applications"

Contact: Scientific Organizing Secretariat Fondazione Giovanni Lorenzini

Tel: +39 02 29006267 – Fax: +39 02 29007018 – Email: lorenzfo@icil64.cilea.it

Florence, Italy

July 15-20, 2000

VII World Conference on Clinical Pharmacology and Therapeutics of IUPHAR–Division of Clinical Pharmacology and 4th Congress of the European Association for Clinical Pharmacology and Therapeutics

Contact: CPT 2000 – Tel: +39-045581111 – Email: gpvelo@farma.univr.it

Florence, Italy

August 5-10, 2000

FASEB Summer Research Conference on Cytokines and Lipid Mediators

Contact: FASEB Summer Research Conferences – 9650 Rockville Pike, Bethesda, MD 20814-3998

Fax: 301-571-0650 – Email: ahewitt@faseb.org – Website: www.faseb/meetings/src

Saxtons River, VT

August 24-27, 2000

6th Conference of the International Endotoxin Society

Contact: Jean-Marc Cavaillon – 28 rue Dr Roux – 75015 Paris, France

Tel: 33 1 45 68 82 38 - Fax: 33 1 40 61 31 60 – Email: jmcavail@pasteur.fr

Website: www.pasteur.fr/recherche/unites/ies2000/

Paris, France

September 10-13, 2000

International Conference on Inflammopharmacology

Contact: Prof. K.D. Rainsford – Fax: (44) 114 225-2020 – email: k.d.rainsford@shu.ac.uk

website: www.shu.ac.uk/schools/sci/biomed/INFLAM2000.html

Sheffield, UK

September 24-28, 2000

IRA 10th National Conference

"The Changing Face of Inflammation: Strategies for the New Millennium"

Contact: Registrar Joan Chapdelaine – Fax: 570-585-2383 – Email: joan.chapdelaine@pils.com

Hot Springs, VA

October 3-6, 2000

Lovelace Research Institute "Susceptibility Factors for Respiratory Diseases"

Contact: Alice M. Hannon – Lovelace Respiratory Research Institute – P.O. Box 5890 – Albuquerque, NM

87185 – Tel: 505-845-1124 – Fax: 505-845-1193 – Email: ahannon@LRRI.org

Website: www.lovelace-symposium.org

Santa Fe, NM

October 4-7, 2000

OARSI Fifth World Congress on Osteoarthritis "Treatment of Osteoarthritis: Basic and Clinical Research in the New Millennium"

Contact: OARSI – Email: oarsi@dc.sba.com – Website: www.oarsi.org

Barcelona, Spain

September 22-26, 2001

IAIS 5th World Congress on Inflammation

Contact: Triangle 3 – Triangle House – Broomhill Road – London SW18 4HX

Tel: +44-181-875-2400 – Fax: +44-181-875-2421 – Email: triangle3@immunology.org

Edinburgh, Scotland