Signals

THE **INTERNATIONAL CYTOKINE AND INTERFERON SOCIETY** NEWSLETTER

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IN THIS ISSUE:

Brendan J. Jenkins

Paul J. Hertzog

Dear Meeting Attendees,

On behalf of the Scientific Organizing Committee, we would like to welcome you to the 2nd Annual Meeting of the International Cytokine and Interferon Society (ICIS). In particular, we appreciate those of you who have travelled a long way to come to Melbourne. The meeting will provide an outstanding forum for basic science and clinical researchers to present their latest data and exchange ideas relating to the broad role of cytokines, interferons and pattern recognition receptors in human disease, and applications to therapies.

There will also be networking opportunities for researchers in the biotechnology and pharmaceutical industries, and we believe the blend of senior scientists and physicians, as well as graduate students and post-doctoral fellows will help ensure a vibrant and exciting conference for all. For this purpose, keynote, symposia and mini-symposia sessions will be based around topics including the biology, signal transduction and gene regulation related to cytokines and interferons and their receptors in innate and adaptive immunity, pattern recognition receptors and their role in host-pathogen interactions, infectious diseases, inflammation, cancer, autoimmunity and metabolism. Importantly, these sessions will be complemented by several poster sessions which we encourage you to attend since these are often where our emerging younger scientists are presenting. All of these themes are aligned with the well-recognized strengths of the many world-class research institutions in Australia, as well as the research interests of the broader ICIS membership.

In addition to this exciting scientific program, we hope that you will take the time to experience the sights and multicultural flavours of Melbourne, voted 3 times in a row (2011-2013) as "the world's most liveable city", and its beautiful surrounds, as well as visit other major cities in Australia which also frequently list in the top 20 of the best cities in the world to live in.

The dissemination of knowledge that takes place at such eminent international meetings and the interactions and collaborations that are established are essential for future advances in biomedical research. Finally, we would like to express our gratitude to the substantial support provided by numerous companies, foundations, and institutes, which will ensure the success of our meeting.

We welcome you "Down Under" in what promises to be an exciting meeting.

Sincerely,
Brendan J. Jenkins and **Paul J. Hertzog**
(Co-convenors)

Future Meetings

2014 Meetings

Cytokines2014
Oct. 26-29, 2014
Melbourne, Australia

Cytokines2015
Oct. 11-14, 2015
Bamberg, Germany

Newsletter Editors

Howard Young
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Marta Catalfamo

ICIS
International Cytokine & Interferon Society

2014 ICIS AWARD WINNER

THE MILSTEIN AWARD

DR. STEFANIE N. VOGEL

Professor of Microbiology and Immunology
Professor of Medicine
University of Maryland School of Medicine
Baltimore, MD

Dr. Stefanie Vogel received her Ph.D. from the University of Maryland, College Park in 1977 and then did postdoctoral research at the National Institute of Dental Research; Laboratory of Microbiology and Immunology, NIH under Dr. Joost Oppenheim where she characterized inheritance and mapped the *Lps* gene in macrophages and showed that interferons, and particularly endogenous IFN-b production by macrophages, contributed significantly to macrophage responses to bacterial products such as LPS. In 1980, she began a 22 year academic career at the Uniformed Services University of the Health Sciences, Bethesda, MD where she rose to the rank of Professor. In 2002, she joined the University of Maryland School of Medicine as Professor of Microbiology and Immunology and Professor of Medicine. Throughout her career, she has had continuous NIH grant support for her research (including an NIH Merit Award) and has received numerous invitations to speak on her current studies at many national and international meetings, including the NIH Immunology Interest Group, the American Association of Immunologists, the former ISICR, the International Endotoxin and Innate Immunity Society, the Society for Leukocyte Biology, and Toll Meetings. Her CV lists over 290 peer-reviewed publications, many in high impact journals, 37 book chapters and reviews and 5 patents. To date, she has mentored 35 post-doctoral fellows and 11 graduate students, and is currently director of a NIH Training Grant, Signaling Pathways in Innate Immunity.

Dr. Vogel's research is focused on the capacity of macrophages to respond to bacterial products such as the endotoxic lipopolysaccharide (LPS) of Gram negative bacteria. Their studies on the role of Toll-like receptors (TLRs) in this process has led to the dissection of intracellular signaling pathways that define TLR responses to different pathogens, suggesting that these receptors have evolved to enable the host to respond appropriately to specific pathogens. In addition to examining the expression of a variety of proinflammatory genes and interferons as a consequence of exposure of macrophages to LPS and other microbial products, the Vogel laboratory is also actively studying mechanisms by which the inflammatory response to infection is controlled in mice and in humans. Specifically, they have utilized a paradigm of in vitro and in vivo "endotoxin tolerance"˜ in which macrophages or mice exposed to a relatively low dose of LPS become transiently refractory to subsequent challenge to a variety of TLR agonists. An analysis of the kinase and DNA binding activities of signaling components involved in the TLR4 and TLR2 signaling pathways have been examined systematically by her group, in addition to studies that demonstrate dysregulated interactions among intracellular proteins required for this activation. This is best exemplified by work carried out by her group that identified the underlying genetic defect in a child with severe, recurrent bacterial infections as an IRAK4 deficiency. Lastly, the Vogel laboratory has also pursued mechanisms of inflammatory damage in many animal models where cytokines and IFNs figure centrally in disease progression, pathology, and resolution (*e.g.*, stroke, encephalitic viruses, cecal ligation and puncture-induced polymicrobial sepsis, hemorrhagic shock, Respiratory Syncytial Virus (RSV) infection, and more recently, influenza infectoin). The work in the Vogel laboratory is highly translational: using TLR4 antagonists to block influenza-induced acute lung injury, the re-purposing of FDA-approved drugs that increase expression of M2 macrophages to resolve RSV-induced pathology, and development of a TLR2 antagonist using Computer Aided Drug Design to target a region within the TLR2 TIR domain, are all examples of her most recent efforts to apply our basic understanding of the role of cytokines and interferons to the resolution of diseases.

2014 ICIS AWARD WINNER

THE MILSTEIN AWARD

DR. KATHERINE A. FITZGERALD

Professor of Medicine
University of Massachusetts Medical School
Worcester, MA

Dr. Fitzgerald received her B.Sc. in Biochemistry in 1995 from University College Cork, Ireland, and her Ph.D. in 1999 from the laboratory of Professor Luke O'Neill in Trinity College Dublin, Ireland. From 1999 to 2002, she was a post-doctoral fellow in the Department of Biochemistry at Trinity College Dublin. Dr. Fitzgerald joined the Division of Infectious Disease at the University of Massachusetts Medical School as a recipient of a Wellcome Trust International Award in 2001. In 2004 she joined the Faculty as an Assistant Professor. She is currently Professor of Medicine and Director of the Program in Innate Immunity.

Research in the Fitzgerald laboratory is focused on all things related to innate immunity and the inflammatory process, with signal transduction and gene regulation being her particular area of expertise. Active research areas include: (1) biology and role of inflammasomes in anti-microbial immunity (2) cytosolic nucleic acid recognition systems in anti-viral defense and autoimmune disease, (3) long non-coding RNAs in the immune system and (4) innate immunity to Malaria. Enabling these studies, her research spans the disciplines of immunology, cell and molecular biology, biochemistry and genetics.

Dr. Fitzgerald entered the field of immunology by discovering Mal/TIRAP, a central adapter in TLR4 signaling. Since then, she has discovered TRAM, an adapter molecule important downstream of TLR4 in controlling interferon production. Since starting her own lab at UMASS, she has made multiple discoveries that have continued to impact our understanding of host-pathogen interactions. These include the discovery of TBK1/IKKe responsible for the activation of IRF3 and IRF7. Dr. Fitzgerald has also made major contributions to our understanding of the inflammasome where she identified the AIM2 inflammasome *important* in host-defense to viruses and bacteria. Recent studies have advanced our understanding of how Gram negative bacteria are detected by the NLRP3 inflammasome. Her lab identified a TRIF dependent pathway that licenses NLRP3 inflammasome activation through engagement of the caspase-11 protease. Finally, newer work in her lab has begun to examine the impact of long non-coding RNA species which are induced during host-pathogen interactions and which in turn act to coordinate transcriptional responses in innate immunity.

The Milstein Award

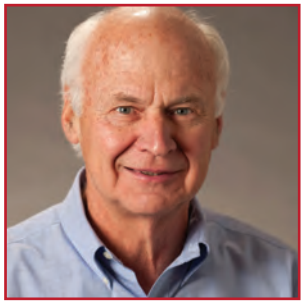
The Seymour and Vivian Milstein Award for Excellence in Interferon and Cytokine Research, represents the pinnacle of scientific achievement in interferon and cytokine research. This Award is bestowed upon a leading biomedical research scientist who has made outstanding contributions to interferon and cytokine research, either in a basic or applied field. Many laureates have made seminal advancements that have enabled the successful treatment of disease or have the potential to lead to significant health benefits.

2014 ICIS AWARD WINNER

HONORARY LIFETIME MEMBERSHIP

Honorary Lifetime Membership Award

The Honorary Lifetime Membership Award is made to individuals who have made substantive contributions to the interferon/cytokine field over much of their careers, either in basic, clinical or applied research. Honorary members are the treasures of the society and provide us with an historical perspective and valued research tradition.



CHARLES E. SAMUEL, PH.D.

D.A. Storke II Professor
Molecular, Cellular, and Developmental Biology
University of California, Santa Barbara
Santa Barbara, CA

Charles Samuel is the C. A. Storke II Professor at the University of California at Santa Barbara. He earned a B.S. in Chemistry from Montana State University and his Ph.D. in Biochemistry from U.C. Berkeley. He was a Damon Runyon Scholar at Duke University Medical School where he began work on interferon action. Research of the Samuel Laboratory has focused on the regulation and function in virus-infected as well as uninfected cells of PKR and ADAR1, two IFN-inducible enzymes that are also double-stranded RNA binding proteins. PKR, an RNA-dependent protein kinase, controls the translational pattern in cells through phosphorylation of initiation factor eIF2a. ADAR1, an RNA-specific adenosine deaminase, catalyzes the C-6 deamination of adenosine to yield inosine in RNAs with double-stranded character, thereby leading to genetic recoding and altered RNA structure as I base-pairs as G instead of A.

At UCSB Dr. Samuel has served as Director of the Interdepartmental Biochemistry & Molecular Biology Program (BMSE) from 1987-95, as Founding Chair of the Department of Molecular, Cellular & Developmental Biology from 1995-98, and again as MCDB Chair from 2001-04. He is an NIH Research Career Development Awardee, an NIH MERIT awardee, a FASEB Wellcome Professorship awardee, a Humboldt Forschungspreis recipient, and an elected Fellow of the American Association for the Advancement of Science and the American Academy of Microbiology. He is an Associate Editor of the Journal of Biological Chemistry, and Journal of Interferon and Cytokine Research, and serves on the editorial board of the Journal of Virology. He was President of the ISICR in 2012 and served as co-President of the ICIS in 2013.

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AMANDA PROUDFOOT, PH.D.

Amanda Proudfoot received an Honours Degree in Biochemistry from the University of Witwatersrand, Johannesburg, South Africa and a Ph.D. in Biochemistry from the University of Geneva, Switzerland. She worked as a postdoctoral fellow in the Department of Medical Biochemistry, University of Geneva before joining the Glaxo Institute for Molecular Biology, Geneva, in 1988. Since 1994 she has concentrated on the Chemokine family, first at Glaxo Wellcome's Geneva Biomedical Research Institute. This interest continued when the institute became the Serono Pharmaceutical Research Institute (SPRI) and recently the Merck Serono Geneva Research Centre. Her current research interests concentrate on chemokine receptor antagonists, including modified chemokines and chemokine binding proteins, to supplement small molecule and antibody programs.

2014 ICIS DISTINGUISHED SERVICE AWARD

CHRISTINE W. CZARNIECKI, PH.D.

National Institute of Allergy and Infectious Disease

Dr. Czarniecki received her Ph.D. training at Georgetown University School of Medicine where she studied Sindbis virus RNA replication in the laboratory of Dr. T. Sreevalsan. That work led to a post-doctoral staff fellowship with Dr. Robert Friedman at the National Institutes of Health where her research focused on the biological and biochemical mechanisms of antiviral and antiproliferative actions of interferon. The mentorship from these two interferon research pioneers was invaluable to her establishment of research collaborations and long-term friendships with many international interferon and cytokine researchers. Genentech, Inc. – with their initial cloning and manufacture of numerous different interferon molecules - offered Dr. Czarniecki the ideal setting to: pursue her interests in structure/function relationships of interferons with the goals of separating the different activities ascribed to the molecules; and to conduct translational research that would support initiation of clinical trials that could lead to product licensure. Over 12 years at Genentech she held positions of increasing responsibility, first in the Pharmacology Department where she led a group responsible for the nonclinical efficacy studies of Interferon gamma and other cytokines in animal disease models (e.g. sepsis, malaria, chlamydia, candidiasis) and later in the Department of Regulatory Affairs where she wrote sections of Genentech's FDA application for licensure of Actimmune (Interferon gamma-1b). She is an inventor on several Genentech patents that were based on her research. She continued to expand her drug development experience as Head of Regulatory and Quality at several start-up biopharmaceutical companies (ICOS, AXYS, InterMune) before finding her way back to NIH in 2001 where she currently holds the position of Chief of the Office of Regulatory Affairs in the Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Disease. Her office oversees the global regulatory oversight of 100 clinical trials being conducted by NIAID at over 800 clinical sites. She is also an adjunct Associate Professor at Georgetown University where she lectures on Pharmaceutical drug development and FDA oversight of clinical trials.

In 1990, Dr. Czarniecki joined Dr. Budd Colby, Dr. Lois Epstein and Dr. Chuck Samuel as organizers of the annual meeting of the International Society of Interferon Research (ISICR) held in San Francisco and the experiences gained from that meeting led to her appointment in 1993 as the Chair of the ISICR Meetings Committee. In 2008 she worked with Dr. Carl Ware of the International Cytokine Society (ICS) to establish the Joint ISICR/ICS Meetings Committee and together they co-chaired that committee until 2014. Since becoming a member of the ISICR in 1980, she also served on the Editorial Board of the Journal of Interferon Research, as US Delegate to the Society and as member of the Membership and Newsletter Committees. Based on these many, notable contributions to ISICR and now ICIS, Dr. Czarniecki was chosen for the 2014 ICIS Distinguished Service Award.

2014 ICIS Awards

2014 Milstein Young Investigator Awardees:

Dominic De Nardo
Institute of Innate Immunity
University of Bonn
Bonn, Germany

Stacy Horner
Molecular Genetics and Microbiology
Duke University Medical Center
Durham, NC

Maria Liaskos
Centre for Innate Immunity and Infectious Diseases
MIMR-PHI Institute of Medical Research
Melbourne, Australia

Seth Masters
Inflammation Division
The Walter and Eliza Hall Institute
Victoria, Australia

Kate Schroder
Institute for Molecular Bioscience
The University of Queensland
Brisbane, Australia

2014 Christina Fleischmann Awardee:

Sophie Broughton
St Vincents Institute For Medical Research
Victoria, Australia

2014 ICIS Journal of Biological Chemistry Herbert Tabor Awardee:

Yeonseok Chung
Seoul National University
Seoul, South Korea

2014 ICIS Sidney and Joan Pestka Awardees

Graduate Student Award:

Annie Bruns
Molecular Biosciences
Northwestern University
Evanston, IL

Postgraduate Award:

Amanda Huber
Neurology
University of Michigan
Ann Arbor, MI

NEW ICIS MEMBERS

We welcome these new members to the ICIS and look forward to their participation in the annual meeting and in the society.

Suad Abdirahman
Walter and Eliza Hall Inst
Australia

Inna Afonina
Inflammation Research Center
Belgium

Ines Amado
Pasteur Institute
France

Yuriy Baglaenko
Univ of Toronto
Canada

Paul Baker
Walter and Eliza Hall Inst
Australia

Marcin Baran
Trinity College Dublin
Ireland

Marie Bodinier
INRA
France

Gregory Bouchard
INRA
France

Sophie Broughton
St Vincents Inst
Australia

Vipin Bulani
Inst of Chemical Tech
India

Rebecca Coll
Inst for Molecular Bioscience
Australia

James Collier
Pennington Biomedical Research Ctr
USA

Laura Dagley
Walter & Eliza Hall Inst
Australia

Dominic De Nardo
Institute of Innate Immunity
Germany

Colleen Elso
St. Vincents Inst
Australia

Yen Fong
Univ Putra Malaysia
Malaysia

Jane Grogan
Genentech
USA

Timothy Hercus
Centre for Cancer Biology
Australia

Jeremy Hirota
Univ of British Columbia
Canada

Seungmin Hwang
University of Chicago
USA

Detlef Jakschies
AOP Orphan Pharmaceuticals AG
Austria

So Ri Jung
University of Sydney
Australia

Thirumala-Devi Kanneganti
St Jude Children's Hospital
USA

Lukasz Kedzierski
Walter and Eliza Hall Inst
Australia

Katrian Ki
Australian Red Cross Blood Service
Australia

Taeil Kim
Baylor Inst for Immunology Research
USA

Tatiana Kolesnik
Walter and Eliza Hall Inst
Australia

Pankaj Kothavade
Inst of Chemical Tech
India

Florian Kurschus
Univ Medical Ctr of the Johannes Gut Univ
Germany

Chun Wang Lao
MIMR-PHI of Medical Research
Australia

NEW ICIS MEMBERS

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Katie Lawlor
Walter and Eliza Hall Inst
Australia

Soyoung Lee
Osaka University
Japan

Maria Liaskos
MIMR-PHI Inst of Med Rsch
Australia

Carolina Lopez
University of Pennsylvania
USA

Pei Ching (Regine) Low
UCL Cancer Inst-Univ College London
United Kingdom

Ellen Menkhorst
Ctr for Reproductive Health
Australia

Andrew Murphy
Baker IDI Heart & Diabetes Inst
Australia

Jae-Hwan Nam
The Catholic Univ of Korea
Republic Of Korea

Theng Ng
Univ Putra Malaysia
Malaysia

Tan Nguyen
Walter and Eliza Hall Inst
Australia

Robert O'Donoghue
Walter and Eliza Hall Inst
Australia

Olusegun Onabajo
National Cancer Institute, NIH
USA

Ken Pang
Walter and Eliza Hall Inst
Australia

Hye-Lim Park
The Catholic Univ of Korea
Republic of Korea

Sowmya Pattabhi
Univ of Washington
USA

Cathleen Pfefferkorn
Inst for Virology
Germany

Silvia Preite
Inst for Research in Biomedicine
Switzerland

Kylie Quinn
University of Melbourne
Australia

Mahesh Raundhal
Univ. of Pittsburgh School of Medicine
USA

Ina Rudloff
MIMR-PHI Inst of Medical Research
Australia

Marvin Sandoval
NYU School of Medicine
USA

William Schneider
Rockefeller University
USA

Kate Schroder
The University of Queensland
Australia

Jason Twohig
Inst of Infection & Immunology
United Kingdom

Antiopi Varelias
BMT Lab
Australia

Shih-Min Wang
National Cheng Kung Univ & Hospital
Taiwan

Raphaela Goldbach-Mansky, M.D

Paper of Interest

Activated STING in a Vascular and Pulmonary Syndrome

Liu Y[1], Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GA, Tenbrock K, Wittkowski H, Jones OY, Kuehn HS, Lee CC, DiMattia MA, Cowen EW, Gonzalez B, Palmer I, DiGiovanna JJ, Biancotto A, Kim H, Tsai WL, Trier AM, Huang Y, Stone DL, Hill S, Kim HJ, St Hilaire C, Gurprasad S, Plass N, Chapelle D, Horkayne-Szakaly I, Foell D, Barysenka A, Candotti F, Holland SM, Hughes JD, Mehmet H, Issekutz AC, Raffeld M, McElwee J, Fontana JR, Minniti CP, Moir S, Kastner DL, Gadina M, Steven AC, Wingfield PT, Brooks SR, Rosenzweig SD, Fleisher TA, Deng Z, Boehm M, Paller AS, Goldbach-Mansky R.

N Engl J Med. 2014 Jul 16. [Epub ahead of print]

Abstract

Background The study of autoinflammatory diseases has uncovered mechanisms underlying cytokine dysregulation and inflammation. Methods We analyzed the DNA of an index patient with early-onset systemic inflammation, cutaneous vasculopathy, and pulmonary inflammation. We sequenced a candidate gene, TMEM173, encoding the stimulator of interferon genes (STING), in this patient and in five unrelated children with similar clinical phenotypes. Four children were evaluated clinically and immunologically. With the STING ligand cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), we stimulated peripheral-blood mononuclear cells and fibroblasts from patients and controls, as well as commercially obtained endothelial cells, and then assayed transcription of IFNB1, the gene encoding interferon-β, in the stimulated cells. We analyzed IFNB1 reporter levels in HEK293T cells cotransfected with mutant or nonmutant STING constructs. Mutant STING leads to increased phosphorylation of signal transducer and activator of transcription 1 (STAT1), so we tested the effect of Janus kinase (JAK) inhibitors on STAT1 phosphorylation in lymphocytes from the affected children and controls. Results We identified three mutations in exon 5 of TMEM173 in the six patients. Elevated transcription of IFNB1 and other gene targets of STING in peripheral-blood mononuclear cells from the patients indicated constitutive activation of the pathway that cannot be further up-regulated with stimulation. On stimulation with cGAMP, fibroblasts from the patients showed increased transcription of IFNB1 but not of the genes encoding interleukin-1 (IL1), interleukin-6 (IL6), or tumor necrosis factor (TNF). HEK293T cells transfected with mutant constructs show elevated IFNB1 reporter levels. STING is expressed in endothelial cells, and exposure of these cells to cGAMP resulted in endothelial activation and apoptosis. Constitutive up-regulation of phosphorylated STAT1 in patients' lymphocytes was reduced by JAK inhibitors. Conclusions STING-associated vasculopathy with onset in infancy (SAVI) is an autoinflammatory disease caused by gain-of-function mutations in TMEM173. (Funded by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases; ClinicalTrials.gov number, NCT00059748 .).

I have interviewed the lead investigator of this work, Raphaela Goldbach-Mansky, M.D., MHS, Acting Chief, Translational Autoinflammatory Disease Section (TADS), National Institute of Arthritis, Musculoskeletal and Skin Diseases, National Institutes of Health and asked her to fill us in with the background that led to this discovery.

Howard Young

What got you interested in Vascular and Pulmonary Syndrome?

My group, the Translational Autoinflammatory Disease Section (TADS) in NIAMS, is interested in evaluating pediatric patients with early onset autoinflammatory diseases, patients who have uncontrolled systemic and organ specific inflammation, such as fever, elevation of acute phase reactants and organ specific inflammation that is not infectious or malignant.

How do patients get classified with this condition?

As mentioned above these patients have systemic inflammation, a specific pattern of destructive vasculitis and pulmonary disease presenting with a restrictive lung pattern and microscopic emphysema. Their clinical similarity is striking and the combination of vasculitis involving the distal phalanges (fingers and toes) with development of gangrene and pulmonary disease is quite unusual.

How many of these patients do you see in a year?
We see over 100 patients with autoinflammatory diseases a year, I saw the first patient with the disease we now call SAVI in 2004, another patient in 2009 one in 2011 one in 2012 and I heard about 2 more between 2013 and now. We tested 2 more patients and heard about another mutation positive SAVI patient in May this year.

Is the disease only inherited or are there sporadic cases?
In all SAVI patients we know of so far the disease is caused by de novo mutations in TMEM173, the gene that encodes STING. One of our patients with SAVI has somatic mosaicism, so the cause for their sporadic disease are de novo mutations, 4 of the 6 we included in the publication have the exact same de novo mutation.

What led you to think that the interferon pathway might be involved?
We had performed cytokines studies and found very high IP-10 level in serum of patients. We had also performed gene expression studies in whole blood and found that interferon response genes were strongly up-regulated. The IP-10 levels were much higher than the levels we observe in patients with IL-1 mediated autoinflammatory diseases who respond well to drugs that block the IL-1 pathway. In contrast to someone just having a viral disease, the IP-10 levels and the interferon signature persisted when the clinical disease was less active, and was present even on treatment with all drugs that these patients had been places on the past.
All above characteristics are observed in another disease we have been studying for the last three years, CANDLE, which we think is an IFN mediated disease.

Given all the genes affected by interferon, did you sequence many of them? If not, what led you to focus on STING?
We hypothesized that the disease may be caused by de novo mutations as we see in patients with other early onset severe autoinflammatory and immunodeficiency diseases. We therefore performed whole exome sequencing in a trio, an index patient and her parents. We wanted to test whether WES of trios would allow us to use the parents' variants to filter the patient's variants and thus detect mutations that occurred de novo in the patient. Dr. Zuoming Deng in NIAMS used our trio samples to develop a pipeline that allowed us to do exactly that, in addition to the typical filters that are commonly used, he filtered the patient's variants against the parents' to reveal de novo mutations. In our index patient there were only three de novo variants that passed the filter, these were only present in the patient but not the parents, one of them was a missense mutation in STING that was predicted by software packages to be damaging due to conservation in many species; the other variants seemed to be false positives. Dr. Yin Liu, the staff scientist in my group had been examining the possibility to block STING in another IFN mediated autoinflammatory disease that we study, so when we saw the results of the whole exome sequencing analysis we were initially skeptical of such a coincidence. But Dr. de Jesus, a visiting fellow performed Sanger sequencing screening on another patient with a similar clinical phenotype who had been seen by a collaborator at the University of Chicago, Dr. Amy Paller. This patient also had a de novo mutation in STING leading to a missense mutation in the amino acid right next to the missense mutation we identified in the first patient. I had seen 2 other patients who I believed had the same clinical disease. One of them in 2004 was as a consult from Dr. Steven Holland's group and indeed Sanger sequencing identified the same mutation we found in patient 1. Another patient referred by 2 collaborators in Germany who we had received samples on was also positive for the same STING mutation. By then we knew that the mutations we had identified were indeed disease causing and started working on functional studies. We ended up sequencing a total of 8 patients with suggestive clinical phenotypes for mutations in STING, 6 of whom had de novo mutations, indicating how phenotypically similar patients with SAVI present.

Can you briefly summarize the consequences of the mutation to the interferon pathway?
Clinically, the mutations we identified seemed to confer a gain of function in STING. The mutations are closely clustered in or near an area of STING named "dimerization interface", and STING was known to function as a dimer. This was confusing as most mutations tested experimentally in this area of STING led to loss of function. So Drs. Liu and Marrero in my group performed transfection studies and found that STING constructs with the disease associated mutations but not wildtype STING constructs caused constitutive IFNβ reporter transcription. In collaboration with Dr. Paul Wingfield's laboratory we found that recombinant STING protein with the disease associated mutations forms stable dimers, like wild type STING. In my group we also confirmed constitutive activation of the STING –IFNβ pathway in PBMCs of patients. Specifically, IFNβ is constitutively transcribed in patients' PBMCs and STAT1 are maximally phosphorylated in patients' cells without stimulation. In endothelial cells, STING activation leads to endothelial cell activation and damage, suggesting a mechanism for the vasculitis seen in the patients.

Now knowing the cause of the syndrome, will it change how the patients are treated? What does the future hold for them?
These findings have already changed our treatment approach and will do that further in the future. We have conducted studies blocking the IFN pathway using several pan-JAK inhibitors in in vitro studies that indicate that the STING-IFNβ pathway is activated in an autocrine fashion in a feed-forward loop mediated by IFN signaling. Blocking the JAK pathway and thus inhibiting IFN signaling led to a decrease in the activation

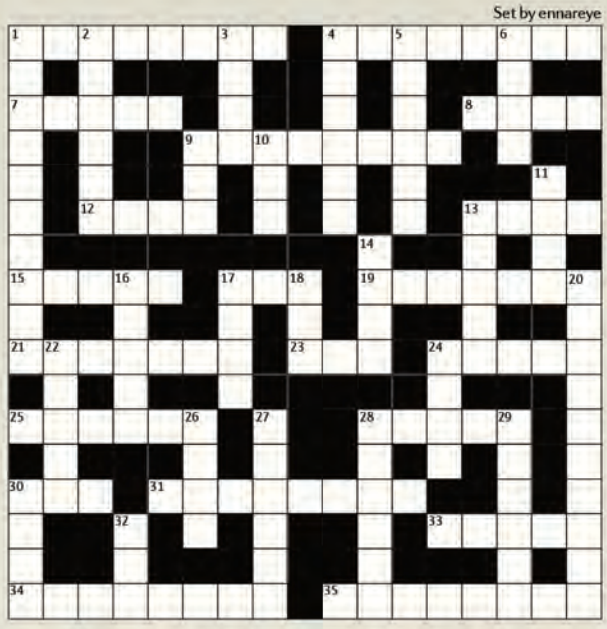
of interferon response genes and in reduction in TMEM173/STING transcription. We are using the Jak inhibitor (Jakinib) baricitinib (Lilly) in a compassionate use study to treat SAVI patients and patients with other immunedysregulatory diseases we believe may be interferon mediated. The interferon signaling pathway has never been blocked in patients with autoinflammatory diseases and the discovery of SAVI provides genetic evidence of immune dysregulation in the interferon pathway leading to an autoinflammatory phenotype. Given the role of STING as a gatekeeper of interferon beta signaling that is "coordinating" IFNβ transcription triggered by a number of upstream pathways, targeting STING directly would likely be an efficient way to treat not only SAVI patients; blocking STING may emerge as a treatment strategy in other conditions that are thought to be interferon mediated.

What other diseases are you investigating and do you expect to find more connections to the cytokine/interferon pathways?

We follow a number of patients who have strong interferon signatures in the blood and systemic and organ specific inflammation. These patients may ultimately have other mutations in the interferon pathway. We follow patients with inflammatory diseases caused by mutations in the IL-1 pathway that either have constitutively increased IL-1 production or lack inhibition of IL-1 signaling. These patients can successfully be treated with IL-1 blocking agents. We found patients with dysregulation in the IL-18 plus IL-1 pathways and in NF-κB signaling in keratinocytes that all lead to immune dysregulatory phenotypes presenting primarily with sterile excessive and continuous inflammation.

To celebrate the 10th anniversary of *Nature Reviews Immunology*, we have 'cross presented' some words for you in this immunology-themed puzzle. An online version of the crossword is available at www.nature.com/nri/pdf/crossword.pdf and the answers will be published in our November 2011 issue. Good luck!

Set by ennareye



Across

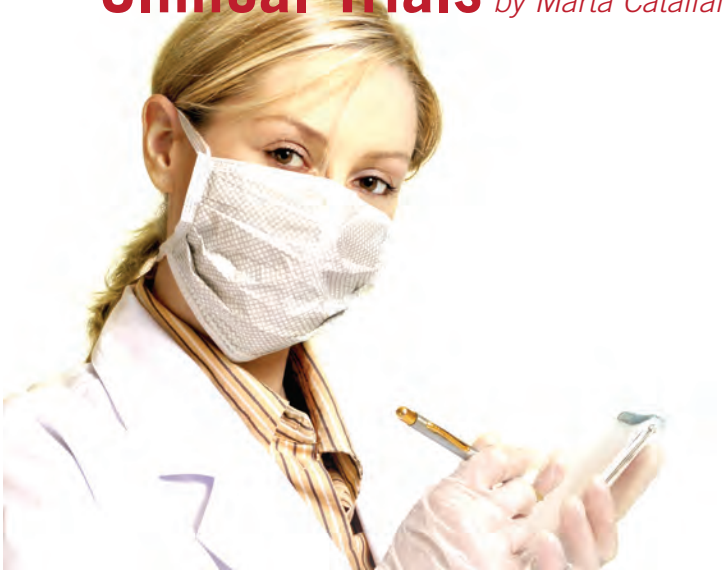
1. Sounds like this white blood cell has only one eye (8)
4. Receptor, similar to a road charge (4-4)
7. Activated T cells go for a ride (5)
8. A protein you can deal with (4)
9. Defence against invasion, either innate or adaptive (8)
12. A part of the globe such as you'd find in the thymus (4)
13. A protein that's on the rails (4)
15. The price to pay for hypersensitivity (5)
17. A type of oxygen in prose (3)
19. The pit opens to reveal a piece of antigen (7)
21. Changing receptors will save a cell's life (7)
23. A family of proteins amongst fussy kin (3)
24. See 28 down
25. A disease that could leave you breathless (6)
28. A class of molecules that pampers without hesitation (5)
30. Subepithelial dome, initially found in gut (3)
31. 2 and 20 down are angular, right? (8)
33. A signalling pathway that leaves its mark (5)
34. Protein molecule in the tonic key (8)
35. In the lab, I shop for this leukocyte (8)

Down

1. Could this cell poach a germ? (10)
2. A born assassin (2,4)
3. A protein that's a cut above the rest (4)
4. A mesmerizing cytokine (6)
5. This client can activate the immune system (6)
6. A signal transducer that sounds like it comes from the middle-East (4)
9. For example, I bind to allergens in reverse (3)
10 and 27. Which way to phosphorylation? The chart says something akin to South-East... (3,6)
11. Protein that could shed some light on organelles (4)
13. A trite way of expressing concentration in the UK (5)
14. Chemokine that sounds like a detective, in short (4)
16. Found on Johann's old clothes, or in the ileum? (5)
17. This multi-ligand receptor sounds furious! (4)
18. Exchange factor? Help! (3)
20. White blood cells I pool shine in acid (10)
22. Is there such a space for APCs in the liver? (5)
24. Molecule one might find living in a field? (4)
26. This regulator sounds fresh (4)
27. See 10 down
28 and 24 across. I hear blood's liquid component flies off the shelves! (6,5)
29. Class act for antibody production (6)
30. This synapse sounds like a hit! (4)
32. Enzyme one might find on a bride's lips (3)

Answers: page 26. Reprinted with Permission: Nature Publishing Group

Clinical Trials *by Marta Catalfamo*



Interleukin-1 Blockade in HF With Preserved EF (D-HART2) Sponsor:Virginia Commonwealth University
Collaborator: National Heart, Lung, and Blood Institute (NHLBI)
ClinicalTrials.gov Identifier: NCT02173548
Principal Investigator: Antonio Abbate, MD, PhD
Virginia Commonwealth University
Principal Investigator: Benjamin Van Tassell, PharmD
Virginia Commonwealth University
Contact: Antonio Abbate, MD, PhD
804-828-0513 aabbate@vcu.edu

Inflammation in Chronic Kidney Disease and Cardiovascular Disease - The Role of Genetics and Interleukin-1 Receptor Antagonist (IL-1ra)
Sponsor: Department of Veterans Affairs
ClinicalTrials.gov Identifier: NCT00897715
Principal Investigator: Adriana M Hung, MD MPH
Department of Veterans Affairs
Contact: Cindy A Booker (615) 343-5828
cindy.a.booker@vanderbilt.edu

Systemic Therapy With Interferon, Interleukin-2 and BRAF Inhibitor
Sponsor: M.D. Anderson Cancer Center
ClinicalTrials.gov Identifier: NCT01603212
Principal Investigator: Rodabe N. Amaria, MD UT MD Anderson Cancer Center
Contact: Rodabe N. Amaria, MD 713-792-2921

Evaluation of the Efficacy and Tolerability of Treatment With Interleukin-2 in Severe and Resistant Alopecia Areata (IL2)
Sponsor: Centre Hospitalier Universitaire de Nice
ClinicalTrials.gov Identifier: NCT01840046
Principal Investigator: Thierry Passeron, PhD
CHU de Nice - Hôpital de l'Archet - Dermatology
Contact: Thierry Passeron, PhD
+33494026488 passeron.t@chu-nice.fr

Role of Interleukin-6 in Exercise (Exil-6) Sponsor:University of Zurich
Collaborator: European Foundation for the Study of Diabetes
ClinicalTrials.gov Identifier: NCT01073826
Study Director: 01 Studienregister MasterAdmins
UniversitaetsSpital Zuerich
Contact: Marc Donath, Prof. Dr.
061 265 25 25 donathm@uhbs.ch

Adipocyte, Insulin-resistance and Immunity : Evaluation of Interleukin-7 in Lipodystrophy, Diabetes and Obesity (IL-7norm)
Sponsor: University Hospital, Lille
ClinicalTrials.gov Identifier: NCT01784289
Principal Investigator: Marie Christine Vantyghem, Ph. D.
Lille University Hospital
Contact: Marie Christine Vantyghem, MD PhD
+33 3 20 44 45 35 mc-vantyghem@chru-lille.fr

A Phase III Study of Genetically Modified Recombinant Human Interleukin-11 (mIL-11-III)
Sponsor: Beijing Northland Biotech. Co., Ltd.
ClinicalTrials.gov Identifier: NCT01663441
Principal Investigator: Shikai Wu, M.D.
Contact: Shanshan Ma, Master
86-10-82890893 ext 19 mashanshan@northland-bio.com

Interleukin-12 Gene and in Vivo Electroporation-Mediated Plasmid DNA Vaccine Therapy in Treating Patients With Merkel Cell Cancer
Sponsor: OncoSec Medical Incorporated
Collaborator: National Cancer Institute (NCI)
ClinicalTrials.gov Identifier: NCT01440816
Principal Investigator: Shailender Bhatia
Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium
Contact: Nichole Real 206-288-7476 nreal@seattlecca.org

Tumor Infiltrating Lymphocytes (TIL) Transduced With TGFbDNRII
Sponsor: M.D. Anderson Cancer Center
Collaborator: CPRIT
ClinicalTrials.gov Identifier:NCT01955460
Principal Investigator: Patrick Hwu, MD
M.D. Anderson Cancer Center
Contact: Patrick Hwu, MD 713-792-2921

A Two-Part, Phase 1, Single-Dose Study of IL-31 mAb (Anti-Interleukin 31 Monoclonal Antibody); in Healthy Subjects and Adults With Atopic Dermatitis
Sponsor: Bristol-Myers Squibb
ClinicalTrials.gov Identifier: NCT01614756
Study Director: Bristol-Myers Squibb
Contact: Clinical.Trials@bms.com
Contact: First line of the email MUST contain NCT# and Site #.

DNX-2401 (Conditionally Replicative Adenovirus) With Interferon Gamma (IFN-γ) for Recurrent Glioblastoma or Gliosarcoma Brain Tumors (TARGET-I)
Sponsor: DNAtrix, Inc.
ClinicalTrials.gov Identifier: NCT02197169
Contact: DNAtrix, Inc.

The Effects of Interferon-gamma on Sepsis-induced Immunoparalysis
Sponsor: Radboud University
ClinicalTrials.gov Identifier: NCT01649921
Principal Investigator: Peter Pickkers, MD, PhD
Radboud University
Contact: Peter Pickkers, MD, PhD 0031-24-362378
P.Pickkers@ic.umcn.nl

New Member MINIBIOs

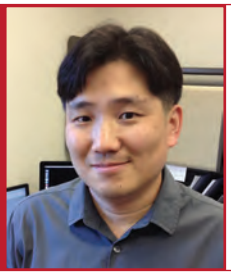
Dr. Jeremy Hirota
Department of Medicine
University of British Columbia

My main research interests revolve around respiratory mucosal immunology in the context of airway disease. For my research program I use a translational approach consisting of in vitro studies with primary human airway epithelial and dendritic cells, in vivo mouse models of airway disease, and clinical samples from well phenotyped patients following controlled environmental exposures. My research program focuses on identifying the mechanisms governing how environmental exposures can contribute to allergic sensitization and exacerbations of asthma. To this end, I induce inflammatory responses in human airway epithelial cells and determine how these influence adaptive immunity and chronic inflammation. I am able to induce inflammatory responses using a variety of methods including exposure to urban particulate matter, diesel exhaust particles, allergens, and viruses in both single and multi-exposure models. I parallel my in vitro studies with in vivo models using genetically modified mice that will allow me to explore mechanisms of allergic sensitization in an intact organism. Lastly, I use clinical models and isolated samples from well phenotyped patients to test and confirm observations observed in my in vitro and in vivo studies. My research platform will be focused on asthma but will be adaptable to explore other respiratory diseases including cystic fibrosis and COPD.

Antiopi Varelias, PhD
QIMR Berghofer Medical Research Institute
Bone Marrow Transplantation Laboratory
Brisbane, Queensland, Australia

Dr. Antiopi Varelias was awarded her PhD from The University of Adelaide, Australia, in 2002. Her doctoral studies focused on cell adhesion molecules and their role in Renal Transplantation. Subsequently, she undertook post-doctoral positions which allowed her to investigate molecular and cellular mechanisms of several diseases in the fields of bone cancers, leukaemia, vascular disease and wound healing. In 2008, she joined the Bone Marrow Transplantation laboratory at QIMR Berghofer, Brisbane, Australia, headed by Professor Geoffrey Hill. Dr Varelias's research has focused on investigating mechanisms which underlie graft-versus-host disease (GVHD), one of the major complications following haematopoietic stem cell transplantation (HSCT), which limits its use as a therapy for haematological malignancies. Her research has focused on the role of cytokines, particularly IL-6 and IL-17 in regulating GVHD in pre-clinical models and in clinical correlative studies, the later which has provided the basis for a Phase I/II clinical trial to examine the efficacy of IL-6 inhibition to prevent acute GVHD following allogeneic HSCT.

New Member MINIBIOs



Seungmin "Sam" Hwang, Ph.D.
Assistant Professor
Department of Pathology
University of Chicago
Chicago, IL
seungminhwang@uchicago.edu

Seungmin Hwang earned his B.S. and M.S. degrees from the Korea Advanced Institute of Science and Technology and then moved to the U.S.A. for his doctoral training at the University of California, Los Angeles (UCLA). After obtaining his Ph.D. and short postdoctoral training at UCLA, he completed his postdoctoral training in Washington University in St. Louis under the mentorship of Herbert "Skip" Virgin, M.D., Ph.D. and started his independent position at the University of Chicago in the March of 2013. Over the years, Dr. Hwang has been particularly interested in the control of pathogens by the host immune system and the immune evasion strategies of pathogens. The focus of Dr. Hwang's current research is to elucidate the role of autophagy pathway/proteins in the control of various pathogens by interferons.

Dr. Carolina B. López
Assistant Professor
Department of Pathobiology
School of Veterinary Medicine
University of Pennsylvania

Dr. López received a B.S. (1992), a M.Sc., and a professional title of Biochemist (1995) from the Pontificia Universidad Católica de Chile and obtained her Ph.D. in Biomedical Sciences (2002) from The Mount Sinai School of Medicine in New York. She continued at Mount Sinai as a post-doctoral fellow and non-tenure track Assistant Professor before she joined the Department of Pathobiology at The University of Pennsylvania in September, 2010. The López laboratory uses viruses that infect the respiratory tract to investigate the mechanisms involved in viral recognition, control of virus replication, development of the immune response, and protection of the lung from excessive damage.

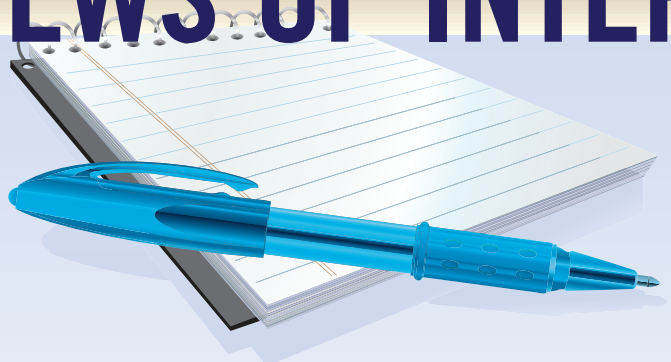
Dr. Marie Bodinier
First Class Junior Scientist
Researcher in the Biopolymers Assemblies and Interactions Unit
French National Institute for Agricultural Research, INRA, CR1

Dr. Marie Bodinier received her Ph.D. from the University of Nantes in 2001. From 2003-2009 she was a Second Class Junior Scientist (CR2), INRA of Nantes where she performed research in food allergies to wheat: allergens identification, development of cellular and animal models. In 2009 she was promoted to First Class Junior Scientist (CR1). Her research focuses on characterization of allergens and epitopes, especially in two food ingredients: wheat and egg; mechanisms of sensitization and of allergy reaction; impact of food processing on allergenicity and the establishment of strategies aiming to prevent food allergies by acting on perinatal feeding (mother or new born baby feeding) by the introduction of prebiotic oligosaccharides.

UNICELLULARITY TO MULTICELLULARITY

Illustration by Lynn Fellman at www.FellmanStudio.com. Fellman specializes in iBook and multimedia presentations for genomic science. This work was commissioned by the Center for Evolution and Cancer at UCSF for the 2013 IBECC conference.

REVIEWS OF INTEREST



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HOW TO TELL GOOD CHOCOLATE

SHEILAH KAUFMAN - award-winning author, cooking teacher, food editor, culinary lecturer
www.cookingwithsheilah.com

- **Smell it:** the aroma is very important. If it has no aroma it can't be too good.
- **Look at it:** Dark chocolate should have a nice "sheen" and if there is any "bloom" (white discoloration) it has been stored or tempered improperly.
- **Sound:** it should have a sharp or clean "snap" when the piece is broken into two pieces. This means it has a high percentage of cocoa rather than sugar.
- **Feel:** It should have a smooth, almost sensual fee ling in your mouth. If it feels waxy, according to Marilyn Mueller, it could mean that paraffin was added to the chocolate as a stabilizer.

Bitterness, acidity, sweetness, and astringency are the taste sensations likely to be found in chocolate. The cocoa should by slightly bitter, but not acrid. There should be the slightest touch of acidity and light sweetness to help highlight other, more interesting flavors. The intense aromas of the chocolate are released on the tongue before the 'finish', a distinct final note.

CHOCOLATE TASTING TECHNIQUES

- Pinch your nose to cut off the aroma, so you just experience taste and texture.
- Place chocolate in your mouth, let it rest for a few seconds to taste the base notes of bitterness, acidity, sweetness, and astringency.
- Stop pinching your nose and note the aroma.
- Spread the chocolate around by chewing it 5 times or so. This releases the secondary flavors and aromas.
- Gently press it against the roof of your mouth for a few moments to get it up on your palate, where your nose takes over from the inside.
- Now let it melt slowly and feel the texture – which should be totally smooth.

HOW TO STORE CHOCOLATE

- Chocolate should be stored at cool room temperature and in a dark place with plenty of air circulation. The ideal conditions are 65 F and 50% humidity.
- Chocolate keeps best when it is wrapped first in foil and then in plastic.
- If stored a suggested, unsweetened and dark chocolate will last up to 10 years, and milk chocolate and white chocolate will last for 7 to 8 months.
- Fat bloom results when chocolate is exposed to heat, while sugar bloom (which makes your chocolate feel rough) is caused by storing chocolate in damp conditions.
- Never store chocolate near items with strong odors such as potpourri, as the chocolate will absorb these scents (so will butter).

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WWW

BloodChIP: a database of comparative genome-wide transcription factor binding profiles in human blood cells

http://www.med.unsw.edu.au/CRCWeb.nsf/page/BloodChIP

Introduction

Haematopoiesis serves as a model system for the multi-lineage differentiation of adult stem cells. The current paradigm of sorting cells based on cell surface markers and performing functional assays to reconstruct the hierarchy of haematopoietic stem cell differentiation is evolving. There is a growing emphasis on transcriptional drivers that assign cell states by altering the genomic landscape. Cell type specific expression of transcription factors, and cell type specific accessibility of enhancer elements, control gene expression profiles that give blood cells of various lineages their distinct identities. A core set of transcription factors work in combination to regulate gene expression in HSPCs. Knowledge of how these transcription factors cooperate with each other and interact with other lineage specific transcription factors to regulate gene expression during HSPC differentiation is key to improving our understanding of normal blood development and how these processes are corrupted in leukaemia.

What is BloodChIP?

BloodChIP is a user friendly database that integrates genome-wide binding profiles of haematopoietic transcription factors in human blood cell types with chromatin accessibility profiles from the Human Epigenome Atlas and corresponding gene expression. An interactive web interface allows users to query BloodChIP and ascertain the relative expression level of their genes across different cell types. Importantly, the user is then able to associate expression levels in these cell fractions with chromatin accessibility and transcription factor binding profiles in primary human HSPCs and other cell types to gain insights into the transcriptional regulation of these genes. The database supports exploration and selection based on either genes or transcription factors of interest. All queries, as well as the complete database, can be exported by the user for further data analysis.

ClinVar: a public archive of reports of the relationships among human variations and phenotypes

http://www.ncbi.nlm.nih.gov/clinvar/

ClinVar provides a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence. By so doing, ClinVar facilitates access to and communication about the relationships asserted between human variation and observed health status, and the history of that interpretation. ClinVar collects reports of variants found in patient samples, assertions made regarding their clinical significance, information about the submitter, and other supporting data. The alleles described in submissions are mapped to reference sequences, and reported according to the HGVS standard. ClinVar then presents the data for interactive users as well as those wishing to use ClinVar in daily workflows and other local applications. ClinVar works in collaboration with interested organizations to meet the needs of the medical genetics community as efficiently and effectively as possible.

ClinVar supports submissions of differing levels of complexity. The submission may be as simple as a representation of an allele and its interpretation (sometimes termed a variant-level submission), or as detailed as providing multiple types of structured observational (case-level) or experimental evidence about the effect of the variation on phenotype. A major goal is to support computational (re)evaluation, both of genotypes and assertions, and to enable the ongoing evolution and development of knowledge regarding variations and associated phenotypes. ClinVar archives and versions submissions which means that when submitters update their records, the previous version is retained for review.

The level of confidence in the accuracy of variation calls and assertions of clinical significance depends in large part on the supporting evidence, so this information, when available, is collected and visible to users. Since the availability of supporting evidence may vary, particularly in regard to retrospective data aggregated from published literature, the archive accepts submissions from multiple groups, and aggregates related information, to transparently reflect both consensus and conflicting assertions of clinical significance. A review status is also assigned to any assertion, to support communication about the trustworthiness of any assertion.

Accessions, of the format SCV000000000.0, are assigned to each submission. If there are multiple submissions about the same variation/phenotype relationship, they are aggregated within ClinVar's data flow and reported as a reference accession of the format RCV000000000.0.

Because of this model, one allele will be included in multiple RCV accessions whenever different phenotypes are reported for that allele. Groups wishing to evaluate a set of ClinVar records can also submit a review of a set of SCV or RCV records, with the result being the creation of a novel record assigned an RCV accession.

ClinVar archives submitted information, and adds identifiers and other other data that may be available about a variant or phenotype from other public resources, but ClinVar neither curates content nor modifies interpretations independent of an explicit submission. If you have data that differs from what is currently represented in ClinVar, we encourage you to submit your data and the evidence supporting your intepretation.

References

More information about ClinVar is available in these sources:

1. *Nucleics Acid Research*
Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, Church DM, Maglott DR. ClinVar: public archive of relationships among sequence variation and human phenotype. Nucleic Acids Res. 2014 Jan 1;42(1):D980-5. doi: 10.1093/nar/gkt1113. PubMed PMID: 24234437

2. *NCBI Handbook*
Melissa Landrum, PhD, Jennifer Lee, PhD, George Riley, PhD, Wonhee Jang, PhD, Wendy Rubinstein, MD, PhD, Deanna Church, PhD, and Donna Maglott, PhD. ClinVar. http://www.ncbi.nlm.nih.gov/books/NBK174587/

CR Cistrome: a ChIP-Seq database for chromatin regulators and histone modification linkages in human and mouse

http://cistrome.org/Cistrome/Cistrome_Project.html

The cistrome refers to "the set of cis-acting targets of a trans-acting factor on a genome-wide scale, also known as the in vivo genome-wide location of transcription factor binding-sites or histone modifications". The term cistrome is a portmanteau of cistron + genome and was coined by investigators at the Dana-Farber Cancer Institute and Harvard Medical School.

Here we build integrative analysis pipelines (Cistrome) to help experimental biologists, and conduct efficient data integration to better mine the hidden biological insights from publicly available high throughput data.

Cistrome Analysis Pipeline: An integrative and reproducible bioinformatics data analysis platform based on Galaxy open source framework. Besides standard Galaxy functions, Cistrome has 29 ChIP-chip- and ChIP-seq-specific tools in three major categories, from preliminary peak calling and correlation analyses to downstream genome feature association, gene expression analyses, and motif discovery.

CistromeMap Data Collection: A web server that provides a comprehensive knowledgebase of all of the publicly available ChIP-Seq and DNase-Seq data in mouse and human. We have manually curated metadata to ensure annotation consistency, and developed a user-friendly display matrix for quick navigation and retrieval of data for specific factors, cells and papers.

Nuclear Receptor Cistrome DB; A curated database of 88 nuclear receptor cistrome data sets and other associated high-throughput data sets including 121 collaborating factor cistromes, 94 epigenomes, and 319 transcriptomes. All the ChIP_chip/seq peak regions are annotated with enriched HRE and co-regulator motifs. A list of predicted hormone response genes from integration of nuclear receptor ChIP_chip/seq data and differential expression data is also readily available to the users.

Cistrome Chromatin Regulator; A knowledgebase on chromatin modifying enzymes and chromatin remodelers. All the chromatin regulators (CR) which possess ChIP-seq data are divided into four categories: reader, writer, eraser and remodeler. Then their basic information and their ChIP-seq data are collected and analysed.

CistromeFinder: CistromeFinder is an application for checking binding sites around a given gene. It has the most comprehensive collection of public ChIP/DNase-seq datasets in human and mouse (over 7,000 samples, including all of ENCODE, epigenome, and more published data from individual papers), which have all gone through a uniform QC and analysis pipeline. .

CaSNP: A comprehensive collection of copy number alteration (CNA-ys of 34 different cancer types in 105 studies to profile the genome-wide CNA and SNP in each..

DPRP: a database of phenotype-specific regulatory programs derived from transcription factor binding data

http://syslab.nchu.edu.tw/DPRP/

The DPRP database provides three major functions:

1. **Gene expression database:** the database has collected 984 gene expression datasets including a total of 29,744 arrays. These datasets were originally generated to explore differential gene expression under different conditions or treatments, e.g. gene expression changes during development; differential gene expression between different subtypes of breast cancer. Thus, each dataset has several subsets and each subset has a number of samples. To identify differentially expressed genes (DEGs) for each dataset, we selected the subsets with at least 3 samples, and then performed t-test for all subset pairs without overlap samples. It resulted in 3777 subset pairs.
2. **Phenotype annotation:** to systematically annotate gene expression data and address synonymous issue, we used UMLS technology that provides a comprehensive catalog of medical concepts. To concentrate on human disease study, we limited the UMLS concepts to three semantic types: "Pathologic Function", "Injury or Poisoning" and "Anatomical Abnormality". UMLS also provides the

language processing tool MetaMap to enable the automated mapping of text onto UMLS concepts. Given a GEO dataset, we determined the phenotypic context of this dataset based on the Medical Subject Headings of its corresponding PubMed record and its dataset summary in GEO, and then parsed these texts to identify relevant UMLS concepts using the MetaMap program. These UMLS concepts provided the GEO dataset level annotation. These datasets were organized in the database in a searchable manner and provide a useful resources for specific biological or clinical research. For example, a user can type in "Breast Carcinoma" as a keyword to obtain a list of datasets related to breast cancer. To facilitate user-friendly text search, we adopt the jQuery AutoComplete technique to guide the user for keyword selection. When a specific dataset is selected, the database will list a number of phenotype pairs (e.g. breast cancer subclasses) for comparing regulatory activity of TFs.

3. **TF regulatory program:** the database identified regulatory programs underlying each phenotype associated with a dataset. When two different phenotypes for a given dataset are specified (e.g. estrogen treated versus untreated MCF7 cell lines), we inferred the regulatory programs responsible for the differential gene expression between them. The database provide a list of TFs that show significant differential activity and the regulatory network consisting of these significant TFs based an integrative framework that combine expression data with ChIP-seq data.

If you use DPRP in your projects, please cite the following reference:

David T.W. Tzeng†, Yu-Ting Tseng†, Matthew Ung, I-En Liao, Chun-Chi Liu*, Chao Cheng*. (2014) DPRP: A database of phenotype-specific regulatory programs derived from transcription factor binding data. Nucleic Acids Research 42: D178-183 (†co-first authors, *corresponding authors)

FunCoup: database of genome-wide functional coupling networks

http://funcoup.sbc.su.se/search/

The name FunCoup [fən kəp] stands for functional coupling. FunCoup is a framework to infer genome-wide functional couplings in 11 model organisms. Functional coupling, or functional association, is an unspecific form of association that encompasses direct physical interaction but also more general types of direct or indirect interaction like regulatory interaction or participation the same process or pathway.

Framework: Briefly, the FunCoup framework integrates 9 different evidence types derived from high-throughput genomics and proteomics data in a naive Bayesian integration procedure. The evidence types are discussed in more detail below. Evidence is transfered across species using orthology assignments from InParanoid.

The naive Bayesian integration combines the likelihood for coupling and no coupling in the form of log-likelihood ratios (LLRs) for all data sets. LLRs for data of the same type are corrected to account for cross-data redundancies. The sum of LLRs for a gene pair is called the a final Bayesian score (FBS) and expresses the amount of support the data shows for a coupling. To simplify the interpretation the FBS is transformed into a probabilistic confidence score that ranges from 0 to 1.

Networks: FunCoup differentiates between four different classes of functional couplings: protein-protein interaction (PPI), complex co-membership, co-membership in a metabolic pathway, and co-membership in a signaling pathway. For each class a separate network is created. Additionally a composite or summary network is created by taking the strongest coupling from the different classes for each pair.

Evidence types: Evidences are the signals that support or contradict the presence of functional coupling. Typically some kind of scoring function is used to convert raw data into evidence. FunCoup integrates 9 different evidence types listed below.

Protein-protein interaction (PPI): Physical protein-protein interaction (PPIs) from iRefIndex are combined, where interactions confirmed by multiple publications get a higher score. The scoring function further down-weights interactions from large scale experiments and prey-prey interactions.

mRNA co-expression (MEX): mRNA co-expression across multiple experimental conditions or tissues provides a strong signal for functional coupling. FunCoup evaluates co-expression as Spearman correlation of expression profiles. For each species multiple selected large scale experiments from GEO are integrated.

Protein co-expression (PEX): The concordance between mRNA and protein expression is low. Directly measured protein expression from the Human protein atlas provides a more accurate estimation of protein abundances and is used to complement the mRNA expression data.

Genetic interaction profile similarity (GIN): FunCoup does not explicitly consider genetic interactions as functional coupling. Rather, between pathway genetic interactions are integrated in the form of genetic interaction profile similarity. The underlying assumption is that genes in same process or pathway have similar genetic interactions with genes in other alternative processes or pathways.

Shared transcription factor binding (TFB): Genes are regulated by multiple transcription factors (TFs) and FunCoup uses TF profile similarity as a evidence for functional coupling.

Co-miRNA regulation by shared miRNA targeting (MIR): Similar to shared transcription factor binding, co-regulation by multiple miRNA is used as evidence for function coupling.

Sub-cellular co-localization (SCL): Shared sub-cellular localization and dissimilar localization are good positive and negative indicators for functional couplings. FunCoup uses localizations from the cellular component GO ontology. Co-localizations is weighted by the specificity of the localization, where specific localizations get a high weight and unspecific localizations get a low weight.

Domain interactions (DOM): Predicted domain interaction

from UniDomInt are used a evidence. The confidence score provided by UniDomInt is summed up for all domain pairs of two proteins.

Phylogenetic profile similarity (PHP): A phylogenetic profile is a gene conservation pattern across multiple species. Phylogenetic profile similarity provides an indication for functional coupling. FunCoup scores profile similarity as fraction of branch lengths shared by both genes or exclusive covered by only one gene in a phylogeny of 93 species derived from InParanoid.

Citation: Schmitt, T., Ogris, C., & Sonnhammer, E. L. (2013). FunCoup 3.0: database of genome-wide functional coupling networks**.** *Nucleic Acids Research, 42(Database issue)*, D380-8

LenVarDB: Database of length variant protein domains

http://caps.ncbs.res.in/lenvardb/

Protein domains are the functional and evolutionary units of protein structure and are independent in its functionality and folding pattern. These protein domains (across certain protein folds) has the ability to tolerate changes in sequence and length during evolutionary drifts, without changing its folding topology or functionality. Length variations at protein domain level have been known to cause functional impacts like, increasing structural stability, diversifying substrate specificity etc. A comprehensive resource of length variant protein domains at superfamily level (LenVarDB) will help users solve issues like; will the presence of length variations hinder substrate entry by formation of a capping loop or will they form a new interface and diversify the social skills of a protein domain? Though these variations have been recorded only at the level of protein domain "structures", this database attempts (for the first time) to include sequence information, by gathering homologues of superfamily members and deriving indels from their multiple sequence alignment. Detection of multiple length variants (indels) along with their spatial orientation in a given query protein structure, could be very useful in highlighting the deviations caused from its usual structure and function. Users can also align their query proteins with the existing multiple sequence alignments to trace putative indel positions. Insight into the indel locations whether they are proximal or distant from the functionally relevant sites can provide pointers to probable changes in functionality of their protein or tips in modeling and structural studies.

BIOLOGICAL SIGNIFICANCE: Length variations (indels) are instrumental in causing changes in protein structure and function (Zhang et. al.,MBE,2010). They have also been implicated in disease related genes (Kim et. al., Journal of Genetics, 2012). Protein domain superfamilies having long length variations found to be interacting with diverse substrates and were also found to be in various oligomeric states.(Sandhya et.al., PlosONE, 2009).Please cite us: Mutt, E., Mathew, O. K., Sowdhamini, R., Jan. 2014. LenVarDB: database of length-variant protein domains. Nucleic Acids Research 42 (D1), D246-D250. URL

Manteia: a predictive data mining system for vertebrate genes and its applications to human genetic diseases

http://manteia.igbmc.fr

Manteia is an advanced data mining system that allows researchers to combine a variety of data and tools in order to test hypotheses and address complex biological questions. To start with Manteia select a tool from the menu above or using the links provided. Data can be combined using our query builder or the refine tool as explained in our tutorials. If you don't know where to start, you probably want to look for a particular gene using Molecule search or analyze a list of genes using Batch gene entry.

Metacyc: a database of experimentally elucidated metabolic pathways from all domains of life

http://metacyc.org/

MetaCyc contains more than 2151 pathways from more than 2515 different organisms, and is curated from the scientific experimental literature.

MetaCyc contains pathways involved in both primary and secondary metabolism, as well as associated compounds, enzymes, and genes. The goal of MetaCyc is to catalog the universe of metabolism by storing a representative sample of each experimentally elucidated pathway.

MetaCyc applications include serving as an encyclopedia of metabolism, providing a reference data set for the computational prediction of metabolic pathways in sequenced organisms, supporting metabolic engineering, and helping to compare biochemical networks.

NGSmethDB: an updated genome resource for high quality, single-cytosine resolution methylomes

http://bioinfo2.ugr.es/NGSmethDB

WHAT NGSmethDB IS?

DNA methylation is an epigenetic mark involved in embryonic development, transcription, chromosome stability and genomic imprinting. Aberrant methylation is implicated in the appearance of several disorders such as cancer, immunodeficiency or centromere instability.

NGSmethDB [1] is a dedicated database for the storage, browsing and data mining of whole-genome, single-base-pair resolution methylomes. We collect NGS data from high-throughput sequencing together with bisulfite conversion of DNA from literature and public repositories, then generating high-quality chromosome methylation maps for many different tissues, pathological conditions and species.

A coupled next-generation genome-browser allows the visualization of methylation maps in a genomic context. In addition, we provided a direct link to the UCSC Track Hub facility, thus allowing the comparison of methylomes with many other third-part annotations. Database-mining and statistical tools allow the user to download, filter, analyze and retrieve methylation data in many different ways.

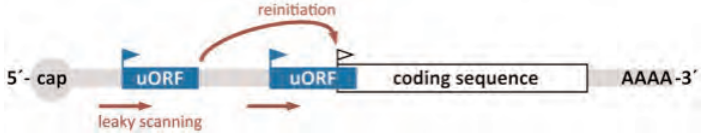
Finally, we also provided a connection to *CpGislandEVO*, a database joining together CpG islands and methylation data which allows for the comparative evolutionary analysis of CpG islands in the best assembled mammalian genomes.

[1] Hackenberg M, Barturen G, Oliver JL. (2010) NGSmethDB: A database for next-generation sequencing single-cytosine-resolution DNA methylation data. **Nucleic Acids Research** 39(1): D75-D79.
http://dx.doi.org/10.1093/nar/gkq942

A comprehensivw literature database on eukaryotic uORF biology

http://cbdm.mdc-berlin.de/tools/uorfdb/

Translation initiation sites that precede the main coding sequence (CDS) of a transcript give rise to upstream open reading frames (uORFs). The presence of uORFs affects initiation rates at the CDS by interfering with unrestrained progression of ribosomes across the 5´-transcript leader sequence.
Accumulating evidence suggests that uORF-mediated translational control is of outstanding importance for the regulation of protein expression in health and disease.



uORFdb:

- aims to collect all literature on uORF biology in eukaryotic organisms, including viral transcripts
- categorizes individual uORF-related publications by a variety of denominators, including taxon, gene, and the type of study.
- can be queried for multiple structural and functional uORF-related properties to allow convenient and targeted access to the complex field of uORF biology

PubChem: PubChem provides information on the biological activities of small molecules

http://pubchem.ncbi.nlm.nih.gov/

PubChem includes substance information, compound structures, and BioActivity data in three primary databases, Pcsubstance, Pccompound, and PCBioAssay, respectively.

- Pcsubstance contains more than 140 million records.
- Pccompound contains more than 51 million unique structures.
- PCBioAssay contains more than 1 million BioAssays. Each BioAssay contains a various number of data points.

The Substance/Compound database, where possible, provides links to BioAssay description, literature, references, and assay data points. The BioAssay database also includes links back to the Substance/Compound database. PubChem is integrated with Entrez, NCBI's primary search engine, and also provides compound neighboring, sub/superstructure, similarity structure, BioActivity data, and other searching features.

PubChem contains substance and BioAssay information from a multitude of depositors.

PubChem Substance Database

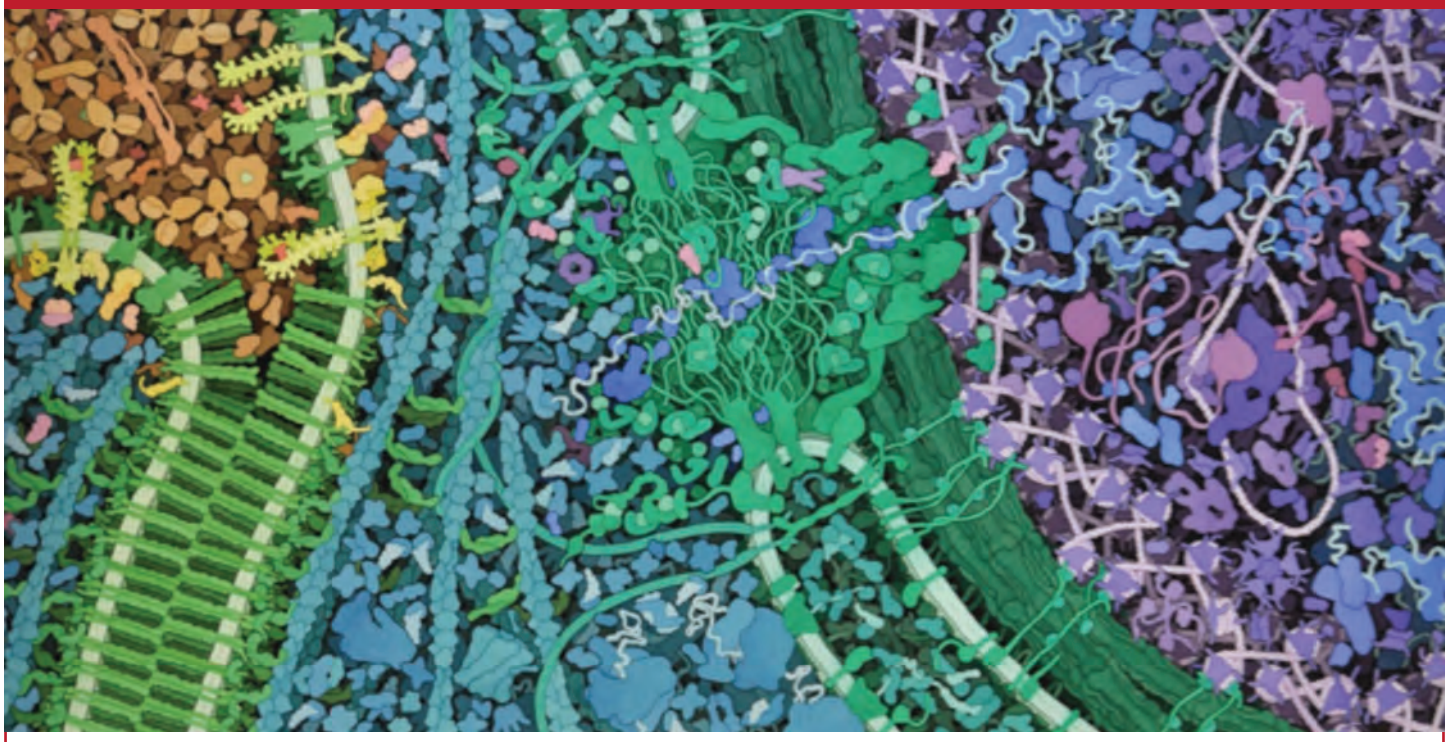
The PubChem substance database contains chemical structures, synonyms, registration IDs, description, related urls, database cross-reference links to PubMed, protein 3D structures, and biological screening results. If the contents of a chemical sample are known, the description includes links to PubChem Compound.

topPTM: a new module of dbPTM for identifying functional post-translational modifications in transmembrane proteins

http://topptm.cse.yzu.edu.tw/

topPTM is a database that integrates experimentally verified post-translational modifications (PTMs) from available databases and research articles, and annotates the PTM sites on transmembrane proteins with structural topology. The biological effects of PTMs on transmembrane proteins include phosphorylation for signal transduction and ion transport, acetylation for structure stability, attachment of fatty acids for membrane anchoring and association, as well as the glycosylation for substrates targeting, cell-cell interactions, and viruses infection. The experimentally verified PTMs are mainly collected from public resources including dbPTM, Phospho.ELM, PhosphoSite, OGlycBase, and UbiProt. For transmembrane proteins, the information of membrane topologies is collected from TMPad, TOPDB, PDBTM, and OPM. In order to fully investigate the PTMs on transmembrane proteins, the UniProtKB protein entries containing the annotation of membrane protein and the information of membrane topology are regarded as potential transmembrane proteins. To delineate the structural correlation and consensus motif of these reported PTM sites, the topPTM database also provide structural analyses, including the membrane accessibility of PTM substrate sites, protein secondary and tertiary structures, protein domains, and cross-species conservations of each entry.

SCIENCE AS ART
The Molecular Landscape Depicting VEGF Signaling



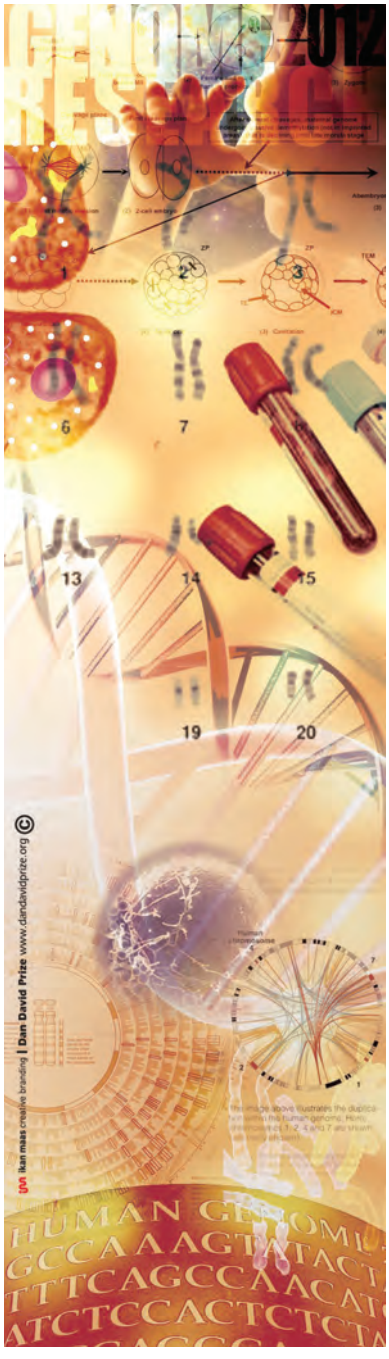
Blood plasma is shown in tan at the upper left. VEGF is depicted as the small red shape sitting in the VEGF receptor (shown in yellow). The adherens junction between two cells is in green at left, with the cytoplasmic proteins in turquoise. The nuclear pore is at the center in green and the nucleus is at the right, with proteins shown in blues and purples.[1]

Courtesy of David Goodsell. http://mgl.scripps.edu/people/goodsell/ Reprinted with permission

[1]Protein structure in context: the molecular landscape of angiogenesis. Span EA, Goodsell DS, Ramchandran R, Franzen MA, Herman T, Sem DS. *Biochem Mol Biol Educ*. 2013 Jul-Aug;41(4):213-23.

SCIENCE AS ART

2012 Dan David Prize image in the field of Genome Research www.dandavidprize.org



MEETINGS OF INTEREST

IMPORTANT ANNOUNCEMENT CHANGE of VENUE for CYTOKINES2015

THE 2015 ICIS MEETING, CYTOKINES2015, HAS BEEN MOVED FROM FREIBURG TO BAMBERG DUE TO CIRCUMSTANCES BEYOND THE CONTROL OF THE ORGANIZERS

The town of Bamberg is a UNESCO World Heritage Center (http://whc.unesco.org/en/list/624). Bamberg is located in northern Bavaria and can easily be reached from Frankfurt-Airport by express train. It offers excellent meeting facilities, plenty of hotel rooms and a charming environment.

The date of the meeting remains Oct. 11-14, 2015

Answers to crossword Puzzle from page 12

MEETINGS OF INTEREST

GTCBIO'S CYTOKINES AND INFLAMMATION CONFERENCE

SAN DIEGO, CA
JAN. 29-30, 2015
http://goo.gl/OnbQDW

ICIS members can get a 35% discount in registration fees by using the code CY1135

Over the years, GTCbio's Cytokines & Inflammation Conference has become an established meeting point for academic scientists, industry clinical developers, and government researchers to discuss complementary approaches in the field of cytokine biology. Some focused topics we will discuss this meeting include developments in the therapeutic application of cytokines and proposal of new targets, the complex relationship between the immune system and microbes in the homeostasis of mucosal tissues, new findings in the biology and regulation of IL-23 and IL-17, novel means to modulate immune pathways to promote anti-tumor activity and impact on the development of autoimmune disease, and many more.

Session topics include:

I. Novel Approaches in Cytokines Metabolism
II. Cytokines and the Impact of the Microbiome
III. Advances in Innate and Adaptive Immunity
IV. Cytokines and Cancer Immunotherapy
V. Targeting Cytokines & Chemokines for Therapeutic Interventions

T Cells: Regulation and Effector Function

29th March - 3rd April 2015
http://www.keystonesymposia.org/15D3

Organization: Keystone Symposia
Type: Conference Venue: Snowbird Resort
Location: Snowbird, United States
Website: T Cells: Regulation and Effector Function

Dendritic Cells and Macrophages Reunited

8th - 13th March 2015
http://www.keystonesymposia.org/15C4

Organization: Keystone Symposia
Venue: Fairmont The Queen Elizabeth
Location: Montreal, Canada
Website: Dendritic Cells and Macrophages Reunited

MEETINGS OF INTEREST

International Conference on Cytokine Signaling in Cancer

Major Conference Themes:

- Direct and indirect anti-tumorigenic cytokine action
- Cytokines, polypeptide hormones, inflammation and tumor progression
- Regulation of immune system and tumor microenvironment
- Use of cytokines and novel signaling targets for anti-cancer therapies

AVRA IMPERIAL

Confirmed Speakers

- **Jessica Altman,** *Northwestern*, USA
- **Siddharth Balachandran,** *Fox Chase/Temple*, USA
- **Iris Behrman,** *Univ. of Luxembourg*, Luxembourg
- **Charles Clevenger,** *VCU*, USA
- **Thomas Decker,** *University of Vienna*, Austria
- **Eleanore Fish,** *University of Toronto*, Canada
- **Serge Fuchs,** *University of Pennsylvania*, USA
- **Ana Gamero,** *Temple University*, USA
- **Sergei Grivennikov,** *Fox Chase/Temple*, USA
- **Paul Hertzog,** *Monash University*, Australia
- **Dhan Kalvakolanu,** *Univ. of Maryland*, USA
- **Pavel Kovarik,** *University of Vienna*, Austria
- **Natasha Kyprianou,** *Univ of Kentucky*, USA
- **Xin-Yuan Liu,** *Shanghai CAS*, China
- **Alberto Mantovani,** *Istituto Clinico Humanitas*, Italy
- **Richard Moriggl,** *Ludwig Boltzmann Institute*, Austria
- **Mathias Müller,** *Vet Med University*, Austria
- **Drorit Neumann,** *Tel Aviv University*, Israel
- **Marja Nevalainen,** *Thomas Jefferson University*, USA
- **Belinda Parker,** *Latrobe University*, Australia
- **Lawrence Pfeffer,** *UTHSC*, USA
- **Leonidas Platanias,** *Northwestern*, USA
- **Nancy Reich Marshall,** *SUNY Stonebrook*, USA
- **Hallgeir Rui,** *Thomas Jefferson University*, USA
- **Gideon Schreiber,** *Weizmann Institute*, Israel
- **Veronika Sexl,** *Vet Med University*, Austria
- **Dagmar Stoiber,** *Ludwig Boltzmann Institute*, Austria
- **Birgit Strobl,** *Vet Med University*, Austria
- **Tadatsu Taniguchi,** *University of Tokyo*, Japan
- **Andrei Thomas-Tikhonenko,** *University of Pennsylvania*, USA
- **Mariusz Wasik,** *University of Pennsylvania*, USA
- **Hua Yu,** *City of Hope Cancer Center*, USA
- **Dong-Er Zhang,** *UCSD*, USA

MEMBER BENEFIT: **FREE JOB POSTINGS**

If you have an open position of any type, members are able to post it on the ICIS website (www.cytokines-interferons.org) at no cost!! Take advantage of this member benefit and post your open positions today!!!

FINAGLE'S LAWS:

1. If an experiment works, something has gone wrong.

2.1 No matter what result is anticipated, there is always someone willing to fake it.

2.2 No matter what the result, there is always someone eager to misinterpret it.

2.3 No matter what happens, there is always someone who believes it happened according to his pet theory.

3. In any collection of data, the figure most obviously correct, beyond all need of checking, is the mistake.

4. Once a job is fouled up, anything done to improve it only makes it worse.

Create an ICIS app icon for your smartphone!

YOUR APP HERE !

Access the ICIS website (www.cytokines-interferons.org) from Safari, clicked on the little icon symbol to airdrop, bookmark, ADD TO HOMESCREEN. You will then have an ICIS App Icon on your smartphone.

DR. RICHARD FLAVELL, ICIS President

ICIS President, Dr. Richard Flavell, has received the 2014 Star of Hope Award from the Juvenile Diabetes Research Foundation Connecticut chapter. Congratulations Dr. Flavell!!!!!!

SYMPOSIUM HONORS DR. JOOST OPPENHEIM

by Howard Young

On Aug. 11, 2014, a symposium was held at the National Cancer Institute at Frederick to honor the 80th birthday (actually on Aug.11) of Dr. Joost Oppenheim. Over 120 people were in attendance to hear a variety of speakers that included a perspective by Dr. Oppenheim on his career at the NIH, followed by 3 speakers from his current lab: **Zack Howard**: 25 years of Inflammation and and Pain - Mapping the immune system and nervous system intersections with Jo Oppenheim ; **Xin Chen**: Tregs: Signals that make them stronger; **De Yang**: From chemokine to alarmin – a exciting journey with Jo Oppenheim.

These talks were followed by presentations from friends and colleagues who had worked and collaborated with Jo over the years, including **Tom Waldmann** (NCI): The good an evil faces of the Janus kinesis' in T cell biology and malignancy; **Phil Murphy** (NIAID): Chemokine Receptors: Tails from the Clinic; **Scott Durum** (NCI): IL-7: Its' role in health and disease; **Charles Dinarello** (Univ. of Colorado School of Medicine): Blocking IL-1beta and IL-1alpha in a broad spectrum of inflammatory diseases; **Bill Paul** (NIAID: Innate Functions of ILCs and CD4 T Cells; **Stefanie Vogel** (Univ. of Maryland School of Medicine): So what? - A guiding principle; **Sergei Nedospasov** (Engelhardt Institute of Molecular Biology, Moscow): The role of lymphotoxin in the control of microbiota composition and IgA; **Kouji Matsushima** (Univ. of Tokyo): Making antibodies even better tools: applications to cancer therapy and **Ji-Ming Wang** (NCI): Motility is the driving force of life. A good time was had by all with plans already being made to celebrate his 90th birthday.

PEGINTERFERON BETA-1A; A NEW TREATMENT FOR RELAPSING REMITTING MULTIPLE SCLEROSIS

by Darren P. Baker, Ph.D., Global Medical BiogenIdec Inc.

Interferon beta has been used for the treatment of relapsing remitting multiple sclerosis (RRMS) in the United States and the European Union since the mid 1990's. While interferon beta, with respect to reduction of annualized relapse rate (ARR), has less efficacy compared to more recent therapies such as Tysabri® (BiogenIdec) or Gilenya® (Novartis), it is generally considered a safe treatment and is not associated with an increased incidence of adverse events such as progressive multifocal leukoencephalopathy that may result from the administration of Tysabri, or bradyarrhythmia and atrioventricular blocks, and macular edema that may result from the administration of Gilenya. Of the available (unmodified) interferon beta drug products, two are of the interferon beta-1a class and two are of the interferon beta-1b class. The 1a and 1b classification relates to the amino acid sequence where 1a denotes the natural human interferon beta sequence and 1b denotes a mutant sequence; in this case methionine at position 1 is absent and cysteine at position 17 is mutated to a serine.

The two interferon beta-1a drug products (Avonex®, BiogenIdec; Rebif®, EMD-Serono) are expressed in mammalian cells resulting in glycosylation at asparagine-80. By contrast, the interferon beta-1b products (Betaseron/Betaferon®, Bayer Healthcare; Extavia®, Novartis) are expressed in bacteria and lack the glycan chain at asparagine-80. As removal of the glycan chain from interferon beta-1a leads to the formation of aggregated forms (Runkel and others 1998), and protein aggregates are a trigger for anti-drug antibody formation, the higher levels of neutralizing antibodies (NAbs) in patients receiving interferon beta-1b versus interferon beta-1a may be explained, at least in part, by this difference in product quality (van Beers and others 2010). Higher levels of NAbs were also reported in patients receiving Rebif compared to those receiving Avonex in a head-to-head phase 3 study (EVIDENCE). The higher NAb incidence in Rebif-treated patients was associated with reduced efficacy on magnetic resonance imaging (MRI) but had no measurable impact on relapse outcomes (Panitch and others 2005).

The dose, frequency of administration, and route of administration also differ between the interferon beta drug products. Avonex is given as a 30 μg intramuscular injection once per week, while Rebif is given as 22 or 44 μg subcutaneous injections three times per week. Betaseron/Betaferon and Extavia are both given as 250 μg subcutaneous injections every other day. While generally safe therapies, administration of interferon beta is commonly associated with the development of flu-like side effects such as fever, chills, muscle ache, and fatigue, as well as rare but more serious adverse events. The reader is referred to the respective prescribing information available on each product's web site (i.e. www.drug name.com) for a full description of adverse events.

Given that treatment initiated early after diagnosis and adherence to therapy are critical for beneficial clinical outcomes, a need was identified for a longer-acting form of interferon beta that was safe, efficacious, and that could be administered less frequently than the interferon beta drug products described above. Despite the availability of interferon beta and other classes of therapy, there remain a significant number of RRMS patients who are untreated, including those with relatively mild disease who choose not to initiate therapy, those wary of injections or potential side effects associated with therapy, those for whom frequent injection is a reminder of their disease, and those who have stopped therapy due to perceived lack of efficacy. Moreover, even with the introduction of non-injectable therapies for RRMS such as Gilenya and Tecfidera® (BiogenIdec), potential adverse events and the need for daily or twice daily oral administration may make a less frequently administered injectable drug preferable to some patients.

With the recent approval of Plegridy® (peginterferon beta-1a, BiogenIdec) by the European Medicines Agency (EMA) and the US Food and Drug Administration, a new therapy for the treatment of RRMS has become available to neurologists and their patients. Peginterferon beta-1a is an interferon beta-1a to which a linear 20,000 Da poly(ethylene glycol) is attached to the α-amino group of the N-terminal amino acid residue (**Figure 1**), and which has greater in vivo exposure in rats, rhesus monkeys, and humans compared to unmodified interferon beta-1a (Baker and others 2006, Baker and others 2010, Hu and others 2011, Hu and others 2012). Following phase 1 clinical studies in which the safety, tolerability, pharmacokinetics, and pharmacodynamics of peginterferon beta-1a given intramuscularly or subcutaneously were evaluated in healthy human subjects (Hu and others 2012), a dose of 125 μg [protein mass excluding the mass of the attached poly(ethylene glycol)] given subcutaneously every two

or four weeks was selected for the phase 3 clinical study ADVANCE. Based on the phase 1 study data and a large database of Avonex safety, tolerability, pharmacokinetics, and pharmacodynamics, it was deemed appropriate to move directly to phase 3.

The ADVANCE trial was a randomized, placebo-controlled, double-blind study carried out in 183 sites in 26 countries. In the first year (placebo-controlled), patients were randomized 1:1:1 to receive either placebo, 125 µg peginterferon beta-1a every two weeks, or 125 µg peginterferon beta-1a every four weeks. A dose titration of 63, 94, and 125 µg was carried out for the first three injections to help ameliorate flu-like side effects. After 48 weeks of treatment, patients who had received placebo were re-randomized to one of the peginterferon beta-1a treatment arms, with those already receiving peginterferon beta-1a continuing with the treatment they were first assigned to. 1512 RRMS patients received at least one administration of study treatment and were included in the intention-to-treat population; 500 placebo, 512 peginterferon beta-1a every two weeks, and 500 peginterferon beta-1a every four weeks. The efficacy of peginterferon beta-1a was established using data collected during the first 48 weeks of treatment (Calabresi and other 2014). The data from weeks 48 to 96 was used to confirm maintenance of efficacy as well as to obtain additional safety and immunogenicity data.

The efficacy of peginterferon beta-1a was shown by a significant reduction in ARR. For the every two and four week peginterferon beta-1a groups, the ARR was reduced 36% (p=0.0007) and 28% (p=0.0114), respectively, compared to the placebo group. The percentage reduction in the proportion of patients relapsing was 39% (p=0.0003) and 26% (p=0.02) for the every two and four week peginterferon beta-1a groups, respectively, compared to the placebo group. The proportion of patients with 12 weeks confirmed disability progression was 38% (p=0.038) lower for both the every two and four week peginterferon beta-1a groups compared to the placebo group, while 24 weeks confirmed disability progression (post hoc analysis requested by the EMA) was 54% (p=0.0067) lower for the every two week peginterferon beta-1a group compared to the placebo group.

Patients receiving peginterferon beta-1a had fewer new or newly enlarging hyperintense lesions on T2-weighted MRI than those receiving placebo. For the every two and four week peginterferon beta-1a groups, the number of T2 hyperintense lesions was 67% (p<0.0001) and 28% (p=0.0008) lower, respectively, compared to the placebo group. Patients in the every two week peginterferon beta-1a group had significantly fewer new T1 hypointense (53%, p<0.0001) and gadolinium-enhancing (86%, p<0.0001) lesions compared to the placebo group. Patients in the every four week peginterferon beta-1a group had fewer new active lesions and smaller T1 and gadolinium-enhancing lesions compared to the placebo group (Calabresi and other 2014).

The most common adverse events in the peginterferon beta-1a groups compared to the placebo group were injection site reactions, influenza-like illness, fever, and headache. The incidence of serious adverse events was similar in all groups. Reductions of hematological parameters and increased liver enzymes was more prominent in the peginterferon beta-1a groups than in the placebo group, but most were not clinically significant and did not result in discontinuation of treatment. The development of NAbs to the interferon beta-1a portion of peginterferon beta-1a was low at less than 1% for all groups (Calabresi and other 2014).

Based on the data from ADVANCE, peginterferon beta-1a was approved for the treatment of RRMS in the EU and US as a 125 µg dose given subcutaneously once every two weeks.

As the ADVANCE trial compared peginterferon beta-1a to placebo, no direct comparisons of the efficacy of peginterferon beta-1a relative to other interferon beta therapies for RRMS can be made. However, the safety and efficacy data are consistent with interferon beta therapies as a class. The significant increase of in vivo exposure of peginterferon beta-1a versus the unmodified interferon beta drug products and the corresponding reduction in the number of injections required to achieve efficacy is a notable benefit to RRMS patients. The number of injections required per year is 26 for Plegridy compared to 52, 156, and 183 for Avonex, Rebif, and Betaseron/Betaferon/Extavia, respectively.

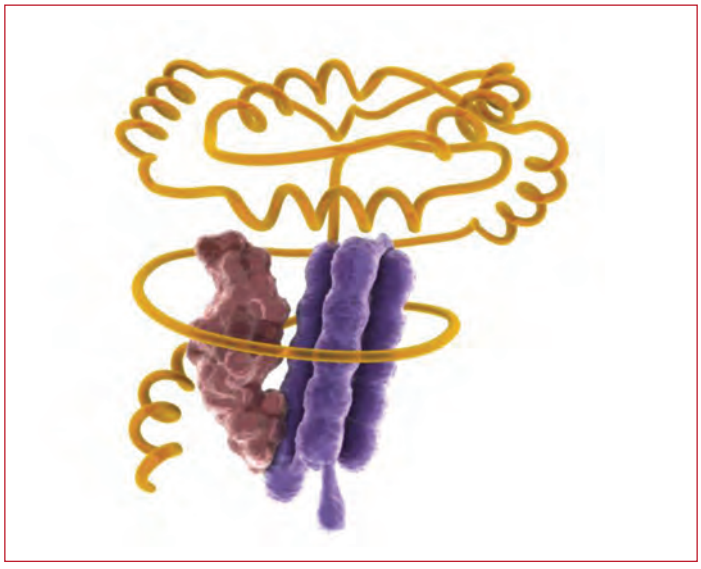


Figure 1: Schematic representation of peginterferon beta-1a. The interferon beta-1a protein portion is shown in purple, the portion of the glycan chain attached to asparagine-80 and which is visible in the crystal structure of interferon beta-1a (Karpusas and others 1997) is shown in pink, and the poly(ethylene glycol) chain attached to the N-terminal methionine is shown in gold. While the calculated molecular mass of peginterferon beta-1a (approximately 44,000 Da) is the sum of its constituent parts, by size exclusion chromatography it has an apparent mass of 320,000 Da (Baker and others, 2006), consistent with the notion that the poly(ethylene glycol) moiety assumes an extended confirmation in solution.

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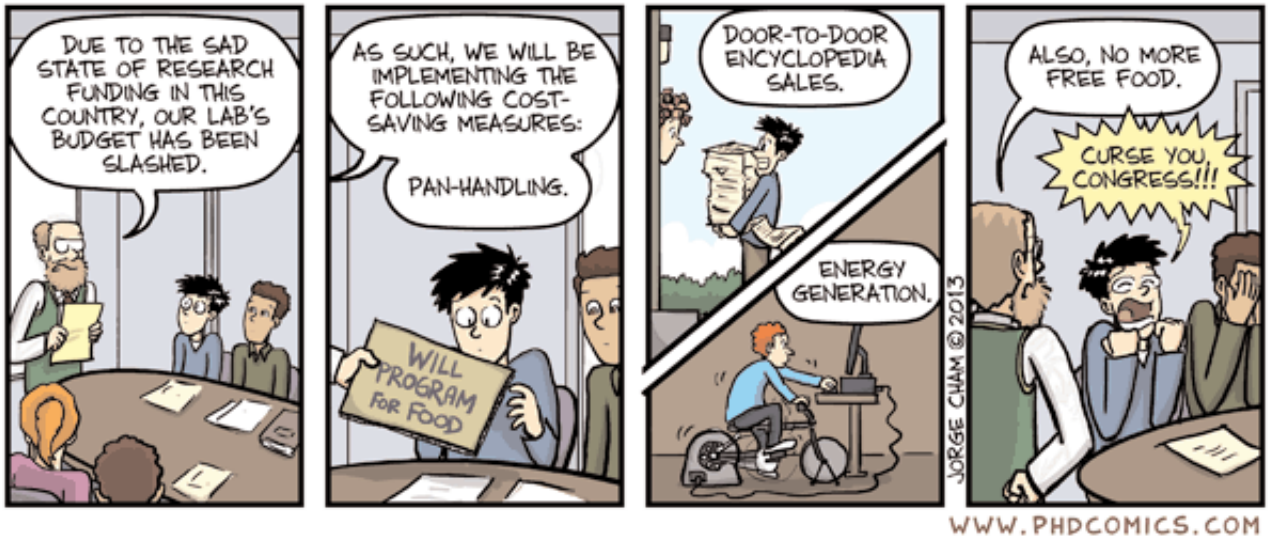
Conflict of interest statement
The author is an employee of BiogenIdec and owns company stock

THE TEN COMMANDMENTS OF STATISTICAL INFERENCE

1. **Thou shalt not hunt statistical inference with a shotgun.**
2. **Thou shalt not enter the valley of the methods of inference without an experimental design.**
3. **Thou shalt not make statistical inference in the absence of a model.**
4. **Thou shalt honour the assumptions of thy model.**
5. **Thy shalt not adulterate thy model to obtain significant results.**
6. **Thy shalt not covet thy colleagues' data.**
7. **Thy shalt not bear false witness against thy control group.**
8. **Thou shalt not worship the 0.05 significance level.**
9. **Thy shalt not apply large sample approximation in vain.**
10. **Thou shalt not infer causal relationships from statistical significance.**

From: http://jcdverha.home.xs4all.nl/scijokes/8_1.html#subindex



Courtesy of "Piled Higher and Deeper" by Jorge Cham
www.phdcomics.com

REMEMBER TO **JOIN** THE INTERNATIONAL CYTOKINE AND INTERFERON SOCIETY OR **RENEW** YOUR MEMBERSHIP FOR 2014 OR BEYOND (3 YEAR, 5 YEAR, LIFETIME (AGE 55+) AND STUDENT MEMBERSHIPS ARE AVAILABLE)

Signals

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Interferon Society

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