newsletter

Inflammation Research Association

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President's Welcome

Dear Colleagues,

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Thank you for your interest in and for being part of the Inflammation Research Association (IRA). This non-profit organization was founded over 40 years ago to "bring together scientists of all degree and experience levels" who are interested in inflammation research and promote open scientific discussion of novel therapeutics and the treatment of inflammatory disease. The IRA includes members from academia, industry and the clinic and unlike most professional organizations, it is an all-volunteer membership and depends entirely on its members to accomplish its goals. Your Officers and Board members are committed to ensuring the continuation of the IRA's mission and success and to improving the efficiency of the IRA as an organization.

That said, these are tough times. Just in the last few years, we've witnessed significant industry-wide layoffs due to pharma mergers or approaching patent cliffs. Recession and government budgetary woes have resulted in significant cuts to funding that supports academic and clinical research. Researchers all over, whether in industry or academia are being asked to do more than ever before, impacting an organization like ours where we depend on volunteers.

For decades, the IRA has sponsored a very successful biennial International Conference as well as one or more yearly regional meetings. To continue this, it is critically important that we attract new members who are willing and able to participate in our organization. This could range from participating in planning the scientific program for the International Conference, to chairing a sub-committee, writing a meeting report, organizing a regional meeting, serving as an Officer or Board member, etc.

So my challenge to you is this. Go out and recruit two new members. If we all did that, we would triple the size of our membership, bringing new vigor and fresh ideas to our organization. It doesn't sound hard, and shouldn't be. Surely, each of us knows at least two colleagues who would be interested in joining the IRA. And since membership in the IRA is free, who can resist? Just direct them to the New Member registration page at our website (www.inflammationresearch.org) Also let them know that through our

Web site, members can access our membership list to contact other inflammation scientists, receive up-to-date information on upcoming IRA-sanctioned meetings and events, examine abstracts and reports from past meetings and link to other inflammation sites of interest. New tools to facilitate careers and opportunities for our members are planned for the web-site, as is an historical section on the IRA and the C. Gordon Van Arman Award.

Two news items that I would like to highlight in closing. First, new Officers and Board members of the IRA were installed at last year's 16th International Conference of the IRA held in Chantilly, VA. They include Andy Glasebrook (President), Arpita Maiti (Vice-President), Joel Tocker (Treasurer), and Lisa Schopf (Secretary), and new Board of Director members Annalisa D'Andrea, Larry de Garavilla, Matteo Levisetti, Karl Nocka, Chris Stevenson, and William Westlin.

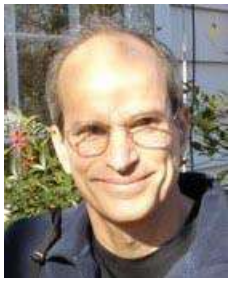
Second, the IRA is in negotiations to return to The Sagamore for the 2012 International Conference! We heard from many IRA members that they yearned to return to the site of many memorable conferences and a consistent message was that the last three International Conferences at Cambridge and Chantilly were missing something special that we had at The Sagamore. More details to follow but we are excited to be returning to The Sagamore and are busily preparing for a return with an exciting scientific program chaired by our Vice-President Arpita Maiti.

That's all for now. Please contact any Officer or Board member to volunteer. You are always welcome to participate in our monthly Board meeting teleconferences. If interested, please visit the website for information or drop a line to our Secretary for details on how you can participate.

And please accept my personal challenge to each of you. If we all follow through, it will have a huge impact on our organization.

Sincerely yours,

Andy Glasebrook
President
Inflammation Research Association



OFFICERS AND DIRECTORS FOR THE 2010-2012 TERM OF THE IRA

Officers

President	Andrew Glasebrook, Ph.D. Eli Lilly & Co. president@inflammationresearch.org
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	Larry deGaravilla, Ph.D. Johnson & Johnson
	Matteo Levinsetti, Ph.D. Merck
	Liwu Li, Ph.D. Virginia Polytechnic Institute
	Karl Nocka, Ph.D. Pfizer, Inc.
	Caralee Schaffer, Ph.D. InterMune, Inc.
	Chris Stevenson, Ph.D. Hoffman-La Roche
	William Westin, Ph.D. Avila Therapeutics
Past President	John E. Somerville, Ph.D. Bristol-Myers Squibb

Have I got a great product to sell you!

By John Somerville, Past President

I can't believe that I volunteered to write a piece for the IRA Newsletter on Fundraising! What was I thinking? First of all I find fundraising to be both complicated and nerve wracking. Timing is important, as is how you approach a person or company, and how do you ever know how much to ask for? It's just like when you are at a Pawn shop and the owner asks how much you want for your item and you really do not have a clue where to start. You want all that you can get for it but are afraid you will alienate the other person to the point that they will not give you anything (yes, I watch too much cable). I'm not good at bartering for cars either!

For me, the key to fundraising is that I am representing something worthwhile. I believe in the IRA and what it does as an organization, so this approach works for me. Since the IRA was formed as a non-profit organization in 1970 it has provided over 40 years of scientific conference organization and networking. Could it be that at an earlier IRA conference an idea was spawned that has led to a current drug that is now improving or even saving lives? Knowing the breadth of our membership and the quality of our scientists, I would say that this is highly probable! So yes, absolutely, undoubtedly, for sure, the IRA does provide a valued service to science and the progress of drug discovery.

In the past, not even a decade ago, raising support for our conferences involved mostly phone calls to our members at each of the major pharmaceutical companies and asking them for a donation. Many could easily commit to $5-20,000, even out of their own departmental budgets. They knew the product was an excellent conference with unmatched social and scientific interactions. Many of the earlier IRA conferences were 100% funded by "big" pharma companies. However in the last few years the pharma environment has changed dramatically. Budgets are much tighter, companies are preparing for patent losses, people are being let go to cut costs, and those that are left are being re-organized as the industry tries to find the path back to a strong, cost efficient, productive pipeline. In this environment the IRA can no longer request and receive support in the same way it has in the past. Many biopharma companies now have grant submission processes, even for just a few thousand dollars. In many cases funds are just not available. In 2010 just 38% of our conference support came from "big" pharma companies. We have had to turn to other partners in our drive to new medicines: the contract research companies and our suppliers. Fortunately, our industry still spends billions of dollars on R&D and at the IRA conferences our attendance is well represented by industry scientists that still have significant capital and operational budgets. Our colleagues at the CROs and suppliers understand this value. Conference income generally comes in just a few forms: donations, registration fees, and exhibitor fees. If you have attended any scientific conference in the past few years, not just IRA sponsored events, you surely have noticed that attendance is down. Lower numbers of registrants means that funding from other sources is absolutely critical to cover costs. We encourage attendance at the IRA event if at all possible from the folks we are contacting. Please keep this in mind when you are planning your schedule for future scientific meetings and please choose the IRA.

The IRA has had a very productive and fortunate past decade. From the success of the 2003 World Congress in Vancouver, BC, through strong attendance and fundraising efforts at all of our subsequent IRA events, we have managed to stretch our treasury and sustain our mission. However, the IRA now supports a website and contracts for accounting services, two critical functions we must utilize as an organization. Thus we have indirect costs in support of our mission that still need to be covered and represent a constant depletion on our treasury. Fundraising for our organization is as important as ever for our continued existence and growth. So please, when a volunteer fundraising committee member comes knocking on your door, please do whatever you can to help them and help the IRA to fulfill its mission. If you cannot help directly, please try to direct us to the person that we should be contacting. We have found that many companies are willing to provide support, but finding that critical contact has often been the most difficult part.

Finally I will put in one last pitch. In this case it is for individual contributions. As you know, the IRA does not charge a membership fee. So, if you value what the IRA does and think it is a worthwhile organization, I encourage you to consider a personal contribution. Many companies have foundations that will provide matching funds to organizations like the IRA that have a 501c3 designation. Often this is a simple process and it can maximize the value of your contribution. Look for a new link on the web site that will provide information if you are interested. Keep in mind that funds can be designated for specific purposes (e.g. women in science, Van Arman, young investigators, etc.), or for general use by the organization as the board directs.

International Meeting Announcements

Nov 3-8, 2011, Boston	ACAAI: American Collagen of Allergy, Asthma & Immunology 2011 Scientific Meeting	www.acaai.org
Nov 5-9, 2011, Chicago	American College of Rheumatology, 75th International Meeting	www.rheumatology.org
Nov 13-16, 2011, Goa	IOIS: 11th Biannual Congress of the International Ocular Inflammation Society	www.iois.memberlodge.org
Jan 8-13, 2012, Breckenridge	Chemokines and Leukocyte Trafficking in Homeostasis & Inflammation	www.keystonesymposia.org
Jan 15-20, 2012, Santa Fe	Fungal Pathogens: From Basic Biology to Drug Discovery	www.keystonesymposia.org
Jan 19-23, 2012, Santa Fe	Rheumatoid Arthritis: Molecular and Clinical insights	www.keystonesymposia.org
Jan 22-27, 2012, Tahoe City	Membranes in Motion: From Molecules to Disease	www.keystonesymposia.org
Jan 29-Feb 3, 2012, Sante Fe	Genetic & Molecular Basis of Obesity & Body Weight Regulation	www.keystonesymposia.org
Feb 5-10, 2012, Keystone	The Biology of Cytokines	www.keystonesymposia.org
Feb 5-10, 2012 Ventura	Oxygen Radicals	www.grc.org
Feb 12-17, 2012, Banff	Advances in Hypoxic Signaling: From Bench to Bedside	www.keystonesymposia.org
Mar 4-9, 2012, Keystone	Innate Immunity: Sensing the Microbes and Damage Signals	www.keystonesymposia.org
Mar 4-9, 2012, Keystone	The Microbiome	www.keystonesymposia.org
Mar 4-9, 2012, Ventura	Molecular Mechanisms in Lymphatic Function & Disease	www.grc.org
Mar 11-16, 2012, Ventura	Autophagy in Stress, Development & Disease	www.grc.org
Mar 18-22, 2012, Boston	Mutations, Malignancy & Memory - Antibodies & Immunity	www.keystonesymposia.org
Mar 18-23, 2012, Whistler	NF-kappaB Signaling & Biology: From Bench to Bedside	www.keystonesymposia.org
Mar 21-26, 2012, Keystone	HIV Vaccines	www.keystonesymposia.org
Mar 25-30, 2012, Big Sky	Molecular Basis of Vascular Inflammation & Atherosclerosis	www.keystonesymposia.org
Apr 15-20, 2012, Whistler	Nuclear Receptor Matrix: Reloaded	www.keystonesymposia.org
May 20-25, 2012, Dublin	The Role of Inflammation during Carcinogenesis	www.keystonesymposia.org
May 26-27, 2012, Lucca	Chemotactic Cytokines	www.grc.org
June 6-9, 2012, Berlin	EULAR: European League against Rheumatism Congress 2012	www.eular.org
June 17-22, 2012, Lucca	Proteolysis	www.grc.org
July 8-13, 2012, Andover	Proteoglycans	www.grc.org
July 15-20, 2012, Davidson	Transglutaminases in Human Disease Processes	www.grc.org
Aug 27-31, 2012, Milan	IASP: International Association for the Study of Pain 14th World Congress on Pain	www.iasp-pain.com/milan
Sept 9-13, 2012, Lake George	17th International Congress of the Inflammation Research Association (IRA)	www.inflammationresearch.org
Oct 28-30, 2012, Maui	2012 45th Annual Meeting of the Society for Leukocyte Biology Inflammation in Innate & Adaptive Immune Mechanisms	www.leukocytebiology.org
Aug 18-23, 2013, Rome	15th International Congress of Immunology	www.ici2013.org
Sept 21-25, 2013, Natal	11th World Congress on Inflammation (IAIS)	www.inflammationsocieties.org
2015, Boston	12th World Congress on Inflammation (IAIS-IRA)	www.inflammationsocieties.org

Focused Topic Meetings

The Inflammation Research Association encourages regional half to one and one-half day Scientific Meetings to promote information sharing between scientists interested in different topics of inflammation. A few years ago, most of these meetings were half-day sessions at the New York Academy of Sciences. We now enjoy full-day meetings at sites around the country.

Do you have an idea for a relevant topic? Contact Arpita Maiti (Arpita_Maiti@vrtx.com) with your ideas for topics, presentations and relevant speakers, and see www.inflammationresearch.org/meet-howto.html for suggestions and guidelines on initiating a Regional or Focused Topic Meeting.

Pulmonary Research Group Symposium

Philadelphia, PA, June 3, 2011

The IRA again joined forces with the Pulmonary Research Group (PRG) and sponsored a one-day symposium entitled "The Role of the Epithelium in Chronic Inflammatory Lung Disease". Larry de Garavilla (Johnson & Johnson), President of the PRG, and Paul Dudas (Johnson & Johnson) organized the Spring 2011 Symposium that was hosted by Temple University at the medical school campus in Philadelphia, Pennsylvania. About 70 people from both industrial and academic institutions attended with presentations highlighting the integral role of the pulmonary epithelium in modulating both normal airway function and disease pathogenesis and what aspects of epithelial dysfunction might be targeted for therapeutic benefit in inflammatory lung disease.

Barry Stripp, Duke University Medical Center, discussed the role of epithelial progenitor cells in normal maintenance and repair and pathological remodeling of lung tissue. Normal tissue maintenance and repair is accomplished through the actions of abundant, widely distributed pools of distinct, region-specific epithelial progenitor cells rather than through a multipotent lung stem cell. These pools of progenitors respond to microenvironmental cues and utilize intrinsic factors to maintain regional specificity. Utilizing in vivo lineage tracing and cell fractionation, regionally distinct progenitors were isolated and examined in 3-D organotypic culture. Colony forming efficiency and clonogenic potential of the airway progenitors were shown to be regulated by Sox2, TGF-β and canonical Wnt signaling.

Mark Inman, McMaster University, discussed how impairment of epithelial barrier integrity contributes to airway hyperresponsiveness. Impaired epithelial barrier function has been detected in asthmatic patients and implicated as a driver of hypersensitivity. In a model of non-specific impairment of airway barrier function by instillation of cationic proteins, there is greater sensitivity to inhaled vs. systemically delivered smooth muscle agonists. Epithelial barrier function was also examined in allergen driven mouse models of asthma where chronic allergen exposure induced barrier impairment and was independent of eosinophilic degranulation. In a transgenic model promoting eosinophilic degranulation there was increased impairment and heightened hypersensitivity suggesting that impaired barrier integrity may be a critical pathological component in human asthma with pronounced eosinophilia.

Kwang Chul Kim, Temple University School of Medicine, discussed the role of MUC1 during airway infection. MUC1 is a transmembrane protein shown to be upregulated following bacterial and viral infection. With infection, TLR activation stimulates TNF-α and IL-8 which induce MUC1 expression on epithelium and macrophages and neutrophil influx, respectively. Neutrophil elastase also further enhances MUC1 expression. In an in vivo model of P. aeruginosa infection MUC1 is upregulated through the course of infection and shown to be critical for clearance of infiltrating inflammatory cells from the lung and dampening of the chronic inflammatory response. The mechanism through which MUC1 may modulate anti-inflammatory activity is through negative regulation of TLR signaling, downregulating TNF-α-mediated inflammatory activity. This may be an important mechanism for suppressing a prolonged inflammatory response.

Darryl Knight, University of British Columbia, who served as conference scientific advisor, discussed how the inherent immaturity of asthmatic epithelium may translate to greater fragility of the epithelium and ultimately render it an ineffective barrier. The asthmatic epithelium has an abnormal genomic signature with associated structural and functional abnormalities. Structurally, the asthmatic epithelium has reduced expres-

sion of junctional proteins and ciliated cells and functionally possesses greater proliferative capacity, however, cannot effectively repair wounds. Together, these characteristics indicate an "immature", less-differentiated epithelial phenotype that might permit allergen penetration and ultimately result in inflammation and remodeling. There is evidence that dysregulation of the transcription factors β-catenin and p63 and epigenomic differences, including histone modifications and differential methylation, contribute to the altered phenotype.

Ken Adler, North Carolina State University, discussed the mechanism of MARCKS protein regulation of epithelial mucin secretion and the development of BIO-11006 (a MARCKS inhibitor) for the treatment of COPD. Membrane-associated MARCKS protein is activated via PKC and translocates to the cytoplasm where it interacts with HSP70 targeting it to the mucin-containing secretory module. MARCKS next interacts with the actin/myosin contractile system to move the complex to the membrane for exocytosis of the mucin containing granules. The MANS peptide, corresponding to the N-terminal region of MARCKS, inhibits mucin secretion in vitro and in vivo and modulates anti-inflammatory activity through inhibition of neutrophil, lymphocyte, eosinophil and macrophage degranulation and inhibition of neutrophil migration. BIO-11006, a MANS peptide analog has progressed through Phase2a in COPD patients with a demonstrated decrease in mucus production and increase in lung function.

Teal Hallstrand, University of Washington, discussed epithelial modulation of eicosanoid synthesis. In patients with exercise-induced bronchoconstriction (EIB) there is aberrant synthesis of eicosanoids such as leukotrienes resulting in activation of airway sensory nerves and bronchoconstriction. Epithelial-derived secreted phospholipase A2 (sPLA2) is elevated in asthma/EIB patients and correlates with a number of inflammatory markers. Utilizing genome-wide expression profiling of asthma subjects with and without EIB, a novel mediator, transglutaminase 2 (TGM2) was found to be elevated in the EIB population and abundantly expressed by the airway epithelium. TGM2 increases sPLA2 enzymatic activity which then potently upregulates eosinophil leukotriene synthesis. sPLA2 and TGM2 therefore may be novel targets for modulating bronchoconstriction and associated airway hyperresponsiveness.

Steven Kelsen, Temple University School of Medicine, discussed the epithelial unfolded protein response (UPR) and how this may play a protective role in response to cigarette smoke. Oxidative stress impacts the ability of the ER to properly modify proteins to obtain their correct structural configuration. Cigarette smoke extract has been demonstrated to increase reactive oxygen species in airway epithelial cells and elicit an UPR, which functions to reduce ER protein uptake, augment protein folding, and promote export of misfolded proteins. It has been shown that the UPR is activated in the human lung by cigarette smoking, evidenced by an upregulation of ER chaperones GRP78 and calreticulin, and foldase PDI. In vitro studies have shown the PERK pathway to be an integral ER sensor detecting misfolded proteins and augmenting the expression of transcription factors Nrf2 and ATF4 which regulate genes involved in protection of the lung from oxidant injury. Interestingly, a UPR was not detectable in COPD lung.

Matthew Poynter, University of Vermont, discussed the role of NF-kB in the development of allergic asthma. NF-kB has been implicated as a critical modulator of inflammation in lung disease and airway epithelial NF-kB activation has been observed in asthmatic patients. Utilizing a mouse model expressing epithelial-specific constitutively active inhibitor of NF-kB (IkB) kinase b (CAIKKb), the role of NF-kB was examined in allergic sensitization. Airway epithelial NF-kB activation in combination with OVA antigen challenge promoted allergic sensitization demonstrated by enhanced methacholine sensitivity, immune cell influx, mucus hypersecretion, serum IgE and T-cell cytokines above that of wild-type controls. Additionally, NF-kB promoted sensitization to an antigen to which tolerance had previously been established via inhalation, allowing for induction of an allergic inflammatory response. Epithelial serum amyloid A is upregulated with NF-kB activation and is a critical intermediate in inducing the downstream inflammatory events via TLR activation and engagement of the Nlrp3 inflammasome.

The fall 2011 PRG Symposium will focus on Obesity as a Modifier of Immunity and Inflammation in the lung. The symposium is scheduled for October 21, 2011 and will be hosted by the University of Vermont at the Trapp Family Lodge in Stowe, Vermont. Benjamin Suratt , Anne Dixon, and Lennart Lundblad of the University of Vermont are the organizers. For more information and to register go to www.pulmonaryresearch.org.

- Paul Dudas and Larry de Garavilla

16th International Conference of the Inflammation Research Association

Chantilly, VA, September 26-29, 2010.

Nearly 200 registrants convened at The Westfields Marriott for the 2010 International Conference. A full program of 18 oral presentations, two Mini-Symposia, four industry sponsored Lunch & Learn sessions and 130 poster presentations promised that this conference would once again provide an excellent overview of current developments in the field of inflammation research.

Sunday, Day 1, began with a focus on the role inflammation plays in metabolic diseases. Weather related flight cancellations prevented some speakers from arriving at the venue and threatened the scheduled program. However, the remaining speakers rose to the occasion and provided a stimulating discussion of adipokines and myokines: cytokine-like molecules released from adipose tissue and skeletal muscle, and their role in metabolism and energy balance.

Kenneth Walsh (Whitaker Cardiovascular Institute, Boston University) described the crosstalk between adipose tissue derived adipokines and immune cells. Adiposity is associated with a chronic inflammatory state resulting from the increased production of pro-inflammatory cytokines and adipokines, and an associated reduction in protective adipokines. Two protective adipokines were described, adiponectin (APN) and secreted frizzled-related protein (Sfrp) 5. Using APN and Srfp5 KO and transgenic mice, a reciprocal feedback loop between adiposity, APN and cytokine production was identified. As BMI increases, adipose tissue crown macrophage numbers increase, proinflammatory cytokines increase and these in turn inhibit APN production. Conversely, increased APN production suppresses pro-inflammatory cytokine production. A modest increase in APN is protective in the leptin deficient ob/ob mouse. Ob/ob-APN-Tg mice continue to be massively obese but are metabolically normal and lack crown macrophages, suggesting that APN plays a role in regulating macrophage phenotype. Sfrp5 is proposed to regulate macrophage function. Secreted by adipocytes, Sfrp5 suppresses Wnt5a signaling in macrophages, modulating innate immune responses by inhibiting both the canonical and non-canonical (JNK) signaling pathways.

Bente Pedersen, University of Copenhagen, followed with an interesting discussion of the protective effects of exercise-induced myokine production. IL-6 released into the circulation during physical exercise is an important myokine that functions as an energy sensor, activating pathways that increase lipolysis and fat oxidation. In addition, IL-6 increases insulin sensitivity by enhancing insulin-stimulated glucose uptake. The ability of exercise induced IL-6 to modulate inflammation was demonstrated in healthy human volunteers where the LPS induced increase in serum TNFa was prevented either by pre-treatment with IL-6, or by having the volunteers exercise prior to receiving LPS. Interestingly, IL-6 infusion failed to trigger fat oxidation in obese Type II diabetics suggesting they are "IL-6 resistant", and indeed these patients have reduced IL-6 receptor expression in their adipose tissue. IL-6R expression can be increased with exercise, indicating resistance can be reversed with physical activity. Another exercise induced myokine, IL-15, has been linked to the regulation of fat mass and muscle mass. IL-15 over expressing mice become very muscular and have little visceral fat even when overfed. In humans, exercise increases IL-15 in muscle tissue, increasing muscle size and reducing visceral fat.

The session ended with a presentation by Jennifer Lachey, Acceleron Pharma, describing a potential new therapeutic that suppresses negative regulators of muscle mass. As we learned in the previous discussions, increasing the mass of metabolically active tissues such as skeletal muscle mitigates increased adiposity and the complications associated with diet-induced obesity. Myostatin and other negative regulators of muscle mass signal through the activin receptor type IIB (ActRIIB). Inhibition of this interaction by treatment with a soluble form of ActRIIB in mice fed a high fat diet resulted in dramatically increased muscle mass. Treatment with ACE-435, a fully human soluble protein comprised of an optimized form of the ActRIIB extracellular domain linked to a human Fc, or RAP-435, the mouse surrogate, resulted in significantly increased lean mass, a reduction in the gain of fat mass, and prevented the diet induced increase in serum lipids without affecting food intake. Following ACE-435 treatment, the white fat of obese mice switched to a more metabolically active state, increas-

ing white fat themogenetic potential. Lastly, treatment with RAP435 increased muscle mass and grip strength in an aging mouse model of sarcopenia. These results support the potential use of ACE-435 in the treatment of morbid obesity and metabolic disorders, and may be of benefit in aging related loss of muscle strength.

Later that evening, the Welcome Reception was opened with an address by John Somerville (BMS), outgoing President of the Inflammation Research Association, followed by the Keynote Lecture presented by Siamon Gordon, Professor Emeritus of Cellular Pathology, University of Oxford. Dr. Gordon provided an excellent overview of macrophage receptors and how they can be used to identify macrophage classes. A series of receptors were described that regulate macrophage activation, polarization, migration, fusion and phagocytosis during inflammatory states. CD200R, a novel marker of macrophage activation, was highlighted. CD200R is expressed on myeloid cells: dendritic cells, macrophages, neutrophils, mast cells and basophils. Ligation of CD200R by ligand CD200 or an agonist anti-CD200R monoclonal antibody inhibits pro-inflammatory myeloid cell functions, suggesting the receptor could be targeted to mitigate inflammatory disease.

Day 2 of the conference focused on advances in translational medicine in inflammatory disease. The term "translational" as it applies to investigative scientific research, clinical medicine and drug discovery often has different meanings according to an individual's perspective. To one investigator, it may mean matching animal and human disease mechanisms; to another using human tissues to model inflammatory disease ex vivo to support drug discovery; and to another translating PK/PD parameters from preclinical models to the clinic. Nevertheless, one of the underlying premises of translational medicine is to apply basic research discoveries to practical applications in the clinic and in drug discovery. However, translational medicine should not be construed to be unidirectional since lessons learned from clinical observations and drug efficacy studies can support further advances in basic science enhancing our understanding of inflammatory disease processes. These concepts were reviewed in a series of presentations by pharmaceutical industry representatives.

Using the example of systemic lupus erythematosus, Jeffrey Voss (Abbott), outlined the importance of aligning disease mechanisms and pathological processes expressed in human disease with those in pre-clinical models. A translational approach using gene array data can be used to identify and correlate mechanistic pathways in preclinical models that recapitulate lupus pathology in humans. Such analysis need not be restricted to animal models of lupus, but can be extended to pre-clinical models of other autoimmune diseases such as RA where similar disease mechanisms may be in operation. With the knowledge gained, investigators can make rational decisions about which preclinical models best reproduce the targeted pathway under investigation. Bitao Liang (Celgene) described his company's research focus on multipotent progenitor cells. Mesenchymal stromal cells, derived from human placenta have been shown to interact with and modulate immune cell function. Christine Ward (MedImmune) outlined how gene array and proteomic analysis can be used to better define patient subpopulations in COPD and asthma. These data can be used to support clinical trial design to target patient populations capable of responding to targeted drug treatment, and to develop individualized treatments for patients that do not respond to standard of care. William Westlin (Avila) then described his company's development of a unique covalent probe based on the permanent binding of drug to target which can be used to precisely measure bound vs free drug. This technology has enabled the translation of PK/PD relationships in preclinical models into useful predictions of dose level and frequency in the clinic.

A highlight of the afternoon sessions was the oral presentations from participants in the C. Gordan Van Arman Scholarship Competition. Elisabeth Ferreira (Harvard Medical School), Miranda Hanson (National Cancer Institute), Qian Qi (Pennsylvania State University/Cornell University), Sivapriya Vanaja (UMASS Medical School), and Amanda Walker (Rider University) gave excellent presentations demonstrating the high quality research being carried out by young investigators in inflammation research.

The scholarship competition was followed by a Special Seminar presented by Michael Steiner (Pharmaceutical Executive Services Group) who spoke about the challenges facing the pharmaceutical industry and how these challenges were affecting career opportunities for research professionals. Discussions around shrinking R&D budgets, leaner workforces, and increased outsourcing, particularly to low cost offshore

CROs, at times presented a bleak picture of the future role of the bench scientist in drug discovery. Nevertheless, opportunities are on the rise for professionals who can extend their knowledge across multiple therapeutic areas, taking leadership roles in the design, execution, analysis and quality control of preclinical and clinical studies.

Tuesday's session, Day 3, focused on how crosstalk between macrophages and dendritic cells and the surrounding environment plays a key role in the pathogenesis of inflammatory disease. Giorgio Trinchieri (NCI) introduced his presentation by suggesting that the classic concept, that early inflammation is necessary for carcinogenesis and that an activated immune response prevents tumor progression, has been replaced by a more subtle understanding that the degree and type of inflammation/immune response can tilt the balance between tumor progression and regression. He provided evidence that TLR signaling though MyD88 mediated pathways on dendritic cells can drive either an IL-12 dependent Th1 response which is anti-tumorogeneic, or an IL-23 dependent Th17 response that is supported by IL-1 family cytokines and favors tumorogenesis. Not surprisingly, MyD88 KO mice are resistant to sarcoma and skin, hepatic and colon carcinoma. However, the KO is very susceptible to irradiation and DSS induced colitis. Colitic KO mice have a high incidence of colon carcinoma, likely due to loss of the IL-12 dependent protective role in DNA repair, thereby shifting the balance towards tumor formation when the colonic mucosa is challenged by a chemical injury.

Carla Rothlin (Yale University) described the role of the TAM receptor tyrosine kinases (Tyro3, Axl and Mer) as pleiotropic inhibitors of the innate immune response. TAM signaling plays a critical role in the recognition of apoptotic cells and their subsequent phagocytosis and processing by phagocytes such as dendritic cells and macrophages, and is therefore involved in negative regulation of the innate immune response to self antigen. Interestingly, TAM mediated inhibition of inflammation is transduced by interaction through the type I interferon receptor (IFNAR) and its associated transcription factor STAT1. IFNAR-STAT1 signaling upregulates the components of TAM system (Mer, Axl) which in turn usurp the IFNAR-STAT1 cassette to induce the cytokine and TLR suppressors SOCS1 and SOCS3 preventing activation of IFNAR by type I IFN, as well as signaling through TLRs. Disruptions in this process result in delayed clearance of apoptotic cells, a factor that has been linked to the development of autoimmunity; and supported by observations in TAM KO mice which develop lupus-like symptoms.

Innate immunity relies on pattern recognition receptors to sense microbial products not normally present in the host. While the recognition of non-host RNA relies on TLRs and cytosolic RNA helicases, the detection of DNA is less well defined. Kate Fitzgerald (UMASS Medical School) described the importance of cytosolic DNA sensing in the innate immune system. The role of absent in melanoma-2 (AIM2), a member of the PYD domain and HIN200 domain (PYHIN) containing proteins, was highlighted as a central mediator of responses to ds-DNA viruses and cytosolic bacterial pathogens. AIM2 binds ds-DNA via a HIN200 and engages the adapter molecule ASC to form a caspase-1 activating inflammasome. Caspase-1 cleaves pro-IL-1β/pro-IL-18 to release their bioactive forms IL-1β and IL-18 which are significant mediators of the inflammatory response to infection. Another member of the PYHIN family, NLRP3, plays a key role in the formation of an alternate caspase-1 activating inflammasome. NLRP3 is synthesized subsequent to the activation of endosomal TLR-MyD88 signaling, and associates with ASC to activate caspase-1 in support of IL-1β production. MyD88 signaling can also drive NFkB activation resulting in Type I interferon production. Inappropriate sensing of self DNA as can occur during failed clearance of apoptotic cells can result in autoimmune disease such as SLE where there is a strong association to overproduction of Type I IFNs.

The afternoon was filled by two mini-symposia; the first focusing on elements of the innate immune system, and the second on adaptive immunity. Scheduled concurrently, it was possible to attend only one of these very interesting symposia. In Mini-Symposium I, Bassil Dahiyat (Xencor) described the use of computational design algorithms and high-throughput screening to engineer Fc domain variants with optimized affinity and specificity for both activating and inhibitory Fcγ receptors, creating biosuperiors for Fcγ receptor classes. Larry Burgess (Array BioPharma) described the safety and PK of ARRY-502, an

antagonist of the prostaglandin D2 (PGD2) receptor CRTh2 on Th2 polarized T cells, a receptor known to play a role in cytokine production associated with allergic inflammation. Using a novel mouse model deficient in marginal zone and bone marrow derived stromal macrophages, You-Wen He (Duke University) demonstrated that impaired neutrophil clearance by macrophages could be reversed by blocking G-CSF but not IL-1β suggesting that a G-CSF-dependent, IL-1β –independent pathway plays a role in promoting neutrophilia in mice deficient in macrophage clearance. Rupinder Kanwar (Deakin University) highlighted the important role played by musosal vascular addressin cell adhesion molecule (MADCAM)-1 in mediating the homing of macrophages to atherosclerotic plaques in apoE KO mice. Lastly, Philip Low (Perdue) described how folate receptor-β can provide a unique marker of activated human macrophage/monocytes, such that a folate-99Tc conjugate can be used to image and quantify inflammation in vivo.

Mini-Symposium II opened with a presentation by Barbara Vilen (University of North Carolina) describing how dendritic cells attenuate B cell receptor (BCR)-induced Ig secretion. Ag/Ab immune complexes engage FcγRIIb inducing dendritic cells to secrete soluble mediators that terminate Ig secretion. Edouard Cantin (Beckman Research Institute) followed with a presentation describing the immunomodulatory effects of high dose intravenous non-specific immunoglobulins (IVIG) in fatal HSV-1 induced encephalitis by suppressing spontaneous degranulation of Ly6Chigh aggressively activated monocytes and by induction of Tregs. Anne De Groot (EpiVax) described how the discovery of natural regulatory T-cell epitopes (Tregitopes) in the sequence of the Fc and Fab framework regions of therapeutic mAbs represents a paradigm shift for protein therapeutics. An understanding of Tregitopes will result in the better design of mAbs where incorporation of these regions may be used to enhance therapeutic potential, or their deletion may reduce off target effects. June Lu (Endocyte) described how the expression of folate receptor-β on persistently activated macrophages may be exploited to selectively deliver aminopterin (AMT) to macrophages via a folate-AMT conjugate. More effective than MTX in preclinical models of RA, the folate-AMT conjugate selectively targeted macrophages while avoiding the generalized toxic effects of free AMT on other cell types. In the final presentation of the day, Grant Stenton (Aquinox) described how AQX-1125 suppresses allergic airway inflammation through a novel mechanism of action involving the inhibition of the PI3K/Akt pathway through activation of SH2-containing inositol-5'-phosphatase (SHIP) 1, resulting in a reduction of pAkt in T and B cells.

Wednesday's session on Day 4, began with a series of presentations highlighting new developments in our understanding of lupus, both at the bench and the bedside. Gregg Silverman (UCSD) described emerging perspectives on the role of B cells in autoimmune responses. The classical view that the primary function of B cells in autoimmunity is the production of autoantibodies via T-cell helper mediated germinal center responses has given way to a clearer understanding of B cell function. There is good evidence that activated B cells can differentiate into parallel subsets of B cells (similar to T cell subsets) that produce either Th1- or Th2-biased cytokines to produce polarized B cells that can act as antigen-presenting cells and T-cell co-stimulators to promote inflammation; or function as regulatory B cells that mitigate inflammation. Polarized B cells may be important for initial recruitment of T cells, and the reciprocal interactions of these B and T cells subsets may be central to the self-perpetuating nature of autoimmune processes. Targeting B cell subset specific surface markers or survival factors may constitute the wave of the future in controlling autoimmune disorders.

Next, Frank Barrat (Dynavax) provided insight into the mechanisms underlying insensitivity to glucocorticoid (GC) therapy in subsets of lupus patients. Autoantibody production by TLR on B cells and pDC is believed to be key to promoting anti-nuclear antibodies and NFκB-dependent production of type I interferons. While the primary method of action of GCs is thought to be NFκB inhibition, their ability to control disease tends to be transient at best. Using the NZBW and Tlr7.Tg6 lupus prone mice in vivo and cultured pDC in vitro, it was observed that signaling through TLR7 and 9 by nucleic acid containing immune complexes activates NFκB and type I interferon production via a GC-insensitive mechanism. These findings suggest that inhibitors of TLR7/9 may be effective corticosteroid-sparing drugs.

An overview of lupus clinical development programs was provided by Joan Merrill (Oklahoma Medical Research Foundation). For the past 50 years, clinical management of lupus has been stymied by unpredictable clinical manifestations, and the fact that the underlying pathophysiology can vary markedly between patients, or even within the same patient over time. This heterogeneity carries over into clinical trials where attempts are made to apply global outcomes measures to disparate, poorly characterized patient populations. Recent developments in our understanding of immune abnormalities have identified reliable patterns of disease within subsets of patients that could lead to simplified treatment regimes and more effective clinical trial design. A move towards a personalized medicine approach to the treatment of lupus may well lead to better treatment options for patients.

In the final session of the conference, a number of novel anti-inflammatory compounds were described. Alison Humbles (MedImmune) discussed MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity for eosinophils and basophils for the treatment of asthma. Marina Roel (XOMA) reported that XOMA-052, a novel therapeutic mAb that neutralizes IL-1β activity by reducing the affinity of the ligand for its signaling receptor, while sparing binding of IL-1β to its decoy and soluble regulatory receptors. It was proposed that this approach could shift the balance between activation and neutralization, and may allow receptor-mediated clearance of antibody/antigen complexes while preserving the beneficial effects of IL-1β. David Martin (Amgen) closed the session with a description of AMG 827, a fully human blocking antibody to IL-17RA. Blockade of the IL-17A axis with AMG 827 inhibits the biological activities of IL-17A, IL-17F, and IL-25 (IL-17E), leading to decreased inflammation in pre-clinical models of RA, asthma, and a psoriasiform model of skin inflammation; as well as psoriasis in human subjects.

The social program, always a highlight of the International Conference commenced Monday evening with an excellent casual dinner held in the Sunset Terrace, followed by Karaoke Night in the Washingtonian room. Dancing and socializing carried on well into the evening with vocal styling's enthusiastically provided by conference attendees. The wine tasting and reception on Tuesday evening was well attended, and attendees were once again treated to a fine meal. Dinner was followed by awards presentations. First place winner of the Van Arman Scholarship Awards, was Sivapriya Vanaja (UMass Medical School, Abstract VA04), with second and third place awards going to Miranda Hanson (National Cancer Institute, VA02) and Qian Qi (Pennsylvania State University/Cornell University, VA03). Amanda Walker (Rider University, VA05) and Elisabeth Ferreira (Harvard Medical School, VA01) received honorable mention. First place winner of the Charles River Poster awards when to Anne DeGroot (Epivax, Poster A105), second price to June Lu (Endocyte, A119), and third to Rupinder Kanwar (Deakin University, Australia, A112). Closing comments were provided by John Somerville, outgoing president of the IRA, who passed the reins to the incoming president, Andrew Glasebrook.

- Bev Moore

Social Science at the 2010 IRA Conference

Winners Named for the 2010 C. Gordon Van Arman Scholarship Awards

The C. Gordon Van Arman Scholarship Competition is truly one of the highlights of the IRA International Conference. This competition is for young investigators that are active in laboratory research as degree candidates or have yet to complete postdoctoral training and nearly 20 entries were received from around the world several months prior to the 2010 conference in Chantilly, VA, when each of the contestants submitted a mini-paper describing his or her work. After review of these mini-papers, five finalists were selected by the IRA Scholarship Committee.

These five finalists received financial support to attend the meeting and were welcomed by members of the Scholarship Committee and members of the IRA Board at a reception luncheon on the opening day of the meeting. After lunch, the committee met with each of the contestants and engaged in a spirited scientific discussion of their work as described through a poster presentation. The final section of the competition involved a fifteen-minute oral presentation that was open to all meeting attendees. This was, as always, well attended and was a chance for the contestants to demonstrate their breadth of scientific knowledge in response to questions from the audience.

The entries for the 2010 competition were of a very high standard making the Scholarship Committee's task of choosing a winner based on the mini-paper, the poster and oral presentations very difficult. After much discussion, Sivapriya Vanaja from the University of Massachusetts Medical School was awarded the first prize of $2000 for her work titled: AIM2, NLRP3, and NLRP12 function in a non-redundant manner to drive IL-1β in response to Enterohemorrhagic Escherichia coli.

Second prize of $1000 went to Miranda Hanson, from the National Cancer Institute, for her presentation: Lactococcus lactis expressing IL-27: A potential therapeutic for inflammatory bowel disease (IBD). In third place ($750) was Qian Qi from Cornell University for her presentation titled: Partial rescue of Itk-/- INKT cell development by Txk/Rlk reveals a unique role for Itk in survival of iNKT cells.

Honorable Mention awards of $500 went to Elizabeth Ferreira from Harvard Medical School who described her work: Inflammation and Osteogenesis: a paradoxical effect of interleukin-1 on the osteogenic differentiation of human, bone marrow-derived mesenchymal stem cells and to Amanda Walker, Rider University, for: Th1/Th2 differences in triggering macrophage-mediated suppression: studies with interferon-γ receptor knockout mice.

The prizes were presented during the Conference banquet on the final day of the meeting. The Scholarship Committee, chaired by Lisa Olson (Abbott Bioresearch) and including Jane Connor (MedImmune), Jim Ellis (Sirtris), Liwu Li (Virginia Polytechnic Institute), Caralee Schaefer (InterMune), Joel Tocker (Centocor) and William Westlin (Avila Therapeutics) dedicated many hours before and during the Conference to the selection of the winners. Their commitment to furthering the education and careers of young scientists and to the IRA is appreciated by all.

Van Arman Scholarship Finalists & Mentors (L-R): Lisa Olson (Abbott Bioresearch), Miranda Hanson, Qian Qi, Elisabeth Ferreira, Amanda Walker, Sivapriya Vanaja, John Somerville (Bristol-Myers Squibb)

2010 Charles River Best Poster Competition

Team of Academic and Industrial Researchers wins 2010 Charles River Best Poster Competition at the 16th International Conference.

Always a focal point of the IRA Conference, this competition is open to authors of posters that describe previously unpublished work, excluding those presented by the C. Gordon Van Arman Award Finalists. Andy Glasebrook (Eli Lilly), Arpita Maiti (Vertex Pharmaceuticals) and Lisa Schopf (Virdante Pharmaceuticals) led the judging team at the 2010 Conference. The winners were announced and prizes were awarded at the Conference Banquet.

First prize of $2500 was awarded to Anne De Groot et al, a team of scientists from EpiVax, Inc., Brigham & Women's Hospital, Children's Hospital of Philadelphia, University of Rhode Island and University of Maryland, for Poster A105: Preclinical Design of Less Immunogenic Biologics: Tregitopes and Tolerance.

Second prize of $1000 went to the authors of Poster A119, authored by Y. June Lu and colleagues from Endocyte, Inc: Targeting Activated Macrophages via a Folate-Aminopterin Conjugate and Its Effectiveness in Animal Models of Inflammation.

Rupinder Kanwar, Jagat Kanwar and Geoffrey Krissansen, researchers from Deakin University and University of Auckland were awarded Third prize ($500) for Poster A112: Mucosal Vascular Addressin Cell Adhesion Molecule-1(MADCAM-1) Plays an Important Role in Macrophage Homing to Atherosclerotic Lesions.

The IRA thanks Charles River, a global provider of research models and preclinical and clinical support services to pharmaceutical and biotechnology companies, government research centers, hospitals and academic institutions for continuing this important tradition of the Inflammation Research Association conferences. The Best Poster Competition has been part of each IRA biannual meeting since the 9th International Conference when three representatives of the Inflammation Research Association Board formed the judging panel and selected three posters judged to describe work with the most therapeutic potential.

Charles River Poster Competition Second Prize (L-R): Lisa Schopf (Kala Pharmaceuticals) June Lu (Endocyte)

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