

9th Cytokines and Inflammation Conference 2011

**San Diego, California, USA
27-28 January 2011**

ISBN: 978-1-61839-965-6

Printed from e-media with permission by:

Curran Associates, Inc.
57 Morehouse Lane
Red Hook, NY 12571



Some format issues inherent in the e-media version may also appear in this print version.

Copyright© (2011) by Global Technology Community (GTCbio)
All rights reserved.

Printed by Curran Associates, Inc. (2012)

For permission requests, please contact Global Technology Community (GTCbio)
at the address below.

Global Technology Community (GTCbio)
635 W. Foothill Blvd.
Monrovia, CA 91016

Phone: (626) 256-6405
Fax: (626) 466-4433

infogtcbio@gtcbio.com

Additional copies of this publication are available from:

Curran Associates, Inc.
57 Morehouse Lane
Red Hook, NY 12571 USA
Phone: 845-758-0400
Fax: 845-758-2634
Email: curran@proceedings.com
Web: www.proceedings.com



Day 1

[Day 2](#)

Day 1 - Thursday, January 27, 2011

7:00 Registration & Breakfast

7:55 Welcome and Opening Remarks

Session I - Cytokine Regulation

Moderator: Scott K. Durum, NIH

DISTINGUISHED KEYNOTE PRESENTATION

8:00 [The TNF Family Receptor HVEM is Critical for the Regulation of Mucosal Immunity and the Prevention of Inflammatory Bowel Disease](#)

1



Mitchell Kronenberg, Ph.D.
President and Scientific Director
La Jolla Institute for Allergy and Immunology

Blockade of the interaction of tumor necrosis factor (TNF) with its receptors is a successful treatment for some patients with inflammatory diseases, such as arthritis and Crohn's disease, but the TNF and TNF receptor families are complex, with many other members that could be important therapeutic targets. The interaction between the TNF super family member LIGHT (TNFSF 14) and the TNF super family receptor herpes virus entry mediator (HVEM or TNFSR 14) co-stimulates T cells and promotes inflammation. However, HVEM also triggers inhibitory signals by acting as a ligand that binds to B and T lymphocyte attenuator (BTLA), an immunoglobulin super family member. The dual nature of the outcomes following HVEM interactions make this receptor particularly interesting, and led us to ask how HVEM participates in mucosal immune responses. I will describe the anti-inflammatory role of HVEM in a mouse model of colitis, and will present recent data showing how HVEM influences the response to *Citrobacter rodentium*, a mouse model for pathogenesis of attaching and effacing bacterial infections, such as those caused by enteropathogenic *E. coli* (EPEC). In the infection model, HVEM acts by promoting the pathway related to the cytokines IL-17 and IL-22, by a STAT3-dependent mechanism that likely affects both the innate and adaptive immune responses.

The audience will gain:

- 1) Increased knowledge of mucosal immunology, an important but relatively unexplored field.
- 2) A greater understanding of relevant animal models for inflammatory bowel diseases and mucosal infections.

- 3) New information about the different cell types that produce and respond to IL-17 and IL-22.
- 4) Will have an increased appreciation of the profound importance of HVEM and its ligands, and why these might be excellent targets for drug development.

Speaker Bio:

Mitchell Kronenberg is the President and Chief Scientific Officer of the La Jolla Institute for Allergy & Immunology. He joined the Institute in 1997, and became President in 2003. As Institute President, he is responsible for leadership, strategic planning, and administration of a \$46M/year research institute, which has grown to 22 independent labs and over 350 employees since establishment in 1988. Dr. Kronenberg received an undergraduate degree from Columbia University and a Ph.D. from the California Institute of Technology in 1983, where he continued as a postdoctoral fellow. He was on the faculty of the UCLA School of Medicine from 1986-1997. He has co-authored more than 260 publications, and according to the Institute for Scientific Information, he is one of the most highly cited immunologists in the world. His research interests are in the areas of mucosal immunology, and inflammatory and autoimmune disease models and the response to bacterial infections. Dr. Kronenberg's awards include an NIH MERIT Award, Kroc Distinguished Professor in Medicine and Immunology at UC Davis, and a Burroughs Wellcome Fund Visiting Professor in Basic Biomedical Sciences at Harvard University. He has served as the Chair of International meetings, such as the Gordon Conference of Immunobiology and Immunochemistry, on editorial boards, and on grant review panels for NIH and other agencies. Dr. Kronenberg also was elected Secretary-Treasurer and Council Member of the American Association of Immunologists.

8:35

[HDL, Microcirculation and the Tumor Promoter Lysophosphatidic Acid](#)

Mohamad Navab, Professor of Medicine, Cardiology, **UCLA**

20

Many disorders including coronary artery disease, stroke, diabetes, arthritis, Crohn's disease, systemic lupus erythematosus, fibrosis and even sickle cell disease or certain types of cancer have the common feature of being influenced by inflammation. Administration of oxidized lipids to laboratory animals induces inflammatory molecules such as TNF alpha and IL-6. High density lipoprotein (HDL) has been shown in many animal models of inflammation to prevent and or reduce the inflammatory pressure. Under excessive pressure however HDL itself can be adversely affected and lose its protective capacity. HDL may be thought of as a shuttle whose size can be estimated by HDL cholesterol levels. The content of the shuttle however is what determines the anti inflammatory potential of HDL and can change from one supporting reverse cholesterol transport to one that is less efficient in carrying out this function. Animal models of many metabolic disorders have proinflammatory HDL and treatment with the peptide mimetic improved markers of inflammation and anti inflammatory capacity of HDL. Whether HDL mimetic peptides will have therapeutic benefit in patients with inflammatory disorders will have to be determined in clinical studies.

Whether HDL mimetic peptides will have therapeutic benefit in patients with inflammatory disorders will have to be determined in clinical studies. The audience will know about the role of lipids in inflammation and in cancer.

Speaker Bio:

Mohamad Navab started his Research at Columbia College of Physicians and Surgeons, Division of Cardiology in 1970 and has continued that at UCLA Cardiology since 1983. His work had focused on artery wall cell interactions; modification of LDL making it pro atherogenic; modification of HDL that abolishes its anti inflammatory capacity; assays to determine the HDL function; development of HDL mimetic peptides that reactivate HDL; contributing to clinical trials in patients with coronary artery disease and recently; has been collaborating with a group of investigators who in pre clinical studies have shown that the action of the tumor promoter lysophosphatidic acid can be prevented by HDL mimetic peptides.

9:00 **Pharmacological Modulation of Th17 cells**

Anne M. Fourie, Ph.D., Research Fellow, Immunology, **Johnson and Johnson PRD**

Speaker Bio:

Anne Fourie received her Ph.D from the University of Cape Town in South Africa, working on characterization of misfolded mutant LDL receptors in patients with Familial Hypercholesterolemia. She performed post-doctoral work at University of Texas Southwestern Medical Center in Dallas on the substrate specificity of HSP70s. Since joining the Immunology team at Johnson & Johnson in 1999, she has held positions of increasing responsibility, and led a number of small molecule discovery programs in respiratory and autoimmune diseases. She is currently a Research Fellow, leading the Translational Immunology team, with responsibility for several drug discovery projects, in addition to pharmacodynamic biomarkers and translational assays to facilitate successful development into human therapeutics.

9:25 **Signaling from the IL-17R for Post-Transcriptional Control of Chemokine Gene Expression**

Thomas A. Hamilton, Ph.D., Chair, Immunology, Lerner Research Institute, **Cleveland Clinic Foundation**

An important target for IL17 is the expression of neutrophil-specific chemokines that orchestrate the trafficking of these cells to sites of injury and inflammation. The primary cell types responding to IL17 include stroma and epithelia and a burst of gene transcription is recognized as an essential component of this process. It is now clear, however, that post-transcriptional prolongation of chemokine mRNA half-life is a major mechanism through which IL17 promotes dramatic increases in both mRNA and the translated protein. The control of mRNA half-life in myeloid inflammatory cells is known to involve adenine-uridine rich sequence motifs (AUUUA) localized within 3' untranslated regions (UTRs) that confer instability through the action of RNA binding proteins such as tristetraprolin (TTP), subject to control by p38 MAP kinases. Recent findings indicate that a distinct mechanism is operative in non-myeloid cells in response to stimuli such as IL-17. These pathways target instability sequences that do not contain the AUUUA pentamer motif, do not signal through p38 MAPK, and function independently of TTP. IL-17 appears to promote enhanced stability of chemokine mRNA in non-myeloid cells via TRAF2 and/or 5 and a member of the SR splicing factor family known as SF2/ASF. TRAF2 or TRAF5 are necessary for stabilization of chemokine mRNA induced by IL-17. Furthermore, these TRAFs bind SF2/ASF in ligand-dependent fashion. SF2/ASF promotes chemokine mRNA instability and its depletion by siRNA results in prolonged mRNA half life. Finally, SF2/ASF binds chemokine mRNA in unstimulated cells but SF2/ASF-mRNA interaction is markedly diminished following stimulation with IL-1 or IL-17. These findings define a distinct signaling pathway linked to the stabilization of neutrophil-specific chemokine mRNA in non-myeloid cell populations.

Speaker Bio:

Thomas Hamilton received his Ph.D. in Biochemistry at the University of Oregon Health Sciences Center with studies focused on tRNA metabolism. Following post-doctoral work in the Department of Pathology at Stanford University Medical School on the function and expression of mammalian alkaline phosphatases, he broadened his research interests to consider the biochemistry and molecular biology of mononuclear phagocytes as an Assistant Member at St Jude Children's Research Hospital and in the Department of Pathology at Duke University School of Medicine. In 1987, he moved to the Research Institute of the Cleveland Clinic Foundation where he has served as the Chair of the Department of Immunology for the last 15 years. Dr. Hamilton's research interests include the regulation of inflammatory gene expression in cells of the innate immune system and in stromal and epithelial cells with particular emphasis on transcriptional and post-transcriptional mechanisms controlling members of the chemokine gene families.

9:50 **Refreshment Break and Networking**

Session II - Cytokine and Chemokine Signaling

Moderator: Scott K. Durum, NIH

FEATURED PRESENTATION

10:20 **IL-36 Cytokines and Psoriasis**



John E. Sims
Scientific Executive Director
Inflammation Research
Amgen

The IL-1 family is now known to comprise 11 members. Four of these – the agonists IL-1F6, IL-1F8, and IL-1F9, and the antagonist IL-1F5 – act through the IL-1Rrp2 (IL-1RL2) receptor paired with the IL-1 receptor accessory protein to deliver inflammatory signals similar to those induced by IL-1. IL-1F6, F8 and F9 are expressed in only a limited set of human tissues, prominent among which is skin. We have found that these cytokines are strongly upregulated in human psoriasis. Overexpression of IL-1F6 in mouse epidermis results in a skin disease with many of the hallmarks of human psoriasis at both the histological and molecular level. Agents effective in treating human psoriasis also ameliorate skin inflammation in the transgenic mouse. Furthermore, blockade of this pathway in human lesional psoriatic skin, transplanted onto an immunodeficient mouse, reduces acanthosis and other signs of disease. We conclude that one or more of IL-1F6, IL-1F8 and IL-1F9 are important in human psoriasis for maintenance of the disease phenotype. In light of the recent information regarding their activity, the IL-1 family nomenclature has been revised so that these cytokines are now called IL-36 alpha (IL-1F6), IL-36 beta (IL-1F8), IL-36 gamma (IL-1F9), and IL-36Ra (IL-1F5).

Benefits:

- 1) Review of the IL-1 Family of Cytokines
- 2) Summary of expression pattern of IL-36 cytokines
- 3) Understanding of the role of IL-36 cytokines in human inflammatory skin disease

10:45 **IL-25-Induced Act1-Mediated Signaling**
Xiaoxia Li, Ph.D., Professor, **Cleveland Clinic Foundation**

11:10 **[Mice That Do Not Express the Jak Kinase Tyk2 Become Obese](#)**
Andrew Lerner, M.D., Ph.D., Professor, Biochemistry and Molecular Biology, **Virginia Commonwealth University**

69

The prevalence of obesity and type 2 diabetes, which are major components of the metabolic syndrome, has reached epidemic proportions worldwide. Among the problems associated with these disorders that contribute to the metabolic syndrome is insensitivity of target tissues to insulin and leptin. Jak/Stat signaling is the primary mediator of the actions of leptin, and it also contributes to the effects of insulin. Leptin activates Jak2, resulting in tyrosine phosphorylation of Stat3 that stimulates the expression of a set of early response genes. Tyk2 is another member of the Jak family that mediates the actions of IL-12, type I interferons and several other cytokines, but does not modulate the actions of either leptin or insulin. Disruption of Tyk2 expression in mice has confirmed the importance of this kinase in a variety of innate and adaptive immune responses. We have made the novel observation that Tyk2^{-/-} mice become spontaneously obese. The expression of Tyk2 is decreased in wild type animals placed on a high fat diet. Expression of a variety of mRNAs that regulate fatty acid and glucose

homeostasis are altered in liver, adipose tissue and skeletal muscle of Tyk2^{-/-} mice, consistent with the role of Tyk2 in the pathogenesis of metabolic syndrome. One of the major defects in Tyk2^{-/-} mice contributing to their obesity is a failure of brown adipose tissue (BAT) to differentiate. Using an in vitro differentiation model of BAT cells isolated from Tyk2^{-/-} mice, we have observed that Tyk2^{-/-} BAT differentiation as well as the expression of BAT-specific RNAs is rescued by the expression of either Tyk2 or a constitutively active form of Stat3 (CAStat3). Furthermore, expression of CAStat3 in BAT of Tyk2^{-/-} mice reverses the obese phenotype. Collectively, these observations suggest novel roles for Tyk2 and Stat3 in BAT that contributes to the etiology of metabolic syndrome.

Speaker Bio:

Andrew Lerner is a Professor of Biochemistry and co-leader of the Cancer Cell Signaling program at Virginia Commonwealth University School of Medicine. He has over 20 years of experience as a principle investigator working either at the FDA or in academic settings.

Prior to his current position, he was a member of the research Staff in the Dept. of Immunology at the Cleveland Clinic where he studied the mechanisms of action of interferons. He initially joined VCU in 2007 as Professor of Biochemistry and Co leader of the Immune Mechanisms group at the Massey Cancer Center. He is also the Martha Anne Hatcher Distinguished Professor of Oncology.

Previously, he held positions at the FDA Division of Biologics and the National Cancer Institute.

Dr. Lerner received a B.A. in Biology from Haverford College and a M.D. and Ph.D. in Pharmacology from the University of Virginia. He did his post-doctoral training at the Rockefeller University and completed a residency in Anatomic Pathology at the National Cancer Institute. He has authored multiple papers, abstracts and review articles.

11:35 **JAK Inhibition Suppresses Osteoclast-Mediated Bone Resorption Through Decreased T Lymphocyte RANKL Production**

Timothy P. LaBranche, D.V.M., Ph.D., Dipl. ACVP, Senior Principal Scientist, Pathologist, Drug Safety R&D, **Pfizer**

In rheumatoid arthritis (RA), the mechanistic link between JAK signaling in T lymphocytes and osteoclast-mediated bone/joint destruction is not well understood. In this study, we investigated how selective JAK inhibition with tasocitinib (CP-690,550) could affect T lymphocyte receptor activator of NF- κ B ligand (RANKL) production and subsequent OC-mediated bone resorption in the rat adjuvant-induced arthritis (AIA) model. We also investigated the impact of JAK inhibition on human osteoclastogenesis and human T lymphocyte RANKL production. The data suggest that JAK inhibition suppresses OC-mediated bone resorption indirectly, not via a direct effect on osteoclastogenesis but rather through modulation of T lymphocyte RANKL production.

1. Multiple orally-available JAK-inhibitors have been tested in human clinical trials for the treatment of RA, and have been shown to demonstrate “biologic-like” efficacy, including tasocitinib.

2. Here, we provide evidence that JAK inhibition with tasocitinib is not only capable of suppressing inflammation, RANKL production and osteoclast-mediated bone resorption but allows for new bone formation.

3. This work provides mechanistic insight into how a drug currently in phase III for RA may prevent structural damage to joints.

Speaker Bio:

Tim LaBranche is a veterinary pathologist and currently works for Pfizer, Inc. in Cambridge, MA. Tim completed both his DVM and Ph.D training at Virginia Tech, followed by an anatomic pathology residency at the University of Georgia. Tim has worked at Pfizer since 2006, originally in the St. Louis Laboratories before moving to the Boston area last year. Tim is engaged in characterizing / validating animal models of

rheumatoid arthritis, and is frequently consulted in this area for projects in early and late-stages of development, including mechanism of action investigative work for tasocitinib (CP-690,550). An employee of the Drug Safety Research & Development organization within Pfizer, Tim also works on various early stage inflammation & immunology project teams and helps identify and manage risk through both exploratory and GLP toxicology studies.

12:00 **Lunch On Your Own**

Session III - Cytokines in Health and Disease

Moderator: Timothy P. LaBranche, Pfizer

1:30 **Interferon-lambda: A Potential New Treatment for Chronic HCV Infection**
Ray Donnelly, Senior Investigator, Division of Therapeutic, Proteins, **FDA CDER**

ILike interferon-alpha (IFN- α), interferon-lambda (IFN- λ) induces anti-viral activity in a variety of target cells. However, the cellular distribution of IFN- λ receptors is much more restricted than IFN- α receptors. A recombinant version of interferon-lambda (IFN- λ) (alias IL-28/IL-29) is now being tested clinically as a novel therapeutic agent to treat patients with chronic hepatitis C virus (HCV) infection. Liver is the primary target organ for HCV because this virus preferentially infects and replicates in hepatocytes. Although several reports have shown that human hepatoma cell lines such as HepG2 and Huh7 can respond to IFN- λ , it is not known whether primary human hepatocytes can respond directly to this cytokine. Also, it has not been determined if primary human hepatocytes can produce IFN- λ in response to viral infection or TLR agonists such as poly I:C. We used cultures of primary human hepatocytes to examine expression of type I (IFN- α and - β) and type III (IFN- λ) interferon mRNA and protein following treatment with poly I:C ex vivo. Poly I:C treatment induced co-expression of IFN- β and IFN- λ mRNA in primary hepatocytes. The peak of IFN- β gene expression preceded and overlapped with the delayed burst of IFN- α and IFN- λ gene expression. The elevated levels of type I and type III IFN gene expression correlated with expression of the corresponding proteins as measured by specific ELISAs. We also found that primary human hepatocytes express IFN- λ receptors (IL-28R), and respond well to IFN- λ stimulation. Although the magnitude of IFN-stimulated gene (ISG) expression induced by IFN- λ was generally lower than that induced by IFN- α , the repertoire of genes that are induced by IFN- λ was essentially the same as that induced by IFN- α as determined by comparative cDNA microarray analyses. Induction of ISG expression by IFN- λ occurs independently of type I IFNs because treatment with an anti-IFNAR antibody largely blocked induction of ISG expression by IFN- α , but did not inhibit induction of ISGs by IFN- λ . These findings demonstrate that primary human hepatocytes can produce high levels of IFN- λ in response to agents such as poly I:C that mimic viral infection, and they can respond to both type I and type III IFNs by up-regulating expression of a common set of ISGs. Finally, I will briefly discuss the potential clinical advantages of IFN- λ versus IFN- α as a therapeutic agent for treating chronic HCV infection.

Speaker Bio:

Dr. Donnelly is a Senior Investigator in the Division of Therapeutic Proteins at the FDA Center for Drug Evaluation & Research (CDER) in Bethesda, MD. He received an M.S. in Microbiology from Oregon State University and a Ph.D. in Microbiology & Immunology from the Medical University of South Carolina. After completing postdoctoral training in immunology at the Boston University School of Medicine, he joined the FDA Division of Cytokine Biology as a Staff Fellow, and was tenured as a Principal Investigator at FDA in 1996. Dr. Donnelly serves as an expert on product manufacturing issues pertaining to a variety of therapeutic proteins, including many cytokines and cytokine antagonists. He also manages a laboratory research program that is focused on defining the receptors for and biological activities of novel cytokines, including the IL-10-related cytokines: IL-20, IL-22, and IFN-lambda (IL-28/IL-29). Dr. Donnelly is a current or former member of several editorial boards, including the Journal of Immunology, Journal of Interferon & Cytokine Research, and Genes & Immunity. He was the 2005 recipient of the FDA

2:00 **IL-1, Inflammasomes & Sterile Inflammatory Diseases**

Kenneth L. Rock, M.D., Professor and Chair, Pathology, **University of Massachusetts Medical School**

The inflammatory response is a double-edged sword. On the one hand it provides rapid defense against injurious agents and helps to remove and repair damage. On the other hand, the effector mechanisms that are mobilized are imprecise and cause damage to normal cells. The most damaging component of the acute inflammatory response is the neutrophil. While this collateral damage is a small price to pay to contain an infection that could become serious or even lethal, it is more costly in situations where the inciting stimulus is sterile and in this latter setting may actually cause or exacerbate disease, while contributing little to host defense. Sterile inflammation occurs in a number of settings, e.g. in the wall of arteries in Atherosclerosis, to urate crystals in gout, to mineral particles in pneumoconioses and to cells dying e.g. from ischemia. Recent data suggest that there may be common mechanisms underlying the neutrophilic inflammatory response to many of these diverse stimuli and diseases. In these settings macrophages sense the inciting stimuli through a pathway involving the NOD-like receptor NLRP3, which is part of the inflammasome complex. Stimulation of this complex then leads to the production of bioactive IL-1 that plays a critical role in initiating the inflammatory response.

Benefits of this talk are:

- 1) Understanding sterile inflammation and its role in disease pathogenesis
- 2) Understanding the cellular mechanisms of sterile inflammation
- 3) Understanding the molecular mechanisms and cytokines underlying sterile inflammation.
- 4) Identifying potential new molecular targets for treating sterile inflammatory diseases.

Speaker Bio:

Kenneth Rock received his M.D. from the University of Rochester. He completed a residency in Pathology at Peter Bent Brigham Hospital and a post-doctoral fellowship at Harvard Medical School. He was on the faculty at Harvard Medical School from 1982-1997 and has been Professor and Chair of Pathology at University of Massachusetts Medical School since 1997. His laboratory investigates the molecular mechanisms of antigen presentation and innate immunity, including the sterile inflammatory response. Dr. Rock has published 179 papers and holds 6 awarded patents. He has served on numerous national committees and editorial boards. He was a founder in the biotechnology companies ProScript and Corixa and has served on a number of scientific advisory boards.

2:25 **The Role of TWEAK/Fn14 in Inflammatory Disease Pathogenesis: It's All About Location**

Linda C. Burkly, Ph.D., Distinguished Investigator, Immunobiology, **Biogen Idec**

TNF superfamily members are compelling therapeutic targets for treatment of inflammatory diseases. TWEAK is a unique, multifunctional TNF family cytokine produced by macrophages and other leukocytes that signals through its receptor, FGF-inducible molecule 14, Fn14. Fn14 expression is relatively low in healthy tissues but is dramatically upregulated on epithelial and mesenchymal cell types in injured and diseased tissue. In contexts of chronic inflammatory disease, TWEAK mediates pathological tissue remodeling locally in the disease target tissue, by amplifying inflammation, promoting tissue damage, and potentially impeding endogenous repair mechanisms. Prior studies have demonstrated a pathological role of TWEAK in murine models of arthritis, lupus, atherosclerosis, multiple sclerosis, and inflammatory bowel disease, supporting that TWEAK/Fn14-mediated signals constitute a universal mechanism contributing to disease target organ pathology. The highly localized nature of its pathogenic contribution makes the TWEAK/Fn14 pathway a unique and promising

therapeutic target. The role of the TWEAK/Fn14 pathway in inflammatory disease pathogenesis was further investigated using human samples, mouse models and in vitro cultures. Our studies support that TWEAK/Fn14 is relevant to human inflammatory diseases and further illustrate mechanistic concepts underlying the pathogenic role of TWEAK/Fn14 in disease target tissues.

Speaker Bio:

Linda Burkly has over 20 years of experience in discovery research and drug development in the biopharmaceutical industry. After completing a Ph.D. in Immunology at Tufts University, Boston, she conducted a postdoctoral fellowship with Richard Flavell, employing transgenic mice with MHC class II selectively targeted to pancreatic islet beta cells to demonstrate a nondeletional mechanism for T cell tolerance. As a scientist and project leader at Biogen Idec, Dr. Burkly has contributed to the biological understanding of promising drug targets and to discovery and advancement of therapeutics/therapeutic candidates, including a novel anti-CD4 mAb HIV inhibitor and a VLA-4 blocking mAb approved for the treatment of multiple sclerosis. In particular, she is an expert in the TNF family of cytokines, advancing knowledge of the biology and development of agents targeting CD40L and TWEAK. Dr. Burkly has made significant contributions to elucidating the critical role of CD40L-mediated costimulation in nonhuman primate allotransplantation, and to development of a novel CD40L blocking agent for the treatment of autoimmune diseases. She has also elucidated the role of TWEAK in inflammation, angiogenesis, and progenitor biology, shown that this multifunctional cytokine mediates pathological tissue remodeling in contexts of chronic inflammatory disease, and contributed to advancement of a neutralizing anti-TWEAK mAb into the clinical development. Dr. Burkly has published over 100 peer-reviewed original papers, numerous reviews and book chapters, and is an inventor on over 20 issued patents and patent applications.

2:50 **LIGHT-HVEM-BTLA Axis in Protective Anti-Viral CD8 T Cell Immunity**

Shahram Salek-Ardakani, Ph.D., Scientist, **La Jolla Institute for Allergy and Immunology**

CD8 memory T cells can play a critical role in protection against repeated exposure to viruses, yet can also contribute to the immunopathology associated with these pathogens. Memory T cell development is still not fully understood in terms of the source and nature of the molecular signals that establish and maintain the memory state. Understanding the mechanisms that control effective memory responses has important ramifications for vaccine design and in the management of adverse immune reactions. The outcome of T cell receptor engagement is influenced by both positive (costimulatory) and negative (coinhibitory) signals that can either amplify or limit T cell function. This regulation is provided through multiple spatially and temporally regulated interactions between receptors on T cells and their soluble or membrane-bound ligands on antigen-presenting cells. We have obtained strong evidence demonstrating that the generation of protective anti-viral CD8 T cell responses are highly regulated by the tumor-necrosis-factor receptor (TNFR) family member, herpesvirus-entry mediator (HVEM). HVEM can act as a molecular switch between proinflammatory and inhibitory signaling by respectively binding with its endogenous ligand (LIGHT) from the TNF family and with B- and T-lymphocyte attenuator (BTLA) from the Ig like CD28/B7 family. The crosstalk between these two different families and especially between co-stimulatory and co-inhibitory receptors has raised many new questions with regards to the precise mechanisms of immune modulation through these interactions. Herein, we will summarize and discuss how the manipulation of LIGHT-HVEM-BTLA co-signaling system could aid in the development of safer and more effective vaccines for a wide range of virus infectious.

Benefits:

Highlights aspects of costimulatory and coinhibitory interactions that are potentially important for protective immunity against viruses.

Highlights the recent advances in the manipulation of such molecules and how they can be applied to combat viral infections.

Discussion of combination therapy as a strategy for generating the maximum therapeutic activity to induce protective anti-viral T cell memory.

Speaker Bio:

Shahram Salek-Ardakani is a Research Scientist at the La Jolla Institute for Allergy and Immunology (LIAI), a private, non-profit research organization that specializes in research of the immune system. He received his M.Sc. in Immunology and Immunogenetics at University of Manchester, U.K, in 1997, and PhD at the Paterson Institute for Cancer research (Manchester University) in oncology and viral immunology in 2001. He was a postdoctoral fellow with Dr. Mick Croft at LIAI, where his research focused on achieving a mechanistic understanding of how various members of the tumor-necrosis-factor receptor (TNFR) family control the response of CD4 and CD8 T cells at mucosal sites. He has worked on several interactions within this superfamily, focusing on those of OX40 with OX40L, 4-1BB with 4-1BBL, CD27 with CD70, and LIGHT with HVEM. His research has been diverse, including work on asthma, as well as studying models of cancer, MS, and more recently work on viruses such as vaccinia and EBV. He possesses a number of patents directed at immune disease therapy targeting the TNFR/TNF family.

3:15 Refreshment Break and Networking

Session III - Cytokines in Health and Disease (Cont'd)

Moderator: Linda C. Burkly, Biogen Idec

3:45 IL-17C, an Autocrine Cytokine that Regulates the Innate Immune Function of Epithelial Cells

Rajita Pappu, Scientist, **Genentech**

Mammalian cutaneous and mucosal epithelial cells constantly encounter environmental microbes and constitute the first line of defense against invading pathogens. Epithelial tissue imbedded immune cells, in particular dendritic cells, sense these microbes through various Toll-like receptors (TLRs) and induce innate and adaptive immune responses, including activation of epithelium defense mechanisms, to control the infection. Although epithelial cells also express TLRs, it is unclear how TLR activation on epithelial cells directly promotes innate defense mechanisms. We have identified IL-17C as an epithelial cell derived cytokine that unlike other IL-17 family members is selectively induced in epithelia upon sensing of bacteria. IL-17C functions in an autocrine fashion via binding to the IL-17RA?IL-17RE complex that is preferentially expressed on tissue epithelial cells. Stimulation of mucosal epithelial cells with IL-17C induces a varied set of host defense responses, including expression of pro-inflammatory cytokines/chemokines and anti-microbial peptides. IL-17C is upregulated in a mouse model of intestinal epithelial damage and loss of IL-17C signaling results in greater colon inflammation and delayed recovery. Thus IL-17C is a unique IL-17 family member that appears to have evolved to rapidly regulate the primary defense response of epithelial cells to bacterial encounter.

Speaker Bio:

Dr. Pappu a scientist at Genentech Inc. who received her B.A from U.C. Berkeley in the department of Molecular and Cell biology. Following graduation she spent a year as a research associate in the laboratory of Dr. Steve Rosen at U.C. San Francisco where she studied the role of L-selectin in T cell trafficking into the brain. The following year, Dr. Pappu moved to St. Louis, MO to join the graduate program in immunology at Washington University. She did her Ph.D training in the lab of Dr. Andy Chan. focusing on the role of the adaptor protein, BLNK, in B cell development and function. Her studies identified BLNK as a critical factor in pre-BCR signaling and mature B cell development. Additionally, they collaborated with Dr. Conley's lab at St. Jude Children's hospital to examine the function of BLNK in human B cell development. After graduate school, she joined Dr. Shaun Coughlin's laboratory at U.C. San Francisco where she studied the

generation of the lipid, sphingosin-1-phosphate (S1P), and its function in lymphocyte migration. Together with Dr. Jason Cyster's lab, they identified a critical role for sphingosine kinases 1 and 2 in lymphocyte egress. They identified erythrocytes as the predominant source of S1P in the blood. After completing my postdoctoral training she joined the department of Immunology Discovery at Genentech Inc. Dr. Pappu's lab is interested in mucosal immunology, and in particular the role of the IL-17 cytokines in host defense and autoimmunity.

4:10 **Cytomegalovirus Targets the TRAIL Death Receptors**

Chris A. Benedict, Ph.D., Assistant Faculty Member, Division of Immune Regulation, **La Jolla Institute for Allergy and Immunology**

Death receptor (DR) regulation of apoptosis is critical for maintaining immune homeostasis during viral infection. In turn, virus inhibition of apoptosis may alter this balance. We describe the identification of genes in both human and mouse cytomegalovirus (HCMV and MCMV) that suppress the function of TRAIL DRs. HCMV UL141 encodes a membrane glycoprotein that binds directly to the ectodomains of the human TRAIL DR. gpUL141 protects HCMV-infected cells from TRAIL-mediated killing by downregulating TRAIL DR from the cell surface and depleting intracellular receptor pools. In MCMV, the function of the single TRAIL DR is suppressed by m166, a gene with no overt sequence similarity to UL141. Surprisingly, an MCMV m166 deletion mutant exhibited enhanced persistent replication in the salivary gland. These results reveal viral genes that attenuate pathogen persistence by limiting apoptosis, highlighting the dichotomous role of death receptors in controlling immune responses.

- identifies a non-canonical interacting partner for TNFR superfamily members
- unexpected role of a viral "persistence attenuating" gene
- dichotomous role for TRAIL in regulating acute and persistent CMV infection

Speaker Bio:

Chris received his Ph.D. in biochemistry and molecular biology at the University of Southern California in 1997 where he worked on retroviral entry and potential gene therapy applications. In 1998 he moved to the La Jolla Institute of Allergy and Immunology to do a post-doc, and was promoted to the faculty in 2005. It was during this time he developed his interest in how persistent viruses, like the herpesviruses, modulate the host immune response in order to establish a lifelong, finely tuned equilibrium with their immune competent hosts. His laboratory focuses on how members of the tumor necrosis factor (TNF) superfamily of ligands and receptors promote innate and adaptive immune defenses, and what cytomegalovirus (a β -herpesvirus) does to counteract signaling by these cytokines.

[Oral Presentations from Exemplary Submitted Abstracts]

4:35 **IL-20 Antibody is a Potential Therapeutic for Rheumatoid Arthritis**

Ming-Shi Chang, Biochemistry, **National Cheng-Kung University**

Interleukin IL-20 is a proinflammatory cytokine involved in the pathogenesis of rheumatoid arthritis RA. We investigated whether anti-IL-20 antibody treatment would modulate the severity of the disease in a collagen-induced arthritis CIA rat model. We generated a CIA model by immunizing rats with bovine type II collagen. CIA rats were subcutaneously treated with anti-IL-20 antibody 7E, TNF blocker etanercept, or 7E combined with etanercept. Arthritis severity was determined by hind-paw thickness, severity score, cartilage damage, bone mineral density, cytokine production, which were evaluated using radiological scans, micro-computed tomography and ELISA. In vivo, IL-20 antibody, 7E alone or combined with etanercept significantly reduced the severity of arthritis by decreasing hind-paw thickness and swelling prevented cartilage damage and bone loss and reduced the expression of IL-20, IL-1 β , IL-6, RANKL and matrix metalloproteinase enzymes MMPs in synovial tissue. In vitro, IL-20 induced TNF- α expression in CIA SFs. IL-20 markedly induced RANKL production in CIA SFs, osteoblasts, and Th17 cells. Therefore, selectively blocking IL-20 inhibited inflammation

and bone loss in CIA rats. 7E combined with etanercept protected CIA rats better than etanercept alone. Our findings provide evidence that IL-20 is a novel target, and that IL-20 antibody may be a potential therapeutic for rheumatoid arthritis.

4:45 **Indoleamine 2,3 Dioxygenase IDO Mediated Tryptophan Depletion Promotes Pro-Inflammatory Response of Macrophage Under LPS Stimulation**

Haiyun Liu, Medical College of Georgia, **Georgia Health Sciences University**

Macrophages display remarkable plasticity modulating their function between pro-inflammatory host defense and anti-inflammatory immune regulation in response to various environmental cues microbes, apoptotic cells, and resting or activated lymphocytes. However, the mechanisms controlling macrophage plasticity are not well understood. Indoleamine 2,3 dioxygenase IDO is an intracellular tryptophan-metabolizing enzyme induced by type 1 and type 2 interferons in many cell types. However, while being induced by pro-inflammatory cues, antigen-presenting cells expressing IDO are known to promote tolerance through T-cell mediated suppressive mechanisms. As macrophages express high levels of IDO in response to interferon IFN- γ stimulation we investigated the effect of IDO expression on the macrophage response to proinflammatory and immunosuppressive stimuli. We observed that constitutive IDO expression in macrophages significantly amplified proinflammatory cytokine production IL-6, TNF- α , etc. in response to LPS exposure without affecting cytokine production in response to IFN- γ stimulation. The amplified LPS response was via amino acid deprivation as we could replicate IDO mediated effects by starving macrophages of tryptophan in vitro. Similarly, enhanced LPS responsiveness was due to activation of the GCN2 arm of the integrated stress response resulting in increased expression of C/EBP homologous protein CHOP and NF- κ B activation. GCN2 KO macrophages showed no response to LPS in the absence of tryptophan demonstrating the dependence on GCN2 mediated transcriptional modulation for this effect. Finally, IDO expression or tryptophan starvation promoted macrophage uptake of bacteria *E. coli* while inhibiting uptake of apoptotic splenocytes. Thus the data suggest that IDO functions to amplify macrophage responsiveness to specific pro-inflammatory via amino acid starvation and the integrated stress response with major implications for infection and resolution of inflammation. Currently we are evaluating the role for IDO and GCN2 in acute inflammation in vivo using mouse models of LPS induced endotoxin shock and intraperitoneal infection to gain a better understanding of the role of this novel macrophage regulatory system in inflammation and tolerance.

4:55 **Antibody Therapies Ameliorate T cell Transfer-Mediated Colitis**

Kathleen Mackay, **Epistem**

Aim: To evaluate the efficacy of test antibodies in a T cell transfer-mediated colitis model.

Methods: Colitis was induced in CB-17 Prkdcscid mice by transfer of CD4+CD62L+ T cells from BALB/c donor mice. Mice either received no additional treatment or were administered PBS vehicle, control mouse IgG1, CTLA4-Fc, or neutralizing antibodies to p19, p40, or IL-17RA x1/week. Mice were euthanised 28 days post-T cell transfer.

Results: Colitis was evidenced by diarrhoea, weight loss and increased large bowel weight: length ratio. Histological analysis revealed epithelial hyperplasia, T cell infiltration and crypt abscesses. The histopathology-based, colitis severity score for mice that received T cells only was 4.5 ± 2.1 mean \pm SD. CTLA4-Fc, anti-p19, and anti-p40 treatments all decreased colitis severity, with CTLA4-Fc demonstrating the greatest efficacy, with a colitis severity score of 0.2 ± 0.2 $p \leq 0.001$. Quantification of the sub-mucosal/mucosal area confirmed test item efficacy. The mean sub-mucosal/mucosal area was 1.0 ± 0.1 mm² for untreated controls, and 1.9 ± 0.5 mm² for the T cell only group CTLA4-Fc reduced this parameter to baseline levels, at 1.0 ± 0.2 mm² $p \leq 0.001$.

Conclusion: CTLA4-Fc, anti-p19, and anti-p40 all demonstrated efficacy in reducing the severity of T-cell transfer-mediated colitis.



Joost J. Oppenheim, M.D.
Head, Cellular Immunology Group
Laboratory Chief
Laboratory of Molecular Immunoregulation
NIH, NCI

Recent studies have identified a group of structurally diverse multifunctional host proteins that are rapidly released following pathogen challenge or cell injury and, most importantly, are able to both chemotactically recruit and activate dendritic antigen-presenting cells. These potent immunostimulants, including defensins, cathelicidin (LL37), eosinophil-derived neurotoxin (EDN), lactoferrin (LF), granulysin, high-mobility group box protein 1 (HMGB1) and HMGN1 serve as early warning signals to activate innate and adaptive immune systems. They interact with chemokine-like receptors and activating receptors on host cells. For example, some beta defensins, LL37, HMGB1 and EDN mimic chemokine and cytokine activities by interacting with CCR6 or CCR2, FPRL-1, RAGE and Toll-like receptors (TLR2) respectively. These proteins also are antimicrobial peptides (AMP's) and are constitutively produced and released by degranulating leukocytes or necrotic cells, but can also be induced by injurious stimulants and cytokines. In addition they are produced by keratinocytes and epithelial cells lining the GI, GU and tracheobronchial tree. We have highlighted the unique activities of these proteins by classifying them as "alarmins", in recognition of their role in rapidly mobilizing the immune system in response to infections and injurious danger signals. I will present our latest evidence that HMGN1 is a non-leucocyte derived alarmin that is required for adjuvant induced immune responses. I will also introduce our data implicating another neurophil granule product, lipocalin2/NGAL as a potent alarmin. This work is supported by the Intramural Program of the NIH, NCI.

Speaker Bio:

Dr. Oppenheim obtained his M.D. degree from Columbia College of Physicians & Surgeons, New York in 1960, trained as a Clinical Associate at the National Cancer Institute, Bethesda, Maryland, and was a post doctoral fellow at the University of Birmingham, England in immunology. He returned to the NIDR and subsequently headed the Section of Cellular Immunology at the NIDR and has been Chief of the Laboratory of Molecular Immunoregulation (LMI), National Cancer Institute at the Frederick Cancer Research and Development Center since 1983. Dr. Oppenheim served 32 years as a Medical Officer of the Commissioned Corp and is currently a Senior Biomedical Research Scientist in the National Cancer Institute, National Institutes of Health.

Dr. Oppenheim has done many pioneering studies of cytokines including IL-1 and participated in the patented discoveries of interleukin-8 and MCP-1. Dr. Oppenheim is currently studying the structure-function relationships of chemoattractant cytokines. His studies are focused on the effects of chemokines and downstream effector molecules such as defensins and cathelicidin LL-37 on innate and adaptive immunity, the regulation of angiogenesis by chemokines, and identification of chemokine inhibitors present in medicinal plant extracts and herbal preparation.

Dr. Oppenheim has also been investigating the "cross-talk" resulting in phosphorylation and mutual inactivation of chemokine and opioid receptors. This results in bidirectional desensitization of the receptors and provides a mechanism by which opioids can suppress the activities of proinflammatory chemokines. Conversely, chemokines can suppress opioid receptor functions thus presumably contributing to the increased perception of pain associated with inflammation.

5:40 **IL-17 Receptor Signaling Blockade in Psoriasis**
Chris B. Russell, Director, Medical Sciences, Amgen

IL-17A and IL-17F are pro-inflammatory cytokines that utilize a shared receptor consisting of IL-17RA and IL-17RC and are implicated in pathogenesis of several autoimmune diseases including psoriasis. These cytokines can exist as homo- or hetero-dimers, and are concomitantly produced by Th17 cells in response to inflammatory signals including IL-23. In turn, stimulation of keratinocytes with IL-17A and IL-17F will induce expression of additional pro-inflammatory molecules including other cytokines, chemokines and anti-microbial proteins building the core of a positive feedback inflammatory cycle. IL-17A and IL-17F are elevated both in human psoriatic lesional tissue and in a mouse model of skin inflammation with similarities to psoriasis. The effects of blockade of this inflammatory cycle in mice were examined at the histological and transcriptional level using monoclonal antibodies specific for IL-23, IL-17RA, IL-17A or IL-17F leading towards restoration of the wild-type state. Broad inhibition of the IL-17 axis with anti-IL-23 or anti-IL-17RA had a stronger effect on the skin phenotype while IL-17A and IL-17F specific inhibition of the individual ligands had less of an effect. Similar effects were also observed with blockade of the IL-17 pathway in human psoriasis, where AMG 827, a fully human monoclonal antibody that inhibits signaling through the IL-17 Receptor A subunit, was examined in a study including subjects with plaque psoriasis. Post-dose biopsies showed rapid and substantial normalization of the inflammatory transcriptional profile, including down regulation of genes for cytokines including the IFNG, TNF, the IL-23 subunit genes, and the IL-17A and IL-17F ligand genes. In both mouse and human, histologic resolution followed gene expression changes. These data suggest that the IL-17 axis may be a key component in an inflammatory gene expression cycle underlying skin inflammation in psoriasis.

Benefits of this talk are:

- Discussion of molecular signals in psoriasis
- Understanding the contributions of multiple IL-17 ligands to skin inflammation
- Understanding the role of IL-17 receptor signaling in keratinocytes and the psoriasis inflammatory cycle

6:05 **Networking Reception and Poster Session**

Day 2 - Friday, January 28, 2011

7:30 **Continental Breakfast**

7:55 **Review of Day One**

Session IV - Inflammation and Cancer

Moderator: Kenneth L. Rock, University of Massachusetts

8:00 **DISTINGUISHED KEYNOTE PRESENTATION**
Control of Tumor Progression and Metastasis by Lymphocyte-Produced Cytokines



Michael Karin, Ph.D.
Professor, Pharmacology, Tumor Growth, Invasion & Metastasis
University of California, San Diego

Inflammation and immunity can intersect with tumor development in more than one way. While chronic inflammation promotes tumor development, many tumors that do not arise in the context of underlying inflammation still exhibit an inflammatory microenvironment. Furthermore, in certain cases, inflammation may act to suppress anti-tumor immunity, but it can also be used to enhance the efficacy of cancer immunotherapy. Undoubtedly, we need to learn much more about how inflammation and immunity affect tumor development. To study the pathogenic roles of tumor-elicited inflammation, we have used mouse models of prostate and breast cancers, two of the most common malignancies in men and women, respectively, which usually do not evolve in the context of underlying inflammation or infection. Yet, in both cases, we found that tumor-elicited inflammation plays a key role in promoting metastatic spread and in the case of prostate cancer, it contributes to the failure of androgen ablation therapy. Interestingly, in both types of cancer, metastatogenesis depends on the accumulation of activated I κ B kinase γ (IKK γ) in the nuclei of primary cancer cells, where it acts both as an activator of chromatin modifiers that control cell cycle progression and as a repressor of an anti-metastatic gene, called maspin. In both cases, IKK γ , whose activation has also been observed in advanced human tumors, may be activated upon production within the tumor microenvironment of two members of the TNF family of cytokines: lymphotoxin (LT) α : β and RANK ligand (RANKL). While the cells responsible for production of these cytokines during metastatic progression of prostate cancer remain to be identified, B cells were found to be a major source of LT α : β during development of castration resistant cancer. In breast cancer, however, the major culprits in metastatic progression are RANKL-producing regulatory T cells (Treg). Both in prostate and breast cancers, the recruitment of lymphocytes into the primary tumor is likely to depend on activation of myofibroblasts which produce a number of tumor promoting chemokines. LT α : β , RANKL, IKK γ and the mechanisms responsible for myofibroblast activation, as well as the chemokines they produce provide several new opportunities for therapeutic intervention.

8:35 [Stat3 in Cancer Inflammation and Immunity](#)

95

Hua Yu, Ph.D., Professor, Cancer Immunotherapeutics & Tumor Immunology, **City of Hope**

Commensurate with their role in regulating cytokine-dependent inflammation and immunity, signal transducer and activator of transcription (STAT) proteins are central in determining whether immune responses in the tumor microenvironment promote or inhibit cancer. Persistently-activated Stat3, and to some extent Stat5 and Stat6, suppresses anti-tumor immunity, while enhancing tumor cell proliferation, survival and invasion. Persistent activation of Stat3 also induces tumor-promoting inflammation. Stat3 achieves this dual role in tumor inflammation and immune evasion by partnering with pro-oncogenic NF- κ B/IL-6/gp130/Jak pathways and by opposing Stat1- and NF- κ B-mediated T-helper 1 anti-tumor immune responses. Consequently, Stat3 is a promising target to redirect inflammation for cancer therapy.

Speaker Bio:

Hua Yu, Ph.D., is Professor of Cancer Immunotherapeutics and Tumor Immunology, Beckman Research Institute, City of Hope Comprehensive Cancer Center, Duarte, California. She received both undergraduate and graduate degrees in Molecular Biology from Columbia University in New York City. Dr Yu is a pioneer in STAT3 signaling in cancer, and was the first to provide the direct link between oncogenesis and tumor immune evasion; first to identify STAT3's role in tumor angiogenesis. Her work has uncovered many aspects of tumor-immune cell interactions. Recently, she has also developed a targeted siRNA delivery technology platform to silence desired genes in both normal and transformed myeloid cells and B cells. A summary of her work can be found in the following recent publications.

9:00 **Crosstalk Between Intraepithelial T Cells and Neighboring Epithelial Cells**

Wendy L. Havran, Ph.D., Professor, Immunology and Microbial Science, **Scripps**

Research Institute

Intraepithelial $\gamma\delta$ T cells play unique roles in homeostasis, tissue repair, inflammation and protection from malignancy. Antigens that activate these T cells are not well defined and they do not express classic costimulatory or coreceptor molecules. We have used molecular, biochemical and functional approaches to define molecules that activate the functions of intraepithelial $\gamma\delta$ T cells. We have identified several molecules that are key regulators of intraepithelial $\gamma\delta$ T cell recognition of damaged epithelial cells leading to activation, cytokine production, and participation in local immune responses. Results show that the rules for activation of $\gamma\delta$ T cells are distinct from the paradigm for $\gamma\delta$ T cell activation. Increasing numbers of elderly and diabetic patients have defects in tissue repair leading to chronic, non-healing wounds. Our studies have shown that T cells from patients with chronic wounds are functionally defective and unable to produce cytokines and growth factors that facilitate healing. Further characterization of the molecules that regulate interactions between tissue-resident T lymphocytes and neighboring epithelial cells may allow for the development of new therapeutic strategies to treat chronic wounds and other inflammatory epithelial disorders.

Speaker Bio:

Wendy Havran received her training in immunology at the University of Chicago where she received her Ph.D. in 1986. She was a postdoctoral fellow in the laboratory of Dr. James Allison in the Cancer Research Laboratory at the University of California Berkeley where she studied T cell development. In 1991 she joined the faculty of The Scripps Research Institute where she is currently a Professor in the Department of Immunology and Microbial Science. Dr. Havran was a Lucille P. Markey Scholar in Biomedical Science and a Scholar of the Leukemia and Lymphoma Society. In 2001 she received the Stohlman Scholar Award from the Leukemia and Lymphoma Society. She has demonstrated a novel role for intraepithelial $\gamma\delta$ T cells in tissue repair in the skin and intestine. Her research is currently focused on understanding mechanisms and molecules that control interactions between intraepithelial T cells and neighboring epithelial cells. Dr. Havran serves on the editorial board of several journals and is currently President of the Board of Directors of the San Diego/Hawaii Chapter of the Leukemia and Lymphoma Society.

9:25 **Sequelae of Inflammatory Cytokines in Cancer** Jordan S. Fridman, Sr. Director Pharmacology, **Incyte**

Inflammation is a well known contributing factor to tumorigenesis for multiple otherwise unrelated cancers. The process of inflammation can remarkably alter the tumor microenvironment resulting in tumor cell autonomous changes and creating a fertile environment for tumor progression. Increased inflammatory cytokines levels have been observed in tumors and in the plasma of cancer patients. Many of these cytokines require members of the Janus family of tyrosine kinases (JAKs) to convey their receptor binding into biological responses. Our research suggests that dysregulated JAK activation by inflammatory cytokines can affect tumor initiation, growth and responses to therapeutic intervention. Moreover, our data point to a causal role for elevated levels of circulating inflammatory cytokines in cancer-associated cachexia and poor performance status. Selective inhibitors of JAK1 & JAK2 can reduce cytokine signaling and improve treatment outcomes in multiple preclinical cancer models.

Speaker Bio:

Jordan Fridman is Senior Director of Pharmacology at Incyte Corporation where he has held various positions over the past 8 years. He received his Ph.D. in Pharmacology from the University of Michigan Medical School and conducted postdoctoral studies at Cold Spring Harbor Laboratory. During this time his primary research focus was the genetics of cancer and how certain lesions affect responses to therapeutic intervention. Currently the core function of Jordan's research group is to support all of the drug discovery programs' in vivo pharmacology needs with emphasis on cancer biology and

inflammatory disease.

9:50 **Refreshment Break and Networking**

Session V - Novel Technological Developments in Cytokines

Moderator: Scott Durun, NIH

10:30 **Dual Targeting of TNF and TWEAK in Inflammatory Bowel Disease: The Promise of a Bispecific Antibody**

Jennifer S. Michaelson, Ph.D., Principal Scientist, Molecular Discovery, **Biogen Idec**

TNF is a validated therapeutic target for the treatment of many inflammatory and autoimmune diseases, including inflammatory bowel disease (IBD). However, despite the clinical success of anti-TNF therapies, a significant proportion of IBD patients fail to adequately respond to treatment. TWEAK is a unique TNF family member ligand which signals through its cognate receptor, Fn14, and functions in parallel to TNF to induce inflammatory pathway mediators. Notably, expression of Fn14 is up-regulated in IBD patients. Moreover, the TWEAK/Fn14 pathway plays a pathological role in mouse models of IBD by inducing inflammatory responses and regulating intestinal epithelial cell turnover. We have generated a bispecific antibody designed to target both TNF and TWEAK, with the goal of more effectively blocking the inflammatory pathologies associated with IBD as compared to TNF inhibition alone. We demonstrate that the bispecific antibody is efficacious in simultaneously neutralizing both TNF and TWEAK in cellular assays and in a mouse system. The bispecific antibody thus represents a powerful approach to deliver targeted combination therapy in a single agent. The promise of a bispecific antibody targeting TNF and TWEAK is to improve upon current TNF therapeutics by providing a safe yet more effective therapy for the treatment of IBD.

Speaker Bio:

Jennifer Michaelson is currently a Principal Scientist at Biogen Idec and has been with the company for over 8 years. She received a B.A. in Molecular Biology from Princeton University followed by a Ph.D. in Cell Biology from Albert Einstein College of Medicine, where her research focused on transcriptional regulation of the immunoglobulin heavy chain gene. She completed post-doctoral work in the laboratory of Dr. Philip Leder at Harvard Medical School, where she characterized an apoptotic phenotype in DAXX deficient mice and generated a transgenic model of Wnt-mediated breast cancer. Since arriving at Biogen Idec, Dr. Michaelson has led multiple research projects in both the immunology and oncology disease areas, with a focus on therapeutic targeting of TNF family members with monoclonal and bispecific antibody technologies.

10:55 **Engineering of Latent Therapeutic Cytokines**

Lisa M. Mullen, Ph.D., Research Associate, Bone & Joint Research Unit, William Harvey Research Institute, **Barts and The London School of Medicine and Dentistry**

Cytokines are important cell mediators in health and disease. However, their pleiotropism and short half lives have limited their therapeutic use. We have developed the concept of 'latent' cytokines aiming to increase half life, reduce toxicity and target the cytokine only to disease sites. These latent cytokines are engineered by the use of a naturally –occurring 'shell' structure, the latency-associated peptide, from transforming growth factor- β (TGF- β), that shields the cytokine from interaction with its cellular receptors. The engineered latent cytokine also possesses a matrix metalloproteinase (MMP) cleavage site so that the active cytokine is released only at sites of inflammation and can thereby exert its effects locally. The first of these latent cytokines to be engineered was IFN- γ , which has a 37-fold longer half-life than the free cytokine. Latent IFN- γ , when delivered via gene therapy, results in inhibition of paw swelling and reduced clinical score when used to treat collagen-induced arthritis in mice (Adams et al., Nat. Biotechnol. (2003) 21, 1314-1320). A number of latent cytokines have now been engineered for the treatment of a range of pathological conditions from autoimmunity to cancer. This versatility is achieved by modulating the cleavage site in the latent molecule

to take advantage of disease-specific changes that occur locally at the sites of disease to release the active cytokine (Vessillier et al., Protein Eng Des Sel. (2004) 17, 829-835).

Benefits:

- Discussion of the challenges involved in use of therapeutic cytokines
- Highlights the advantages of the latent cytokine technology
- Opportunity to discuss new strategies for delivery of therapeutic cytokines using variations of the latent cytokine technology

Speaker Bio:

Lisa Mullen received her Ph.D. in Immunology and Endocrinology at the School of Biological and Chemical Sciences, Birkbeck College, University of London, where her research focused on the interactions between the innate immune and endocrine systems. She completed a postdoctoral fellowship at University College London, where she developed a number of phage display libraries as tools for the identification of bacterial adhesins involved in host inflammatory responses. Lisa then moved to a Research Fellowship at Imperial College, London where her research was concerned with the host anti-inflammatory cytokine responses to nematode parasites. Lisa is currently a Research Associate at the Bone and Joint Research Unit at Barts and the London School of Medicine and Dentistry, where she is working on the development of latent therapeutic cytokines. The use of cytokines as therapeutics is fraught with difficulties, due to the pleiotropic nature and short half-lives of these molecules. The latent cytokine technology aims to address these issues, making it possible to safely treat a number of inflammatory conditions using recombinant anti-inflammatory cytokines.

11:20

[TLR/Inflammatory Immune Mediator Signaling Pathways in Dendritic Cells and Regulation of T Cell Subset Responses](#)

106

Jonathan Rosenberg, Ph.D., **IMGENEX Corporation**

Toll-like Receptors (TLRs) on Dendritic Cells recognize exogenous ligands (PAMPs) or endogenous ligands (DAMPs) and activate the immune response through major signaling pathways such as NF- κ B or IRF pathways. Induction of specific sets of mediators depends upon the ligand, its' receptor, the cell type and the signaling pathway.

The presentation will focus on TLR activation of specific Dendritic Cell subsets and the inflammatory mediator response pathways which polarize and drive T cells into a Th17, Th1 or Th2 response.

Platforms utilized are Flow Cytometry for phenotyping of DC subsets and cytokine responses as well as new ELISA assays including IL-17A and IL-17AF as examples of pathways eliciting a Th17 or polarized T cell response

This presentation will provide insights into

- Examination of TLR activation pathways on Dendritic Cells
- TLR and other inflammatory agonists and antagonists
- DC and T Cell Subset networks, including inflammatory mediators and cytokines which comprise the immunoregulatory network spanning innate and adaptive immunity.

Speaker Bio:

Jonathan Rosenberg, Ph.D., combines technical expertise and business experience in the development of reagent biopanel for read-outs on Flow Cytometry, Image Cytometry and ELISA instrument platforms as integrated bioreporting systems. This approach enables simultaneous reporting of quantitative and comparative measurements of biologically related pathway markers or functional markers on cells, within cells or secreted by cells. Jonathan's Cellular Immunology/Flow Cytometry background includes the initial products developed for intracellular staining of cytokines and growth factors, multiplexed bead analysis and cell signaling. Additional projects include development of

antibody array products and ELISA based products. Jonathan received his MPh and PhD from the City University of New York in Biomedical Sciences followed by a Postdoctoral Fellowship at the Scripps Institute. He has served in Strategic Marketing and Market Development positions in the biotechnology/biomedical sector and currently directs Corporate Development at IMGENEX Corporation in San Diego. IMGENEX focuses on development of pathway analysis systems for cell regulatory and immune/inflammatory signaling pathways.

Session VI - Therapeutic Applications of Cytokines and Chemokines

Moderator: Ray Donnelly, FDA

11:45 **Therapeutic Inhibition of Chemokine Receptor CCR9: A New Understanding of the Inflammatory Response in the Gut and Beyond.**

Thomas J. Schall, President and CEO, **ChemoCentryx**

Speaker Bio:

One of the earliest investigators in the field of chemokine biology, Dr. Schall founded ChemoCentryx in 1997 to focus on the discovery and development of chemokine-based therapeutics. Prior to founding ChemoCentryx, Dr. Schall spent several years at a division of Schering Plough, the DNAX Research Institute, where he made fundamental contributions to the understanding of chemokines and their receptors in human disease. Before that Dr. Schall served for some years as a scientist with Genentech, Inc. During his scientific career, Dr. Schall has published over 100 book chapters and articles in noted peer-reviewed journals. In his business capacity, Dr. Schall has led ChemoCentryx through several rounds of major equity investment and business development funding (>\$300 million in total from all sources), in addition to raising significant amounts of non-dilutive funding (in excess of \$24 million) through such sources as DARPA and the NIH / NIAID. He has overseen the company's development of a wide pipeline of drug candidates in clinical trials and preclinical development. Dr. Schall received his Ph.D. in Cancer Biology at Stanford University.

12:10 **Lunch**

FEATURED PRESENTATION

1:15 **Anti-TNF Therapies: A Case Study of Golimumab**



Phillip K. Weck, Ph.D.
Vice President
Compound Development Team Leader
Centocor RnD

SIMPONI® (golimumab) is a human monoclonal antibody with an immunoglobulin G (IgG) 1 heavy chain isotype and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of human tumor necrosis factor (TNF). Golimumab given subcutaneously (SC) is approved in adults for treatment of moderate to severe rheumatoid arthritis (RA) in combination with methotrexate (MTX); active psoriatic arthritis (PsA) alone or in combination with MTX; and active ankylosing spondylitis (AS). Golimumab significantly reduces signs and symptoms, inducing major clinical response, and improving physical function, and health-related quality of life in subjects affected by rheumatologic disorders. Treatment with golimumab also inhibits the progression of structural damage associated with RA and PsA. Golimumab significantly improves signs and symptoms, physical function, and health-related quality of life in subjects affected by rheumatologic disorders. Treatment with golimumab also reduces the rate of progression of structural damage associated with RA and PsA. Regulatory dossiers for these indications are submitted in over 50 countries globally with

approvals in approximately 38 countries. Trials were initiated in China in 3Q 2010 in RA and AS. Additional clinical trials include an IV RA study, two studies in ulcerative colitis (UC), a small study in sarcoidosis, and a juvenile idiopathic arthritis (JIA) study. A large life cycle management (LCM) strategy is being initiated. This includes two ongoing Phase 3b studies in RA patients and new studies to expand the lead indications of RA and AS. Golimumab was the first anti-TNF approved for three indications simultaneously in 2009 and will be the first to offer both SC and IV routes of administration. It is currently offered in the SmartJect® auto injector and UltraSafe® pre-filled syringes. SmartJect® and monthly dosing distinguish golimumab from other anti-TNFs and provide patient friendly administration of the product.

Speaker Bio:

Phillip Weck is a Vice President & Compound Development Team Leader at Centocor. He has over 30 years of experience in the pharmaceutical industry. He has led laboratory research, clinical research, and drug development teams during his career. Centocor is a leading biopharmaceuticals company based in Malvern, PA and one of the Johnson & Johnson companies.

Prior to his current position, he was Director, Drug Discovery Portfolio Management at GlaxoSmithKline where he supported a diverse therapeutic area that included oncology, microbial and musculoskeletal diseases. He initially joined SmithKline Beecham in 1991 as Project Director for numerous projects in various stages of development. He also worked in the Global Marketing Group where he was responsible for scientific and competitive differentiation of cardiovascular and pulmonary products. Previously, he held positions at DuPont Merck as a Senior Project Manager, Burroughs Wellcome as a Senior Clinical Scientist, and Genentech as a Senior Research Scientist.

Dr. Weck holds a B.S. in General Zoology from Kent State University and a Ph.D. in Microbiology from Northwestern University. He completed post-doctoral training at the University of Virginia and continuing education studies at The Wharton School of Business, University of Pennsylvania. He has authored multiple papers, abstracts and review articles.

1:45 **Plerixafor: A CXCR4 Antagonist for Hematological Disease**
Simon Fricker, Ph.D., Distinguished Scientific Fellow, **Genzyme**

The chemokine CXCL12 and its receptor CXCR4 have a central role in hematopoiesis and the homing and retention of hematopoietic stem cells (HSC) in the bone marrow. Disruption of the CXCR4/CXCL12 interaction by the CXCR4 antagonist plerixafor results in mobilization of HSC from the bone marrow. Plerixafor, a selective CXCR4 antagonist, was approved for mobilization of HSC in combination with G-CSF for autologous transplantation for patients with non-Hodgkin's lymphoma and multiple myeloma in December 2008. Plerixafor is also being investigated for HSC mobilization in healthy donors for allogeneic HSC transplant. CXCR4 is expressed on leukemia cells, and a possible role for plerixafor in the treatment of leukemia by mobilization of leukemia cells from the protective environment of the bone marrow is under investigation. The molecular and in vivo pharmacology of plerixafor will be described from the perspective of its discovery, properties, mechanism of HSC mobilization, and clinical development.

Speaker Bio:

Simon Fricker is a Distinguished Scientific Fellow at Genzyme, MA. He obtained his Ph.D. from the University of Warwick, UK with research on the molecular mechanism of action of anti-cancer drugs. This was followed by postdoctoral research at the Universities of Cambridge and Southampton. Dr. Fricker joined the Biomedical Technology department of Johnson Matthey, UK where he worked on several projects related to metal-based drugs including platinum anticancer drugs, and organic molecules for HIV. It was during this period that the potent anti-viral activity of plerixafor was discovered, which was found to be due to inhibition of the chemokine receptor CXCR4.

Dr. Fricker joined AnorMED, a Canadian biopharmaceutical company, as a founding member in 1996. As Director of Biology he was responsible for the biological research on AnorMED's chemokine receptor programs. These programs identified novel CXCR4 and CCR5 antagonists for HIV, and successfully developed plerixafor for hematopoietic stem cell mobilization. Simon Fricker joined Genzyme in 2006 where he continues to pursue research into the therapeutic application of stem cell and chemokine biology.

2:10 **Lactococcus Lactis Expressing IL-27: Therapeutic Promise in Inflammatory Bowel Disease**

Scott K. Durum, Head, Cytokines and Immunity Section, Laboratory of Molecular Immunoregulation, **NIH, NCI**

Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis. These are chronic inflammatory disorders of the gastrointestinal tract involving aberrant activation of innate and adaptive immune responses induced by enteric bacteria. The existing treatments for IBD include anti-inflammatory drugs, immunosuppressive drugs, TNF antagonists and surgical removal of sections of bowel. We sought to develop a treatment for IBD that would act locally in the bowel, aiming to avoid the risks of systemic immunosuppression. The food bacterium *Lactococcus lactis* (L.lactis) has been engineered to express potentially therapeutic proteins with the aim of treating IBD. Following ingestion, engineered L.lactis can deliver proteins locally to gut tissue, and engineered L.lactis has been shown to be safe in IBD patients. IL-27 is reported to have both inhibitory and stimulatory effects on the immune system, however a genetic association of IBD with low IL-27 production has recently been reported. To test a therapeutic potential of IL-27, we engineered it into L.lactis. IBD was induced by transfer of CD45Rb(hi) T cells into Rag1^{-/-} mice, and after symptoms of IBD developed, L.lactis-IL-27 was administered daily by gavage. Whereas control mice died by 7wks after T cell transfer, L.lactis-IL-27 treatment rescued all recipients and restored normal colon histology. This striking therapeutic benefit was associated with decreases in inflammatory cytokines and induction of IL-10 in colon tissue. These studies suggest that, despite the pro-inflammatory activities of IL-27 observed in some contexts, immunosuppression at the local site in the bowel offers a promising therapeutic potential.

2:35 **Immunomodulation: Central Dilemma of Uncoupling Efficacy from Systemic Inflammation**

M. Lamine Mbow, Ph.D., Unit Head, Immunology, **Novartis Vaccines and Diagnostics**

Despite their obvious benefits, decades of research and hundreds of pre-clinical candidates, only a handful of adjuvants are approved for prophylactic vaccination of humans. The slow pace of development is due to a number of knowledge gaps, the most important of which is the complexity involved in designing adjuvants that are both potent and well tolerated. Recent advances in our understanding of innate immunity have led to the identification of immune pathways and adjuvant formulations more suitable for clinical advancement. One area of particular interest is the discovery of agonists that target the toll-like receptors. Recent advances in the rational design of novel adjuvants that are both potent and safe will be discussed.

Benefits of my talk:

1. Novel concept in immunomodulation
 - a. Rational design of safe and effective immunomodulatory agents (focus on vaccine adjuvants)
 - b. Novel small molecule agonists as immunomodulatory agents
 - c. Challenges dogma with novel findings on minimum requirements to generate safe and effective adjuvants

Speaker Bio:

Lamine received his PhD in Immunology from the University of Neuchâtel (Switzerland) working on the local skin immune response against ectoparasitic infections. Lamine

performed his postdoctoral training at the Centers for the Disease Control and Prevention (CDC; Colorado) and at Colorado State University working on the host immune response to infectious agents. Lamine joined Centocor, Inc, a Johnson & Johnson company where he worked on several areas including innate immunity and technologies to improve the development of therapeutic monoclonal antibodies. Lamine moved to Novartis Vaccines & Diagnostics to work on innate immunity and novel adjuvant discovery.

3:00 **Therapeutic Approaches in Development for the Treatment of Systemic Lupus Erythematosus**
Barbara White, UCB

3:30 **Conference Concludes**

Submitted Abstracts

121



Attend **ALL 2011 GTCbio Conferences** for only \$3000.
[Click here](#) to sign up!