

# Signals

THE INTERNATIONAL CYTOKINE & INTERFERON SOCIETY NEWSLETTER

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Message from the ICIS President

**“If it’s both terrifying and amazing, then you should definitely pursue it.” – Erada Svetlana**

We are all passionate sleuths seeking to explain key biological problems. Despite the accelerating pace of today’s discoveries, so many mysteries remain to be solved. Insight often occurs with attention to unexpected results.

I invite you to share with us your unexpected results, and carefully consider the results of others at Cytokines2018. My hope is that the meeting rooms will be overflowing at the plenary sessions, smaller sessions, and poster sessions. It is your lively participation that moves science forward and keeps our society vital.

As a society we take so much pride in the accomplishments of our established investigators as well as our young scientists. The steadfast support from Philip Milstein and family to sponsor the Seymour & Vivian Milstein Awards has made it possible for us to provide these scientists with the recognition that they deserve. The generosity of the Milstein family has been mirrored by sponsors for the BioLegend William E. Paul Award, the Sidney & Joan Pestka Awards, and the Christina Fleischmann Award. Science philanthropy is inspirational, and can empower research and dramatic breakthroughs.

At Cytokines2018 I encourage you to attend talks and posters outside your specific area of research. It doesn’t matter if the topic involves fundamental biochemistry or big computational science. Your perspectives may shift, your excitement may heighten, and your science will expand.

Nancy C. Reich

### Future Meetings

Cytokines 2019  
Oct. 20-23, 2019  
Vienna, Austria

Cytokines 2020,  
November 1 - 4 2020  
Hyatt Regency Seattle,  
Seattle, USA

### Newsletter Editors:

Howard Young  
Marta Catalfamo  
Di Yu

### Managing Director:

Joan Oefner



# 2018 ICIS THE SEYMOUR AND VIVIAN MILSTEIN AWARD for Excellence in Interferon and Cytokine Research



## THE MILSTEIN AWARDS

The ICIS recognizes two world leaders in deciphering the role of innate immunity in the host immune response.



## THIRUMALA-DEVI KANNEGANTI, PHD

The ICIS Awards Committee have chosen Thirumala-Devi Kanneganti, PhD, as one of the recipients of the 2018 Seymour & Vivian Milstein Award for Excellence in Interferon and Cytokine Research in recognition of her numerous contributions and impact on our understanding of immunology, inflammation, cytokine signaling and host-pathogen interactions. The field of innate immunity and inflammation has emerged as a central focus in biomedical research in recent years, and Dr. Kanneganti's contributions are at an outstanding level and at the forefront of this research area.

Dr. Kanneganti is the Vice Chair of the Immunology Department and the Rose Marie Thomas Endowed Chair at St. Jude Children's Research Hospital in Memphis, Tennessee. Her first major contribution to the field of innate immunity was the initial discovery of the role of the NLRP3 inflammasome in caspase-1 activation by microbial components (Nature 2006 Mar 9;440(7081):233-6). Her research identified the activation mechanisms of inflammasomes during infections and autoinflammatory diseases, and the crosstalk between several cell death pathways, namely pyroptosis, apoptosis and necroptosis. Using novel genetic mouse models and in-depth molecular and biochemical analyses, her lab has discovered distinct and previously unrecognized functions of the cytokines IL-1, IL-1 and IL-33 and their signaling pathways in inflammatory diseases and cancer. Her lab has recently identified ZBP1/DAI as an innate sensor of influenza virus that triggers the NLRP3 inflammasome and programmed cell death pathways. Additionally, research from her lab discovered roles for NLRC3 in regulating PI3K signaling and for the cGAS-STING-IRF-GBP-IRGB10 pathway in liberating ligands that are eventually sensed by the AIM2 and NLRP3 inflammasomes. Her studies have contributed significantly to shaping our current understanding of the NLRs, inflammasomes, interferons, and cytokines of the IL-1 family in all areas of immunology. Dr. Kanneganti is well

known for her many original and critically important contributions to our understanding of how the innate immune system recognizes and responds to pathogens and how genetic mutations in innate immunity affect the development of infectious, inflammatory, and autoimmune diseases in humans.

Dr. Kanneganti's story is compelling and her achievements remarkable. Dr. Kanneganti grew up in modest circumstances in India. She was an exceptional student, ultimately receiving a Ph.D. and the Jawaharalal Nehru Award for Outstanding Doctoral Thesis, a competitive award only conferred on 18 Ph.D. doctoral graduates in all of India. Her early efforts focused on understanding plant pathogens and toxins relevant to her region. This led her to question general principles related to how all organisms respond to pathogens, inflammation, and to move to one of the best laboratories in the United States to study this.

Dr. Kanneganti's ascendance, as she has moved through her post-doctoral studies to a junior faculty position at St. Jude Children's Research Hospital to her current position as the Vice-Chair of Immunology and Member (equivalent of Full Professor) in the Department of Immunology, has been phenomenal. Most recently, she received the Rose Marie Thomas Endowed Chair, the highest honor faculty at St. Jude can receive. She is currently the Chair of the NIH Innate Immunity and Inflammation study section and has received the 2015 Vince Kidd Mentor of the Year Award. The American Association of Immunologists (AAI) has recognized her contributions to the field of immunology by selecting her for the AAI-BD Biosciences Investigator Award in 2015, and she also received the Society for Leukocyte Biology (SLB) Dolph O. Adams award, the Eli Lilly and Company-Elanco Research Award from the American Association of Microbiology (ASM) and was recently elected to the Society of Mucosal Immunology Board of Councilors and Telengana Academy of Sciences.



## LUKE A.J. O'NEILL, PhD, FRS

Luke A.J. O'Neill, PhD, FRS is Professor & Chair of Biochemistry in the School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute at Trinity College Dublin, Ireland. Professor O'Neill is awarded the 2018 Seymour & Vivian Milstein Award for Excellence in Interferon & Cytokine Research in recognition for his seminal contributions to our understanding of the molecular basis of inflammation and immunity. He is one of the key figures whose research and publications are responsible for the major increase in interest amongst immunologists in innate immunity over the past 20 years and is listed by Thompson Reuters/ Clarivates in the top 1% of immunologists in the world, based on citations per paper.

His interest in cytokines began in 1985 during his PhD at the Royal College of Surgeons in London on the recently cloned IL1. He worked on the mechanism whereby IL1 could increase production of prostaglandins, providing an early description of inducible cyclooxygenase. He continued investigating IL1 signaling as a postdoctoral scientist working with IL1 co-discoverer Jerry Saklatvala at the Strangeways Research Laboratory in Cambridge where he did work on IL1 signal transduction and NFkappaB. Establishing his own lab back in Dublin he continued to study NFkappaB, providing early descriptions of NFkappaB in brain and studying its redox regulation. His interest in IL1 signaling continued and he wrote a key review describing in detail the Toll-IL1 receptor- resistance (TIR) domain as a critical domain in innate immunity. This led to the discovery of viral proteins with TIR domains which he showed were inhibitors of Toll-like receptor (TLR) signaling, providing the first link between TLRs and viruses. This interest in the TIR domain led to the discovery of the protein Mal, a signaling adapter which he showed to be essential for signaling by the LPS receptor TLR4, which has more recently been shown to be critical for all TLRs (with the exception of TLR3) making it a central player in innate immunity and a key signal linking innate and adaptive immunity. O'Neill then carried out extensive characterization of signaling mechanisms for TLRs, uncovering negative regulatory mechanisms (including miRNAs) and recent important work on

metabolic changes in macrophages triggered by TLR4. His metabolic work also involved the NLRP3 inflammasome, which drives production of the key cytokines IL-1 and IL-18, investigating its role in Type 2 diabetes, uncovering control mechanisms and also reporting the first potent selective inhibitor of NLRP3 which has tremendous potential as a novel anti-inflammatory agent.

His work on metabolic changes induced by TLR4 has made a pioneering contribution to the currently burgeoning field of Immunometabolism, whereby immune cells undergo metabolic reprogramming to elicit specific effector functions. O'Neill identified the metabolite succinate as a key inflammatory signal, driving IL1beta production. More recently he has uncovered a critical anti-inflammatory role for the citrate - derived metabolite itaconate, acting via Nrf2.

All of these contributions have helped to place the field of innate immunity center stage in the effort to understand host defense mechanisms and inflammation and are fundamental findings in biology of the immune system and are also important for efforts to develop new treatments of infectious and inflammatory diseases. In short, O'Neill is a world authority on signaling in inflammation and innate immunity.

In 2013 he served as co-President of the newly inaugurated International Cytokine & Interferon Society with Chuck Samuel.

Professor O'Neill is founder director of three companies exploring innate immune targeting, Opsona, Inflazome and Sitryx. He is also a member of the External Immunology Network at GSK, where he has been a visiting scientist.

He was awarded the Royal Dublin Society / Irish Times Boyle Medal for scientific excellence, the Royal Irish Academy Gold Medal for Life Sciences, The Society for Leukocyte Biology (SLB) Dolph O. Adams award and the European Federation of Immunology Societies Medal. He is a member of the Royal Irish Academy, EMBO (European Molecular Biology Organization) and a Fellow of the Royal Society.

2018  
THE ICIS-BIOLEGEND  
WILLIAM E. PAUL AWARD  
for Excellence in  
Cytokine Research



## GIORGIO TRINCHIERI, MD

Dr. Giorgio Trinchieri is the recipient of the 2018 BioLegend William E Paul Award for Excellence in Cytokine Research in recognition of his collective contributions to the field of cytokine biology. *“The ICIS is honored to present the BioLegend William E. Paul Award to Dr. Trinchieri this year for his pioneering contributions to our understanding of the role of cytokines in inflammation, immunity, and cancer. His discovery of interleukin-12 provided the link between cells and cytokines of innate immunity with those of adaptive immunity. His cutting-edge research on the interface of inflammation and immunity will continue to provide knowledge that will translate basic science discoveries to clinical therapeutics.”* said Dr. Nancy Reich Marshall, President of the ICIS.

Dr. Trinchieri is currently the Director of the Cancer and Inflammation Program and an NIH Distinguished Investigator. Previously Dr. Trinchieri held positions as Professor and Chair of the Immunology Program at the Wistar institute (1990-1999) in Philadelphia, PA and Director of the Schering Plough Laboratory for Immunological Research in Dardilly, France (1999-2004).

Dr. Trinchieri is internationally recognized for his seminal contributions to the field of cytokine biology. Collectively, his work has led to the characterization of critical elements involved in the interplay between inflammation/innate resistance and adaptive immunity, and in the definition of central roles of cytokines and interferons in the regulation of hematopoiesis, innate resistance and immunity in infections and cancer.

Dr. Trinchieri together with his team and collaborators has a long list of seminal discoveries in the field of cytokine biology including but not limited to:

- The discovery and cloning of Interleukin-12
- The identification of Interleukin-12 as the major cytokine regulating Th1 responses
- Demonstration of the critical role of Interleukin-12 in the axis dendritic cells/phagocytic cells/NK cells/ T and B cells at the interface between innate resistance/inflammation and adaptive immunity
- The discovery and cloning of human 2B4 (CD244) receptor on NK and T cells and identification of its functions and binding to CD48

- The identification of human natural interferon producing cells (now known as plasmacytoid Dendritic Cells) and their essential role in NK cell-mediated lysis of virus-infected cells.
- The identification of the mouse Type I Interferon producing cells or plasmacytoid DC and characterization of their role in viral infections and in the immune response
- The identification of the central role of IL-10 in suppressing anti-cancer functions of macrophages and Dendritic cells, and identification of IL-10 antagonism (anti-IL-10 antibodies) as a promising therapeutic approach for inducing both innate and adaptive anti-cancer defense mechanisms

Dr. Trinchieri's work truly defined the area of IL-12 biology and has led to multiple patents for use of IL12 in therapeutics.

In recognition of his work Dr. Trinchieri has been the recipient of numerous prestigious awards including the Cancer Research Institute's W. B. Coley Award for Distinguished Research in Basic and Clinical Immunology, the Milstein Award from the International Society for Interferon and Cytokine Research, the Lifetime Honorary Membership Award, International Cytokine Society, the Richard V. Smalley, MD Memorial Award from Society for immunotherapy of Cancer and was listed as the 1st most cited immunologist in 1993-2003 period by Highly Cited Researchers, Immunology and Clinical Medicine.

## WHO International Cytokine Standards and Reference Preparations

The ability to quantify the activity of cytokines is an essential part of experimental and clinical investigation and is to a large extent dependent upon the availability of suitable cytokine standards and reference reagents. The ICIS Standards Committee was established two decades ago (when part of the ISICR) to make recommendations regarding interferon and cytokine standards and standardization to the ICIS membership, and thereby to the international cytokine scientific community. The Committee works closely with the World Health Organization (WHO), the National Institute for Biological Standards and Control (NIBSC), the U.S. National Institutes of Health (NIH), the Biodefense and Emerging Infections Resources Repository (BEI Resources), pharmaceutical manufacturers, and regulatory agencies. The Committee has included members from several of these organizations. Current potential topics under analysis by the Committee include the establishment of appropriate standards for biosimilars, pegylated biopharmaceuticals, and antibodies directed against protein-based drugs. The role that the Committee plays as a source of information and recommendations to the ICIS membership, and to the international cytokine scientific community as a whole, is very much dependent upon suitable standards and reference materials being made available by the NIBSC. Similarly, the Standardization and Nomenclature Committees of the ICIS reviews the need for cytokine standards and their usage.

Cytokine and growth factor preparations available from the NIBSC are found at <http://www.nibsc.org/products.aspx>

International Standards and Reference Reagents are established by the Expert Committee on Biological Standardization of the WHO. The use of these International Standards and Reference Reagents to calibrate commercially available or laboratory made reagents will facilitate comparisons of data between assays, different laboratories, and individual studies.

**Amanda Proudfoot**  
ICIS Standards Committee Chair

Inquiries concerning NIBSC products should be addressed to Meenu Wadhwa PhD, Leader, Cytokine & Growth Factors Section; [Meenu.Wadhwa@nibsc.org](mailto:Meenu.Wadhwa@nibsc.org)



**2018 ICIS  
AWARD WINNER  
HONORARY LIFETIME  
MEMBERSHIP**

### **Honorary Lifetime Membership Award**

Nominations are solicited for Honorary Life Memberships in the ICIS. Each year an individual will be awarded Life Membership as a tribute to his/her contributions to the field. Nominees should be individuals who have made substantive contributions to the cytokine/chemokine/interferon field over much of their careers, either in basic, clinical or applied research. Honorary members are esteemed members of the Society and provide us with an historical perspective and valued research tradition. Honorary Life Members are accorded all rights and privileges of active members, are exempted from Society dues and annual meeting registration fees, and are listed in the dedicated Honorary Life Members section of the Society web site.



**WILLIAM ROBERT FLEISCHMANN JR., PHD**  
*Central Michigan University College of Medicine, Mt. Pleasant, USA*

Professor Emeritus, William Robert Fleischmann, Jr., Ph.D. has been actively engaged in interferon research since the early 1970's. His research activities have involved examining the antiviral, growth inhibitory and anti-tumor activities of IFN- $\alpha$ , IFN- $\beta$  and IFN- $\gamma$ . His research studies have had widespread clinical implications, particularly on the use of colony stimulating factor to reverse bone marrow suppression. Dr. Fleischmann has been a staunch supporter of the Society journal, JICR, routinely publishing his research findings in the journal over many years. He has served the Society as a member of the International Council, as a member of the Editorial Board of the JICR for 13 years, and as the Chair of the Publications Committee for 20 years. He has demonstrated his commitment to the Society through

establishing the annual Christina Fleischmann Award to Young Women Investigators working in cytokine, chemokine and interferon biology. The award is dedicated to the memory of ISICR member and outstanding interferon research scientist Christina Fleischmann, Ph.D. This prestigious award, showcasing excellence in science and, specifically, promoting women in science has allowed the ICIS to profile young female scientists early in their research careers.

Please join us on Saturday, 27 October, for the presentation of the 2018 ICIS Honorary Lifetime Membership Award to Professor Emeritus William Robert Fleischmann, Jr. We also look forward to having Dr. Fleischmann present the Christina Fleischmann Award to the 2018 winner in Boston.

# 2018 ICIS DISTINGUISHED SERVICE AWARD

The ICIS will on occasion bestow this honor on an ICIS member who has made an extraordinary contribution to the Society. The individual will have devoted significant time and energy over a period of years to elevating the goals of the Society in furthering research on interferon, cytokines and chemokines.



## TADAMITSU KISHIMOTO, MD, PHD

*Professor Emeritus, Osaka University, Osaka, Japan*

Professor Emeritus, Tadimitsu Kishimoto, MD, PhD, is honored with the 2018 ICIS Distinguished Service award in recognition of his extraordinary contributions to science, teaching and drug development within the field of cytokine research. The 2018 ICIS Distinguished Service Award acknowledges Kishimoto's career-long achievements to the field of cytokine research including his commitment to supporting the next generation of scientists as a mentor, teacher and tireless advocate for young investigators.

As a pioneer in the field of cytokine research, Professor Kishimoto is responsible for transforming the cytokine field from a descriptive and phenomenological discipline to one firmly anchored in the molecular biomedical sciences. Perhaps foremost in his career, Dr. Kishimoto discovered and cloned interleukin-6 and its receptor components, IL-6R $\alpha$  and gp130. In the course of the work, Kishimoto also defined the signal pathway including the cloning of the transcription factors NF-IL-6 and STAT3, both central factors in the action of IL-6, and discovery of the negative regulators of cytokine function, suppressors of cytokine signaling (SOCS) family.

Kishimoto is also credited with description of IL-6 in the pathogenesis of cardiac myxomas, multiple myeloma, Castleman's disease, rheumatoid arthritis, Crohn's disease and juvenile idiopathic arthritis. Recognizing the importance of this pathway to human health, Kishimoto was instrumental in developing the anti-IL-6R $\alpha$  monoclonal antibody ACTEMR<sup>A</sup>® (tocilizumab)

which has provided therapeutic benefit across several auto-inflammatory diseases including rheumatoid arthritis and juvenile idiopathic arthritis. That his work has spanned from discovery to the development of an effective therapeutic highlights the breadth and depth of his accomplishments.

With the awarding of the 2018 ICIS Distinguished Service Award, the Society wishes to acknowledge Dr. Kishimoto's great contributions to the field of cytokine research over many decades. Of note, he organized the Cytokine Workshop in Kobe in 1993, as President of the International Cytokine Society in 1995 (which merged with the ICIS in 2013), and as Honorary President of the ICIS meeting in Kanazawa in 2017. His contributions to the Kanazawa meeting doubled the amount of travel awards made available to Young Investigators which contributed to the success of that meeting. He continues to encourage young investigators by administering the Tadimitsu Kishimoto International Travel Award to support around 40 Japanese Society for Immunology (JSI) members presenting his/her data at an international meeting, including the ICIS Annual Cytokines meetings.

Please join us on Saturday, 27 October, for the presentation of the 2018 ICIS Distinguished Service Award to Professor Tadimitsu Kishimoto.

# 2018 ICIS AWARDS



## THE MILSTEIN AWARDS

The Milstein Awards – 30 Years of Support Leading to New Treatments in Immunology, Rheumatology, Cancer, Infectious Disease and Inflammation

### PRESTIGIOUS. IMPORTANT. CELEBRATED

The continued generosity of the Milstein family through the Milstein Foundation, has made a difference to medical research. They have supported the recognition of significant medical breakthroughs by pioneering scientists, as well as ensured the success of our future scientific leaders. Vivian and Seymour Milstein initiated the Milstein Awards for Interferon and Cytokine Medical Research, and their children, Philip and Constance Milstein continue their legacy as generous donors. Their support has made a significant impact on promoting medical science that will benefit the health of society in many years to come. This is the 30th year of the prestigious Milstein Awards, the Milstein Young Investigator Awards, and the Milstein Travel Awards. We are grateful of their selfless philanthropy.

## MILSTEIN YOUNG INVESTIGATOR AWARDS



### 1ST PLACE MILSTEIN YOUNG INVESTIGATOR AWARDEE:

**CRISTINA BERGAMASCHI**, NATIONAL CANCER INSTITUTE AT FREDERICK, FREDERICK, USA

**TREATMENT WITH HETERODIMERIC IL-15 SHAPES THE CYTOKINE AND CHEMOKINE MILIEU OF THE TUMOR, PROMOTING TUMOR INFILTRATION BY CYTOTOXIC LYMPHOCYTES: A GENERAL METHOD FOR LYMPHOCYTE ENTRY IN TUMORS**

**Presentation on Sunday, 28 October, 09:45 – 10:00 in Plenary Session I**



## MILSTEIN YOUNG INVESTIGATOR AWARDEES:



**RICARDO RAJSBAUM**, UNIVERSITY OF TEXAS  
MEDICAL BRANCH, GALVESTON, USA

REGULATION OF NOVEL PATTERN RECOGNITION RECEPTOR  
SIGNALING AND IFN INDUCTION BY UNANCHORED K48-  
LINKED POLYUBIQUITIN CHAINS

Presentation on Sunday, 28 October, 10:00-10:15 in Plenary  
Session I



**GREG SONNENBERG**, WEIL CORNELL, NEW YORK  
CITY, USA

CYTOKINE REGULATION OF INTESTINAL HEALTH

Presentation on Sunday, 28 October, 16:30 – 16:55 in Symposium  
6: Intestinal Homeostasis



**VIJAY RATHINAM**, UCONN HEALTH SCHOOL OF  
MEDICINE, FARMINGTON, USA

THE EXPANDING FUNCTIONS OF THE INFLAMMASOME  
COMPLEXES

Presentation on Tuesday, 30 October, 11:00 – 11:25 in Symposium  
15: Inflammasome and IL1 Family members II



**MUNIR AKKAYA**, NIAID, NIH, BETHESDA, MD,  
USA

TYPE I INTERFERONS REGULATE B CELL DEVELOPMENT AND  
DIFFERENTIATION

Presentation on Monday, 29 October, 10:20-10:35 in Plenary 2:  
Advances in Pathogenic Th17 axis of evil

# 2018 ICIS AWARDS

## THE CHRISTINA FLEISCHMANN AWARD TO YOUNG WOMEN INVESTIGATORS



**SOPHIA DAVIDSON**, WALTER AND ELIZA HALL INSTITUTE FOR MEDICAL RESEARCH, PARKVILLE, AUSTRALIA

**DELINEATION OF THE INFLAMMATORY PATHWAY BEHIND PROTEASOME-ASSOCIATED AUTOINFLAMMATORY SYNDROME**

Presentation on Sunday, 28 October, 10:15 – 10:30 in Plenary Session I

## ICIS GUEST SOCIETY SYMPOSIUM: CYTOKINES IN IMMUNE-STROMAL CELL INTERACTIONS

CHAIR: DR. MANDY MCGEACHY, UNIVERSITY OF PITTSBURGH

Join us in San Diego for the world's leading annual all-immunology event!

[IMMUNOLOGY2019.org](http://IMMUNOLOGY2019.org)

IMMUNOLOGY 2019<sup>™</sup>  
May 9–13, 2019  
AAI Annual Meeting  
San Diego, California

103<sup>rd</sup> ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS (AAI)

The Journal of  
Immunology

 ImmunoHorizons



## THE SIDNEY & JOAN PESTKA POST-GRADUATE AND GRADUATE AWARDS



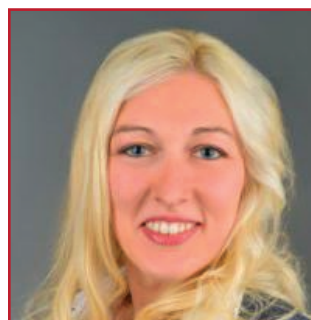
**The Sidney & Joan Pestka Post-Graduate Award**

**CHRISTOPH SCHNEIDER**, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, USA

A METABOLITE-TRIGGERED TUFT CELL-ILC2 CIRCUIT DRIVES SMALL INTESTINAL REMODELING

**Presentation on Sunday 28 October, 12:25-12:35 in Symposium 1: Innate Sensing and Signaling**

Sponsored by PBL Assay Science



**The Sidney & Joan Pestka Graduate Award**

**ERIKA ENGELOWSKI**, HEINRICH-HEINE-UNIVERSITY, DUESSELDORF, GERMANY

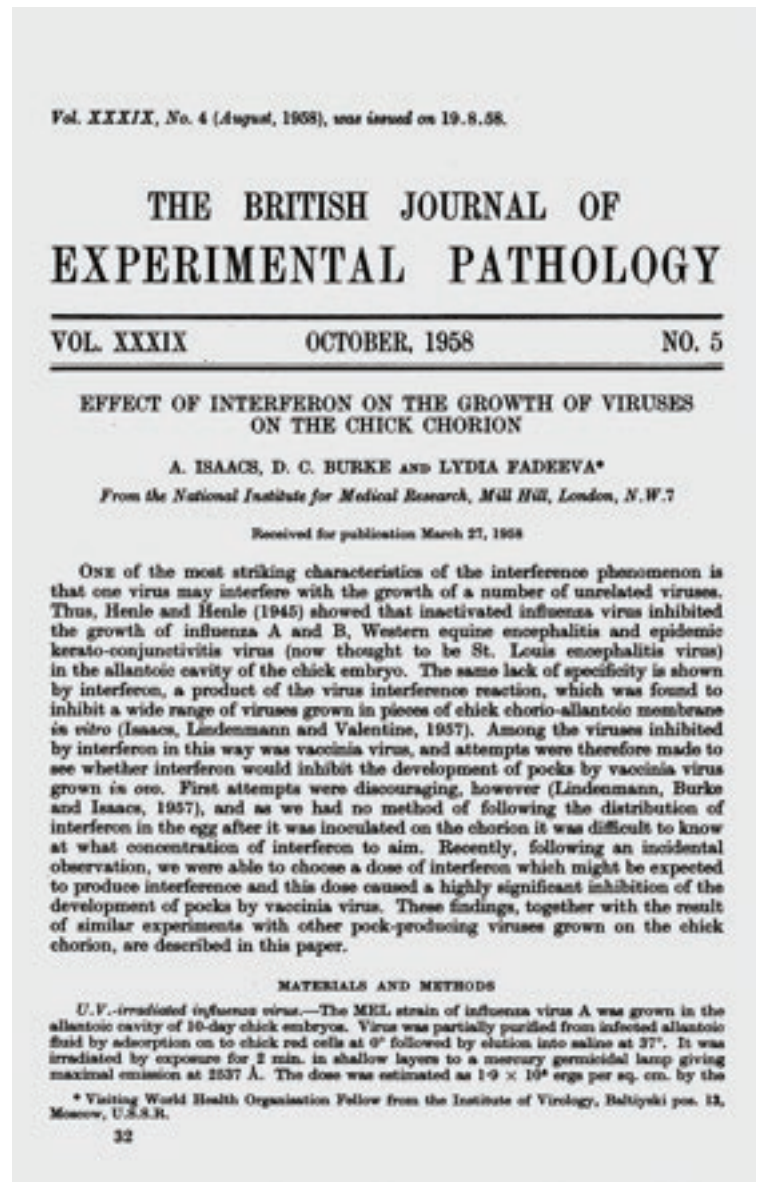
DI- AND TRIMERIC BIOLOGICAL SWITCHES MADE OF NANOBODY-CYTOKINE RECEPTOR FUSION PROTEINS SIMULATE NATURAL SIGNAL TRANSDUCTION

**Presentation on Sunday 28 October, 12:15-12:25 in Symposium 1: Innate Sensing and Signaling**

Sponsored by PBL Assay Science

# DISCOVERING INTERFERON

Derek Burke



It was October 1957 when I first encountered interferon. After six years (1947 -53) in the Chemistry Department at the University of Birmingham, England, I had a BSc and a PhD in organic chemistry, which was followed by two years post-doctoral research in the Chemistry Department of Yale University. I returned to the UK in 1955 with two degrees, a new American wife, but no job and very little money. I was also due to be 'called up' for two years into Britain's peacetime army, who could send me anywhere in the world, but of course without my wife.

But some jobs in scientific research carried ‘deferment’ from call up’ and I started to look for such jobs. The first to be offered to me was one working on rocket fuel development in a company on the west coast of Scotland, just south of Glasgow. It was not very attractive but I could not just turn it down, so I went for an interview and was offered a job I did not want. I temporized. Then a more attractive job was advertised for work in a Government Laboratory in England on secret work. I went for interview there, was offered the job orally, but was told that it would take a few days for it to be approved. It actually took several months, probably for security clearance, by which time I had another job.

For at that interview, someone had mentioned that he thought that ‘there was a job going at Mill Hill’. Even I knew that this was the National Institute for Medical Research, situated on the Northern edge of London and run by the MRC. It was and is one of the elite research institutions in the UK. I wrote to the Director, Sir Charles Harington FRS, an outstanding biochemist with a “conscientious and rigorous approach to research and administration, yet who valued academic freedom and creativity”. To my surprise, I was asked to go for an interview, and to my greater surprise, was offered a three year appointment to work on the biochemistry of influenza virus with Alick Isaacs. Moreover, it carried deferment from call up. It was the job of a lifetime. We found a small flat and I started work at Mil Hill in November 1955 on the base ratios of the RNA of influenza virus, and when, a couple of years later, that was drawing to a close, Alick “wondered whether I would be interested on working on something new they were working on called interferon”. I jumped at the chance; Alick was exciting to work with and the project sounded interesting. Little did I know it would last 25 years.

Very little was known at that time; it was clear that here was something new, but what it was—protein, nucleic acid or carbohydrate was not known, and the only way it could be detected was to incubate it with small pieces of chorioallantoic membrane from fertile hens eggs, then the tissue challenged with influenza virus to determine whether virus growth had been inhibited or not. The amount of interferon was the reciprocal of the dilution that suppressed virus growth to half. It was crude, slow and imprecise but it was all we had.

But it was easy to think of simple experiments to find out more about interferon, and so little was known that effectively

every experiment produced new data. It was a young post doc’s dream. I was so very fortunate: interesting and novel science in a newly developing field, working with a brilliant young scientist, happily married with two young children. What more could a young post doc want? A few things were obvious, some decent scientific publications, a place to work and a job with some security to bring up a family.

But more immediately, there was a problem; Alick was not well. The reception to the announcement of the discovery of interferon had been, to my surprise, half-hearted. The established virology labs were very cautious; one distinguished US scientist calling it ‘misinterpretation’. Now I would see this as the reaction of the establishment to being side lined by a bright younger man. Then I thought that maybe we had got it all wrong. It affected Alick greatly; he became depressed and had to take some time off from work. But there was a nagging worry about our experiments for we were inducing interferon production by treating chick embryo cells with inactivated influenza virus. Initially virus was inactivated by heating, a difficult process to control. However I quickly discovered that inactivation by ultraviolet irradiation was much more effective. But here was the snag; UV inactivated influenza virus itself showed up as positive in our assay. Were the effects we had seen due to traces of UV inactivated virus? If so, we were in trouble. Fortunately, I had discovered that interferon, but not inactivated influenza virus, was stable at pH 2, so the two were readily distinguishable. I spent the summer of 1958 repeating all the initial experiments, but using treatment at pH 2 to avoid false positives, and fortunately the initial data held up. But, as the Duke of Wellington said after the Battle of Waterloo in 1815 “it was a close run thing”. Alick slowly recovered but he was never quite the same again; that mercurial brilliant young scientist, who not many ever met, had gone forever.

Meantime I had started work on the purification of interferon, a project that took years. We had another child, and I got a job in the Biochemistry Department at the University of Aberdeen Scotland, just 500 miles away. But that is another story.

**Professor Derek Burke**

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# WELCOME

## NEW ICIS MEMBERS

We welcome these new members to the ICIS and we look forward to their attendance at the annual meeting and involvement in the society.

**Supreet Agarwal**

NCI, United States  
Research Advisor:

**Kathleen Kelly**

Sponsoring Member:  
**Howard Young**

**Felix Enam Yao Aggor**

University of Pittsburgh, United States

Research Advisor & Sponsoring Member:

**Sarah Gaffen****Sang Hyeon Ahn**

Republic of Korea  
Research Advisor:

**Hyung-Ju Cho****Munir Akkaya**

NIH, United States  
Research Advisor:

**Susan K. Pierce**

Sponsoring Member:  
**Howard Young**

**Sabrin Albeituni**

St. Jude Children's Research Hospital,  
United States

Research Advisor:

**Kim Nichols****Rachel Ancar**

University of Colorado Denver,  
United States

Research Advisor:

**Jay Hesselberth****Mahesh Bachu**

SMGI, PGD, NICHD, NIH,  
United States

Research Advisor:

**Keiko Ozato****Kaushal Baid**

McMaster University, Canada  
Research Advisor:

**Dr. Karen Mossman**

Sponsoring Member:  
**David Hare**

**Connor Gavin George Bamford**

MRC-University of Glasgow  
Centre for Virus Research,  
United Kingdom

Research Advisor:

**Professor John McLaughlan**

Sponsoring Member:

**Dr. Ludmila Prokunina-Olsson****Olivier Bernard**

University of California San  
Francisco, United States

Research Advisor & Sponsoring  
Member:

**Erin Gordon****Preeti Bharaj**

University of Texas Medical  
Branch Galveston,  
United States

**Amrita Bhattacharjee**

Childrens Hospital of Pittsburgh,  
United States

Research Advisor:

**Timothy Hand****Yvonne Bordon**

Nature Research,  
United Kingdom

**Thomas Brodnicki**

St Vincent's Institute, Australia

**Patrick Burkett**

Brigham and Women's Hospital,  
United States

**Sofija Buta**

Icahn School of Medicine at  
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## FROM SUPERNATANTS TO CYTOKINES: A PERSONAL VIEW ON THE EARLY HISTORY OF IL-1, IL-1RA, TNF AND ITS INHIBITOR IN RHEUMATOLOGY



Jean-Michel Dayer

### Abstract

Long-term cell cultures developed early in the twentieth century allowed identification in their supernatants of biological mediators subsequently defined as migration factors, interferons, lymphokines, monokines, cytokines and interleukins. In rheumatology, early in the 1930s, synovial cell cultures revealed two major distinct populations, i.e. synovial fibroblasts and monocyte-macrophages. Discovery of the interstitial collagenase (MMP-1) and its role in tissue destruction, such as in rheumatoid arthritis (RA), raised the question of the cellular source for this enzyme. My personal interest in the field was driven by the lack of understanding for the link between tissue destruction and immunology. This triggered our seminal contribution to the field, establishing in 1976–79 at the Arthritis Unit (Massachusetts General Hospital, with SM Krane) that a mononuclear factor (MCF, around 15 kDa) produced by stimulated macrophage, under direct contact with activated T cells, induced large amounts of collagenase and prostaglandin E2 (PGE2, a bone resorbing agent) in human synovial fibroblasts from RA patients. Our original “MCF” biological observations preceded cloning, and recombinant IL-1 confirmed the biological activity of the purified natural IL-1. Following my return to Geneva in 1980 and searching for a high level of IL-1 in urine and serum of patients with high fever or Still’s disease, to our surprise—“a finding of absence”—we found that IL-1 was masked by a factor of approximately 17 kDa and first presented this in 1984 at the Fourth International Lymphokine Workshop. In 1987, before IL-Ra cloning, my co-worker P Seckinger and I demonstrated first-time observation in cytokine biology that the mechanism was due to the inhibition of IL-1 binding the cell surface receptor, leading to the concept of IL-1 receptor antagonist (IL-1Ra). Having reported in 1985 that TNF/cachectin also induced collagenase and PGE2 in human synovial cells, we found that IL-1Ra did not block TNF- $\alpha$  but was due to another inhibitor. As other investigators, we confirmed that this inhibitory factor was a soluble TNF receptor. The years between the 1970s and 1990s were probably the most exciting period in the field of cytokines and cytokine antagonists; it gave rise to two concepts in the cytokine field—one of the receptor antagonist, and the other of soluble receptor antagonists.

Keywords: Rheumatoid arthritis, Auto-inflammatory diseases, Collagenase, Mononuclear cell factor, IL-1, IL-1Ra, Tumour necrosis factor, TNF inhibitors

The concept of supernatant in cellular biology originated in 1885 when Wilhelm Roux set up a tissue culture to maintain a medullary plate of an embryonic chicken in a warm saline solution for several days. Ross Harrison developed the methodology of cell culture (in 1907) that consisted of the “hanging drop technique”—whereby a small piece of tissue was placed in a drop of medium (including serum)—allowing cells to migrate from tissue to the surrounding environment. Further landmarks were set first in 1911 by Alexis Carrel and Montrose Burrows with their long-term aseptic technique of culture tissue cells and its possibilities, and later in 1935 by Alexis Carrel and Charles Lindbergh who devised new cell and organ culture systems. In rheumatology, a seminal description of “the form and function of synovial cells in tissue cultures” by Ernst Vaubel at the Rockefeller Institute Hospital (in 1933) highlighted early on the difference between macrophage-like cells and fibroblast-like cells, introducing the terminology of “synovioblast”, which in turn gave rise to the question of differentiation from one to the other<sup>[1]</sup>

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The history of the precursor of “cytokines” dates to allergy and infection by permeability factors from supernatant of tissue sensitized to tuberculin by Hans Zinsser and Takeo Tamiya (in 1926) and the conceptualization of its mechanisms by Arnold Rich (in 1927). In 1958, Byron Waksman and Margit Matolfsky realized that “sensitized” macrophages were stimulated rather than damaged by tuberculin protein. In 1957, Alick Isaacs and Jean Lindenmann coined the term “interferon” when observing that the inhibition (“interference”) of the growth of live influenza virus in chicken embryo chorioallantoic membranes was mediated by a protein released by cell membranes treated with heat-inactivated influenza virus. In 1966, a substance inhibiting the migration of normal peritoneal exudate macrophages was reported simultaneously by John David as well as by Barry Bloom and Boyce Bennett, termed migration-inhibitory factor (MIF). Nancy Ruddle and Byron Waksman as well as William Kolb and Gale Granger described lymphotoxin (LT) in 1968, later also referred to as TNF- $\beta$ . The terminology of “lymphokine, monokine” was employed by Dudley Dumonde in 1969, “lymphokines” being defined as “non-antibody mediators of cellular immunity generated by lymphocyte activation”, pointing to the implication of certain lymphocytes in the innate immune system. The “lymphocyte-activating factor” (LAF) was identified by Igal Gery and Byron Waksman in 1972, as was the osteoclast-activating factor (OAF) by John Horton and Lawrence (Larry) Raisz in the same year. In 1974, Stanley Cohen introduced the term “cytokine” as a non-leukocyte also producing cytokines and pointed out that such molecules could be produced by many cells in the body. That same year, Charles Dinarello, Nathan Goldin and Sheldon Wolff described human “endogenous leucocyte pyrogen” (EP).

In rheumatology, from the 1950s until the 1970s, two different approaches in the pathogenesis of rheumatoid arthritis (RA) were concomitantly debated: one focusing on the role of the cellular and humoral immune components, including the immune complexes; the other on the biochemistry of structural matrix components of tissue, mainly collagens and proteoglycans. The terminology of “connective tissue diseases” was in fashion, but the link between immunology and the extracellular matrix (ECM) was poorly understood. Research on the ECM structures prompted biochemists to unravel structural and genetic anomalies of the matrix, leading to the concept that abnormal or denatured endogenous proteins, or collagen peptides—being recognized as foreign antigens—gave rise to autoimmune diseases such as RA. Subsequently, during the 1970s and 1980s, progress in enzymology encouraged scientists to investigate aberrations in enzymes and proenzymes, as well as their autoactivation, suggesting that part of the pathogenesis of RA could be linked to enzyme abnormalities. In the early 1970s,

investigators backtracked to pay closer attention to cellular aspects of the synovial tissue of RA patients (pannus), but very little was known at that time about the molecular pathways between immune cells and mesenchymal cells.

At the end of my specialization in internal medicine in Geneva, I was intrigued by the lack of connection between the field of “connective tissue diseases” involving matrix, tissue destruction, fibrosis, collagen and proteases and the field of “connectivity” involving immune cells, inflammation and mediators. The head of the Department of Medicine, Alex F. Müller, in Geneva advised me in 1974 to spend some time (actually 7 years!) at Massachusetts General Hospital (MGH), Boston, MA, USA. At MGH, Jeremy Gross and Charles Lapière of the Robert W. Lovett Memorial Group for the Study of Diseases Causing Deformities had in 1962 discovered interstitial collagenase (now termed MMP-1) released during limb regeneration in amphibia (tadpole tissue)<sup>[2]</sup>. This led the same group—the Arthritis Unit headed by Stephen Krane—to the discovery of human collagenase from rheumatoid synovium in organ culture<sup>[3]</sup>.

On my arrival at the Arthritis Unit of MGH, Stephen Krane assigned me the project of isolating the RA synovial tissue cells responsible for producing collagenase. At the time, macrophages were thought to be the main source of proteases, fibroblasts being the main source of ECM. After a year of vain and frustrating efforts to detect collagenase in isolated human macrophages from synovial tissue, it was finally in 1976 that I identified large amounts of collagenase and prostaglandin E2 (PGE2) produced in primary mixed cultures of synovial fibroblast cells (adherent stellate fibroblast-like cells); PGE2 being considered at the time to be an important bone-resorbing agent<sup>[4]</sup>. However, although collagenase production decreased progressively, it was still present when the mononuclear cells had disappeared after cell culture passages, suggesting that the previous contact of the synovial fibroblasts with the mononuclear cells was memorized. To unravel this phenomenon, blood mononuclear cells were isolated, stimulated and added to the late-passage fibroblast cultures, resulting in the reactivation of large amounts of collagenase and PGE2 production, along with the stellate aspect of fibroblast-like cells (**Fig. 1**). It turned out that this phenomenon was mediated by a partially purified factor of around 15 kDa that we termed “mononuclear cell factor” (MCF)<sup>[5, 6]</sup>. Consequently, synovial-like fibroblasts were the main source of interstitial collagenase and PGE2, but only in the presence of mononuclear cells. Indeed, interestingly, the cells producing most of the collagenase were also the principal source of their substrate, collagen. Based on this observation in 1979, when analysing the respective functions of the subpopulations of the mononuclear cells, we demonstrated that T lymphocytes (TL)

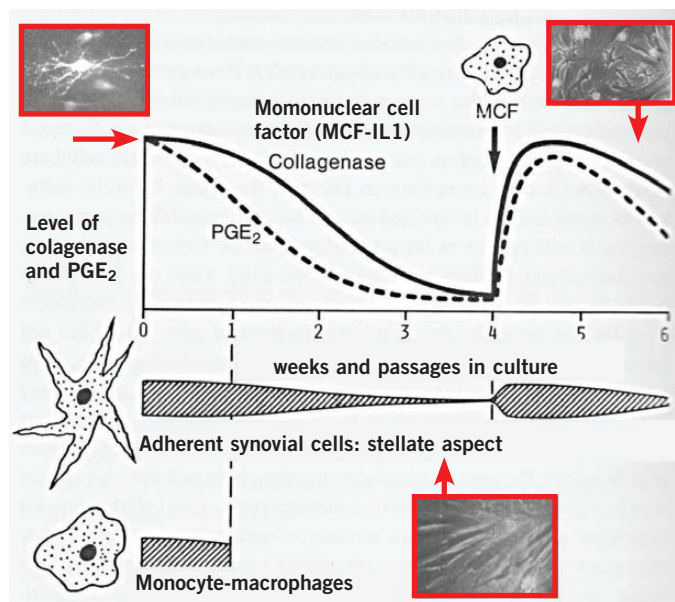
stimulated monocyte-macrophages ( $M\Phi$ ) to produce MCF, thus establishing the sequential pathways from TL to  $M\Phi$  and to synovial fibroblast activation. Except for the absence of B cells, the proposed scheme is still valid after 40 years [7, 8] (Fig. 2). Subsequently, we found that the direct contact between TL and  $M\Phi$  was essential and that it depended on the cell-surface molecules [9]. With regard to RA, self-associating IgG rheumatoid factors proved to stimulate directly MCF production by monocytes [10].

On purification, our “MCF” exhibited similar properties to LAF with a molecular weight of about 15 kDa and shared chromatographic and other biochemical properties [11]. It was not until 1979 that the nomenclature of IL-1 was coined at the Second International Lymphokine Workshop in Ermatingen, Switzerland, in a letter to the Editor of the Journal of Immunology entitled “Revised Nomenclature for Antigen-Nonspecific T Cell Proliferation and Helper Factors” [12], thus unifying previous factors with similar biomedical and biologic properties to LAF such as MCF. The monocyte products were defined as interleukin-1 and the T-cell products as interleukin-2; both were unrestricted to H-2 activity. In contrast to IL-2, which is essential for maintaining long-term T-cell cultures, IL-1 was unenabled [12]. Using cartilage organ culture as a target, John Dingle and Jeremy Saklatvala isolated a cartilage catabolic factor from synovium in 1979, later in 1986 called “Catabolin”. The precursor of TNF- $\alpha$ , cachectin/TNF, was identified in 1985 as a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced cells in Anthony (Tony) Cerami’s laboratory.

Then followed my return to Geneva in 1980, when several research groups were competing for the same objective: to clone IL-1. Starting with lectin-stimulated human blood mononuclear cells, we isolated poly(A) RNA and studied its translation after microinjection into *Xenopus laevis* oocytes. The mRNA translation products stimulated collagenase and PGE<sub>2</sub> production in human rheumatoid synovial cells and

dermal fibroblasts. The size of MCF mRNA was estimated at 10 S [13]. Our original biological observations preceded the cloning, the cDNA of IL-1 $\beta$  being reported by Charles Dinarello in 1984, and by means of recombinant IL-1 $\beta$  we confirmed the biological activity of our purified natural IL-1 [14].

At that same time, we needed large amounts of biological material to purify IL-1. It therefore occurred to us that patients who had great numbers of monocytes, such as patients with monocytic leukaemia (M5) or high fever, would be an ideal source. However, to our surprise—“a finding of absence”—no IL-1 biological activity could be detected in urine and serum of such patients or others with high fever such as those suffering from adult Still’s disease. Puzzled by this observation, we reasoned that the biological activity had to be present, while being masked. In fact, IL-1 was indeed masked by a factor of approximately 17 kDa. This seminal observation was first presented in 1984 at the Fourth International Lymphokine Workshop [15] and published in full papers [16, 17]. By coincidence, at that intense meeting, the first sequence of IL-1 $\beta$  was presented by Charles Dinarello. Afterwards, for us the most important goal was to unravel the mechanism of inhibition. Inspired by the endocrinology field during my stay at MGH, myself, my co-worker Philippe Seckinger and colleagues in Lausanne succeeded in reaching that goal. Indeed, by using the binding to EL4-6.1 cells we demonstrated in 1989 that a purified 125Iodinated natural inhibitor (apparent m.w. around 17 kDa) competed with natural IL-1, which confirmed for the first time the concept of interleukin-1 receptor antagonist (IL-1Ra), and we consequently described how a natural cytokine antagonist blocked the binding of another cytokine, and this from the same family [18]. The principle of the competitive binding assay of the IL-1 inhibitor to IL-1 at the IL-1 receptor level was crucial for researchers at Synergen at Boulder, Colorado, USA who purified and cloned IL-1Ra in 1990. We then collected more than 100 L of urine from patients to purify to homogeneity the IL-1 inhibitory factor [19]. The clinical role



**Fig. 1** Reactivation by MCF of large amounts of collagenase and PGE<sub>2</sub> production, along with the stellate aspect of fibroblast-like cells [5, 6]. IL interleukin, PGE<sub>2</sub> prostaglandin E<sub>2</sub>

of IL-Ra was established in 1987 in a clinical observation when analysing the serum and urine of children with systemic juvenile chronic arthritis (JRA), a typical inflammatory syndrome. An increase in IL-1 inhibition (IL-Ra) was observed following the peak of the fever [20] (Fig. 3, adapted scheme).

The events involving the transition from IL-1-Ra to TNF inhibitor occurred naturally. In the middle of the 1980s, overlapping biological activities between IL-1 and tumour necrosis factor (TNF- $\alpha$ ) were under discussion. Having reported in 1985 that TNF- $\alpha$  also induced collagenase and PGE<sub>2</sub> in human synovial cells, we found that the urinary inhibitor of IL-1 activity—which affected both interleukin-1 $\alpha$  and IL-1 $\beta$ —did not affect TNF- $\alpha$  [21, 22]. However, when analysing other chromatographic fractions, we isolated and purified a human inhibitor to TNF- $\alpha$  [23]. As did other investigators, we confirmed that this factor was the soluble TNF receptor [24].

Further work in our laboratory was focused on the effect of direct cell-cell contact on the regulation of IL-1, TNF and their respective inhibitors such as IL-1Ra and soluble TNF receptors (review [25, 26]).

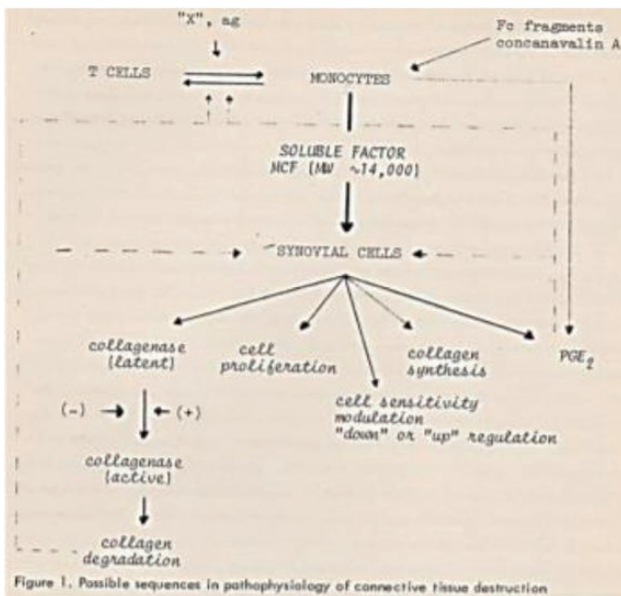
The years between the 1970s and the 1990s were probably the most exciting period in the field of cytokines and cytokine antagonists; it gave rise to two concepts in this field—one of the receptor antagonist, and the other of soluble receptor antagonists.

Cloning of cDNA of IFN- $\alpha$  and IFN- $\beta$  in 1980 and of cDNA of TL (TNF- $\beta$ ) and TNF- $\alpha$  and IL-1 in 1984 was achieved, followed by that of IL-1Ra in 1990. This has revolutionized the field, and since the 1990s recombinant molecules and specific monoclonal antibodies have allowed the expansion of the field of signal transduction, the dissection of the hierarchy of the different cytokines depending on the types of disease and therapeutic approaches. The latest interleukin is now IL-40 specifically produced by B cells.

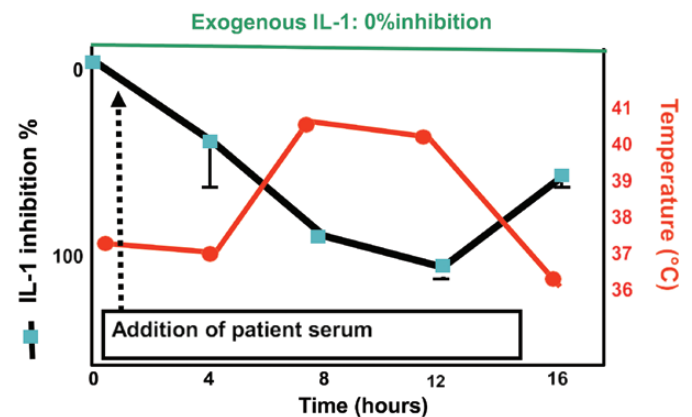
Still, discussion as to the cells responsible for the onset of RA is still the subject of debate and the initial role of synovial fibroblasts continues to be of interest, since there is clear evidence that their subpopulations express different genes and respond differently to cytokines [27]. Even if IL-1 blockade is marginally successful in RA, IL-1Ra—and probably other antagonists to the IL-1 family—has become most important in the treatment of several auto-inflammatory diseases, reminding us of our seminal observation of the inhibitor in JRA [20], whilst TNF or IL-6 has been the key cytokine to be blocked in RA and several other chronic inflammatory diseases.

#### Abbreviations

ECM: Extracellular matrix; EP: Endogenous leucocyte pyrogen; IgG: Immunoglobulin G; IL: Interleukin; JRA: Juvenile chronic arthritis; LAF: Lymphocyte-activating factor; LT: Lymphotoxin; MCF: Mononuclear cell factor; MGH: Massachusetts General Hospital; MIF: Migration-inhibitory factor; mRNA: Messenger ribonucleic acid; M $\Phi$ : Monocyte-macrophages; OAF: Osteoclast-activating factor; PGE<sub>2</sub>: Prostaglandin E<sub>2</sub>; RA: Rheumatoid arthritis; TL: T lymphocytes; TNF: Tumour necrosis factor



**Fig. 2** Sequential pathways from TL to MF and to synovial fibroblast activation [7]. MCF mononuclear cell factor, M $\Phi$  monocyte-macrophages, PGE<sub>2</sub> prostaglandin E<sub>2</sub>, Fc Fragment crystallizable of immunoglobulin, ag antigen



**Fig. 3** IL-1 inhibition (bioassay in presence of constant amounts of exogenous IL-1) following the peak of the fever induced by serum from children with systemic juvenile chronic arthritis (adapted scheme from [20]). IL interleukin

## Acknowledgements

In memorial of Stephen Krane and Phillippe Seckinger  
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## Authors' contributions

J-MD is the sole author. The author read and approved the final manuscript.

Ethics approval and consent to participate  
Not applicable.

## Competing interests

The author declares that he has no competing interests.

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# In Memoriam

## Gianni Garotta, Ph.D. (1943-2018)

On May 16th, 2018 Gianni Garotta, Ph.D. passed away after a short battle with colon cancer. Gianni had a combined record of academic (with over 160 original publications and 15 patents), pharmaceutical and biotech contributions.

He graduated with a degree in Biology from the University of Milan in 1966. He then completed a PhD in Physiology at the University of Milan and worked at the Wistar Institute of Philadelphia, at the Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano and at the Basel Institute of Immunology. From 1984 to 1994 he was the Head of Cytokine and Interferon Research and of Monoclonal Antibodies Development at the Central Research Unit of Hoffmann La Roche, Basel, Switzerland. In those years he provided important contributions to the characterization of the structure and function of the Interferon- receptor and was an early pioneer in the development of monoclonal antibodies in diagnostic and therapy. From 1994 to 1999 he was the Director of the Cell Biology Department and of High-Throughput Biological Screening at Human Genome Sciences Inc., Rockville, MD. His achievements included the preclinical and phase I development of the chemokine MIP1-1, the first drug discovered by the genomic approach and the development of three other drugs in phase I-II. From 1999 to 2004 Gianni was Vice President for Extramural Research and Academic Collaborations at Serono S.A., Geneva, Switzerland where he was a relentless tailor of many academic collaborations. From 2004 to 2012 he was in-house advisor for Life Sciences and Biotechnologies at Index Venture, Geneva, CH. Gianni applied his strong background in drug discovery and development as well as experience in identifying, evaluating and negotiating the transfer of assets from academia to manage many outsourced research programs. He started 4 biotech companies in Switzerland, USA, Italy and Denmark and until his death he was the Scientific Director of the Biotech Incubator Eporgen S.p.A. in Italy.

Gianni always remained close to the interferon and cytokine field. He was a co-chair of the 1st Joint Meeting of the International Society for Interferon and Cytokine Research and the International Cytokine Society, 1996, in Geneva, Switzerland and he was the driving force and committee chair for the 4th Joint Meeting, 2002, in Torino, Italy. Gianni has been a good friend for many of us, fellow cytokinologists and collaborators. We all remember him for his generosity to share his expertise in basic science, drug discovery and drug development. Many have reached out to him for advice and guidance. He and his wife Donata always opened their house to collaborators, colleagues and friends.



Gianni loved his family and his home and always wanted to share with others. He had a great zest for life and shared it with all he knew. His suburban house in Maryland and his mountain barn near Geneva with its sheep, donkeys and more recently horses (that he kept for taking care of the grass in the expansive grounds surrounding the house) will be remembered by many of us as places of relaxation and long discussions about science but also history, art, culture, and politics. Everybody who worked with him in his groups at Hoffman La Roche and at Human Genome Science remember him as a true mentor and friend. They remember his door to be always open and even no matter how stressful sometimes the meetings were, they usually ended up in laughter as Gianni frequently had jokes to tell and with the scientists feeling reassured by Gianni that all would be fine. And Gianni frequently invited them to his house for some risotto and good wine.

Gianni was exceptionally devoted to his family. He is survived by his wife Donata, his children Francesca, Marta and Paolo and four beloved grandchildren. Although Gianni and I have been working in some of the same institutions, we always did at different times. We became, however, very close, I owe him much scientifically and personally, I always appreciated his thoughtful advices and I will miss him greatly as one of my dearest friends.

### Giorgio Trinchieri

Cancer and Inflammation Program, Center for Cancer Research, NCI, NIH, Bethesda, MD

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# New Member MINIBIOs

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## **Sabrin Albeituni, PhD**

Postdoctoral Fellow  
Vice-chair Diversity- Postdoctoral Leadership Council  
St. Jude Children's Research Hospital  
Memphis, USA

I received my PhD training at the University of Louisville, in Louisville, Kentucky. Through my graduate studies, I became very interested in the mechanisms by which myeloid cells function in the tumor microenvironment. I decided to dedicate my postdoctoral training to studying myeloid cells more generally and their roles in other diseases. Currently, I am a post-doctoral research fellow in the lab of Dr. Kim Nichols at St. Jude Children's Research Hospital in Memphis, Tennessee. My research focuses in understanding the mechanisms of T cell regulation by myeloid cells in hemophagocytic lymphohistiocytosis (HLH), a fatal cytokine syndrome that is often triggered by infection. I am also investigating the therapeutic effects and underlying mechanisms of action of ruxolitinib, a potent JAK1/2 inhibitor, in dampening inflammation and promoting survival in HLH.



## **Connor Gavin George Bamford, Ph.D**

Postdoctoral Research Assistant  
MRC-University of Glasgow Centre for Virus Research  
Glasgow, Scotland, UK

Dr Connor Bamford is a postdoctoral research assistant in the laboratory of Professor John McLauchlan at the Medical Research Council – University of Glasgow Centre for Virus Research in Scotland, UK. He completed his PhD at Queen's University Belfast in the group of Professor Paul Duprex and Professor Bert Rima working on developing and characterising novel recombinant mumps viruses that produce fluorescent proteins to track the spread of infection in cell culture and animal models. Dr Bamford began his postdoctoral training in the McLauchlan lab in Glasgow focusing on how host cell proteins, such as interferons and the genes they induce, control hepatitis C virus infection. It was here that Connor developed an interest in how evolution and genetic diversity has – and continues to - shape interferon biology and his work revealed species-specific changes in the antiviral potential of interferon genes that could have negative consequences for viral hosts. Connor wishes to use this approach to understand disease and apply it to inform new therapeutic and preventative measures.

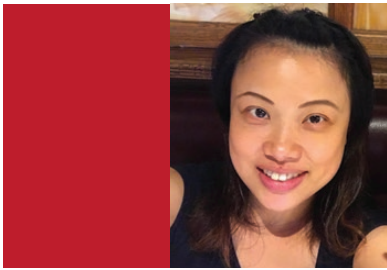


## **Dr Rami Bechara**

Postdoctoral fellow in the Gaffen Lab,  
Division of Rheumatology and Clinical Immunology,  
Pittsburgh, USA.

Dr Rami Bechara is currently investigating the mechanisms of molecular signal transduction mediated by IL-17 and its receptor driving pathogenesis of autoimmunity. Dr Bechara got his Pharm.D from Saint-Joseph University and did his PhD in Immunology in Inserm 996-France under the supervision of Prof. Marc Pallardy. During his PhD, Dr Bechara investigated the interaction between dendritic cells and T-cells in drug and chemical allergy. His work contributed to a better understanding of allergic reactions, on one hand, by studying the fine regulation of the IL-12 cytokines family in dendritic cells and on the other hand, by clarifying the mechanisms of patients immunization against drugs and chemicals.





**Ya-Shan Chen**

Ph.D. candidate  
Graduate Institute of Biomedical Sciences, Division of  
Biotechnology  
Chang Gung University, Taiwan, ROC

My research projects focus on the roles of inflammatory cytokines and their receptors in cancer development. I have investigated the effects of Interleukin 17 on tumor stroma and consequently immune suppressors within tumor microenvironment. Interleukin 17 (IL-17), correlating with advanced stage or poor prognosis of cancer patients, appears to contribute to tumor progression. Thus, I have also been interested in the role of IL-17 on the tumor growth and behaviors of tumor itself though the interference of IL-17/IL-17R signaling. Finally, I have been working on development of a potential gene therapy or vaccine for treating cancers. The recent findings demonstrate that the strategy of blockade against IL-17 successfully reduced tumor development, indicating IL-17/IL-17R is a potential target in cancer therapy.



**Christina Cho, PhD**

Postdoctoral Researcher  
University of Pennsylvania  
School of Veterinary Medicine

I was born and raised in Southern California by my supermom who always encouraged a sense of curiosity. I was first introduced to the fields of immunology and cell biology as an undergraduate at the University of California-Los Angeles, where I majored in Microbiology, Immunology, and Molecular Genetics. During my tenure at UCLA, I met one of the most influential people in my life, Dr. Sherilyn Gordon Burroughs. Dr. Gordon was a transplant surgeon with whom I did research for over a year. Not only was she an excellent surgeon, she was also a great mentor and exceptional role model. She encouraged me to apply for graduate school and continued to mentor me throughout my graduate career. I obtained my Doctor of Philosophy in the Biomedical Sciences at Albany Medical College. My primary research project aimed to delineate the biophysical and biochemical properties of the extracellular matrix protein, Fibronectin (FN), by utilizing a recombinant peptide which recapitulated a stable, unfolded intermediate of FN. Specifically, my project involved identifying the mechanism by which unfolded FN promoted chemoresistance in non-small cell lung cancer. Currently, I am a postdoctoral researcher at the University of Pennsylvania, where I conduct research under the mentorship of Dr. Serge Fuchs, a leader in the field of type I interferon-mediated signaling and ubiquitin-regulated pathways. My projects include investigating the role of type I interferon receptor in the development and metastatic progression of pancreatic and colorectal cancer.



**Min-Kyung Choo, PhD**

Instructor, Cutaneous Biology Research Center  
Massachusetts General Hospital and Harvard Medical School  
Charlestown, USA

Min-Kyung Choo has been working on cancer biology since a graduate student. She studied molecular mechanisms of inflammation-associated cancer for her PhD, and found that TNF-induced TAK1 signaling promoted cancer metastasis. During her postdoctoral training at MGH, she continued to investigate the role of cytokine-activated protein kinase signaling pathways in cancer, microbial infection, and skin diseases. Her findings of cell type-specific NF- $\kappa$ B functions in melanoma chemotherapy and type I interferon-mediated immune evasion in anthrax were published in *Cancer Discovery* and *J Exp Med*, respectively. Her study aimed at revealing the mechanism of p38MAPK-regulated skin stem cell homeostasis was supported by an NIH Dermatology training grant. She is currently an Instructor at MGH/HMS and investigates the interactions between epithelial cells and immune cells in the context of inflammatory diseases.

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## New Member MINIBIOs *Continued*

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**Ellen M. Gravallesse M.D.**

Chief, Division of Rheumatology  
And Program Coordinator, Rheumatology Fellowship  
University of Massachusetts Medical School  
Worcester, USA

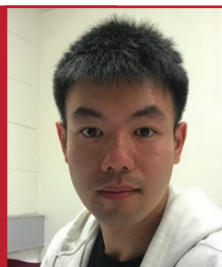
Ellen M. Gravallesse, M.D. is a tenured Professor of Medicine and holds the Myles J. McDonough Chair in Rheumatology at the University of Massachusetts Medical School. She serves as Chief of the Division of Rheumatology and Director of Translational Research for the Musculoskeletal Center of Excellence. Her laboratory investigates the fundamental mechanisms of inflammation and joint destruction in arthritis and has identified key pathways by which inflammation impacts bone in the rheumatic diseases. Her laboratory identified osteoclasts as the cell type responsible for bone destruction in RA, and RANKL as a critical cytokine produced by RA synovial tissues that drives osteoclastogenesis. In addition, work in her laboratory has identified the production of inhibitors of osteoblast function that prevent repair of bone loss in RA. Her current studies are directed at understanding innate immune mechanisms in inflammation and bone loss and formation in rheumatic disease. Dr. Gravallesse has served on the Board of Directors of the American College of Rheumatology (ACR) and as Chair of the ACR Journal Publications Committee. She will serve as President of the ACR in 2019 and currently also serves as an Associate Editor for the New England Journal of Medicine. Dr. Gravallesse is a member of the Henry Kunkel Society and is the recipient of the Sandoz Award for medical research, the Marion Ropes Award from the Arthritis Foundation, the Physician Achievement Award from the University of Massachusetts and the Steven Krane Award from ASBMR (2017). She lectures nationally and internationally.



**Emily Hemann, Ph.D.**

Postdoctoral Fellow  
Department of Immunology  
University of Washington

Dr. Emily Hemann is a postdoctoral fellow in the laboratory of Dr. Michael Gale, Jr. at the University of Washington. She received her Ph.D. in Immunology from the University of Iowa in 2014 where she investigated adaptive immune responses to influenza virus vaccines in the laboratory of Dr. Kevin Legge. Dr. Hemann is supported by an American Heart Association Postdoctoral Fellowship and is currently a Public Policy Fellow for the American Association of Immunologists. Her research seeks to understand how innate immune signaling regulates adaptive immunity, and is currently focused on the contribution of IFN to the generation of adaptive immune responses against respiratory viral infections.



**Ming-Chin Lee, PhD**

Department of Medicine  
The University of Melbourne  
The Royal Melbourne Hospital  
Royal parade, Parkville, Australia

Dr Ming-Chin Lee is currently conducting academic research as a postdoctoral researcher at the University of Melbourne since 2015. His major research focus has been on investigating roles of inflammatory cytokines, in particular the colony stimulating factor (CSF) family, in arthritis and arthritic pain development. He specializes in animal models of inflammation and inflammatory arthritis, having worked in the field for more than 5 years. His Ph.D. research focuses on the role of granulocyte-macrophage CSF (GM-CSF) in inflammation and inflammatory arthritic pain and disease. Most recently his interests have included understanding the role of a chemokine, CCL17, which was shown previously to be downstream of GM-CSF during inflammatory arthritis, on the development of osteoarthritis (OA).



**Jose Ordovas-Montanes, PhD**

HHMI Damon Runyon Postdoctoral Fellow  
MIT, the Ragon Institute, the Broad Institute and Boston  
Children's Hospital

Jose is a Damon Runyon Cancer Research Foundation HHMI Postdoctoral Fellow in the laboratory of Dr. Alex Shalek at MIT, the Ragon Institute, and the Broad Institute. His overarching scientific goals are to elucidate the organizing principles of how cytokines alter the homeostatic set point of human barrier tissues, with a specific focus on the concept of inflammatory memory. His recent work has uncovered how allergic inflammatory memory in human respiratory progenitor cells may contribute to the chronicity of disease.

His PhD thesis aimed to characterize the interactions between the sensory nervous system and how it controls immune responses in skin under the mentorship of Dr. Ulrich von Andrian. The key discovery from his work positioned heat-sensing nociceptors as a required cell type for robust IL-23/IL-17 axis cutaneous inflammatory responses by driving IL-23 production from dermal dendritic cells. His findings have led to further exploration by other investigators, many of which are members of the ICIS, of the communication modalities between these two systems.

Jose's work has been recognized with a Goldwater Scholarship, an NIH pre-doctoral Fellowship, the Jeffrey Modell Prize in Immunology at Harvard Medical School, and the MIT Outstanding Undergraduate Research Opportunities Program Direct Mentor award.



**Dr. Orna Ernst Rabinovich**

Postdoctoral Visiting Fellow  
Signaling Systems Section  
Laboratory of Immune System Biology  
National Institute of Allergy and Infectious Diseases

Dr. Orna Ernst Rabinovich is a postdoctoral visiting fellow in the Signaling Systems Section at the Laboratory of Immune System Biology, the National Institute of Allergy and Infectious Diseases, NIH, USA. She is a member of the American Association of Immunologists. She received her Ph.D. in Biochemistry from Tel Aviv University, Israel, in 2014. Her Ph.D. research focused on the cAMP-mediated regulation of the innate immune response during infection. Her current research aims to identify novel regulators of the non-canonical inflammasome which detects cytosolic LPS and leads to pyroptotic cell death. She is also studying the signaling pathways which regulate the metabolic reprogramming of macrophages during inflammation.



**Zia Rahman, MD, PhD**

Associate Professor of Microbiology and Immunology, and  
Medicine  
Penn State University College of Medicine  
Hershey Medical Center  
Hershey, PA 17033

Dr. Rahman is a tenured Associate Professor leading the autoimmunity research in the department of Microbiology and Immunology at Penn State University College of Medicine. His research interest is focused on understanding the mechanisms by which altered regulation of the germinal center, a major peripheral B cell tolerance checkpoint, drives autoantibody production, an essential initial step required for the development of systemic autoimmune disease SLE. For this purpose, he has developed several spontaneous mouse models of SLE in which he studies the regulation of spontaneously developed germinal centers (designated spontaneous germinal centers) in autoantibody production, and subsequent development of SLE. His laboratory has pioneered in investigating the regulation of spontaneous germinal centers in the context of SLE. Recent data from his laboratory suggest that innate signaling through the pattern recognition toll like (TLR) and interferon (both type I and II IFN) receptors are responsible for altering the germinal center pathway leading to high titers of autoantibody production. Studies are underway in his laboratory to further investigate the possible crosstalk between TLR and IFN signaling in driving the formation of spontaneous germinal centers and subsequent development of SLE. His lab is interested in determining the cell-type specific roles of STAT (Signal Transducer and Activator of Transcription) molecules in the initiation and maintenance of spontaneous germinal centers and the development of SLE; and studying these pathways in human B cells and myeloid cells in SLE patients. He is an active member of the American Association of Immunologists (AAI) and serves as an associate editor for the Journal of Immunology, and Frontiers in Immunology. He is also a member of the American College of Rheumatology (ACR). Recently, he has become a member of the International Cytokine & Interferon Society.

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## New Member MINIBIOs *Continued*



### **Manu Rangachari**

Associate Professor  
Department of Medicine of Laval University, Quebec City, and in the  
Department of Neurosciences at the Quebec City University Hospital  
Research Center, Canada

My lab works on understanding the contribution of T lymphocytes to disease processes in secondary progressive multiple sclerosis. We are particularly interested in how plasticity in the cytokine secretion profile of effector T cells can affect outcomes in disease. To study this, we have developed a new animal model in which the disease pattern closely recapitulates the most common form of human MS. In a parallel line of investigation, we are interested in studying the specific molecular cues that can drive T cell exhaustion. I held the EMD Serono Canada/endMS Network Translational Career Development Award from 2011-2016 and am a scholar of the Fonds de Recherche de Québec – Santé. The lab is funded by operating grants from the Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC) and the MS Society of Canada.



### **Nupur Raychaudhuri, PhD**

Michigan State University  
Ann Arbor, United States  
Nupur Raychaudhuri, PhD  
Michigan State University  
Ann Arbor, United States

I am presently working as a Senior Research Associate, Michigan State University, East Lansing, MI. My research interests range widely, from studying the effect of perinatal metabolic perturbations on the adult phenotype, regulation of gene expression, extracellular matrix, cell signaling, and inflammation and cytokine action in the context of various diseased conditions. My specific interests lie in identifying potentially attractive cohorts of therapeutic targets for modulating the development and progress of disease.



### **Deanna Santer, PhD**

Research Scientist  
Houghton Laboratory  
Li Ka Shing Institute of Virology  
University of Alberta, Alberta, Canada

Dr. Deanna Santer is a research scientist in the Department of Medical Microbiology and Immunology at the University of Alberta, Canada working with Dr. Michael Houghton. In each phase of her career thus far, she has focused on human immunology with projects encompassing all three families of interferons. She received her Ph.D degree in Immunology from the University of Washington working in the lab of Dr. Keith Elkon. Her Ph.D research focused on the role of IFN-alpha in lupus pathogenesis and how the complement protein C1q inhibits IFN-alpha induction by immune complexes. Her current research focuses on understanding how type III IFNs regulate human immune cell responses.



**Celee Spidel, PhD**

Amarillo Biosciences, Inc.  
Amarillo, United States

Hello I'm Celee Spidel. My undergraduate studies were in Sports Medicine at Pepperdine University and my PhD is in Pharmaceutical Sciences with doctoral dissertation in Cancer Biology. I am currently working as a research analyst for Amarillo Biosciences, Inc. and am especially interested in Interferon-alpha signaling and therapeutic potential. I have 6 children and enjoy running, cycling, swimming, hiking, and reading in my spare time.



**Dr. Yunhao Tan**

Boston Children's Hospital, Harvard Medical School  
Boston, USA

I completed my Ph.D. study in the laboratory of Dr. Zhao-Qing Luo at Purdue University, where I used yeast genetic and biochemical approaches to characterize the molecular mechanisms of bacterial virulence factors that manipulate host cellular processes. As a Jane Coffin Childs postdoctoral fellow in Dr. Jonathan Kagan's laboratory at Harvard Medical School, I am excited to interrogate the regulatory mechanisms of diverse receptor proximal events triggered by the activation of Pattern Recognition Receptors (PRRs). These events occur immediately upon microbial encounters, prior to host transcriptional responses, and therefore serve as critical regulatory gauges for host inflammatory cytokine and chemokine production. In particular, I study the assembly and cell biological functions of various macromolecular protein complexes in the innate immune system. Known as supramolecular organizing centers (SMOCs), these protein complexes represent unique "signaling organelles" that integrates diverse signaling cascades. Furthermore, via synthetic biology approaches, I leverage the modularity of innate immune pathways and develop programmable "nano-machines" to control cytokine production. Aberrant innate immune signaling has been implicated in the pathogenesis of cancer and autoinflammatory diseases. Therefore, I envision that elucidating the regulatory mechanism of SMOCs will advance our understanding of innate immune signaling and the molecular mechanisms of host immunopathologies.



**Sharat J. Vayttaden, Ph.D.**

Research Fellow  
Signaling Systems Section  
Laboratory of Immune System Biology  
National Institute of Allergy and Infectious Diseases

Dr. Sharat J. Vayttaden is a Research Fellow in the Signaling Systems Section of the Laboratory of Immune System Biology at the National Institute of Allergy and Infectious Diseases, USA. He is a member of the American Association of Immunologists. He received his PhD in Cell Biology from the University of Texas Health Science Center at Houston, TX USA in 2012. His PhD research was on computational modeling of 2 adrenergic receptor desensitization mechanisms. His current research focuses on how overlapping TLR pathways organize and respond differently to multi- vs. single-TLR signaling in macrophages since a coherent immune response involves crosstalk among multiple host pathogen response signaling pathways. Particularly, he is working on how multi-TLR stimulation causes an Interleukin-1 receptor-associated kinase 1 (IRAK1) containing supramolecular organizing center (SMOC) to form that is distinct from previously described myddosomes or putative trifosomes and mediates a non-transcriptional priming link between TLR signaling and inflammasome activation.

# New Member MINIBIOs *Continued*



## **Stephanie S Watowich, PhD**

Professor, Immunology  
Co-Director, Center for Inflammation and Cancer  
The University of Texas MD Anderson Cancer Center  
Houston, USA

Stephanie S. Watowich, PhD is Professor of Immunology and Co-Director of the Center for Inflammation and Cancer at The University of Texas MD Anderson Cancer Center. Her laboratory studies transcriptional control of innate immunity, with a specific focus on discovering roles for the cytokine-activated signal transducer and activator of transcription (STAT) factors in innate cell development and function. Dr. Watowich obtained her B.A. in Biology from Carleton College. Carleton's unique environment fostered Dr. Watowich's longstanding interest in multidisciplinary approaches in research as well as a desire to teach and mentor the next generation of scientists. Dr. Watowich earned her PhD at Northwestern University under Dr. Rick Morimoto's mentorship. Her work focused on heat shock gene transcription and contributed to early understanding of the protein unfolding response. Dr. Watowich's postdoctoral work with Dr. Harvey Lodish at the Whitehead Institute of Biomedical Research revealed the critical role for dimerization in erythropoietin receptor activation, contributing to the paradigm of cytokine receptor signaling initiation upon ligand-induced receptor oligomerization. Currently, major projects in Dr. Watowich's laboratory focus on mechanisms by which STATs regulate myeloid and dendritic cell activity, and the anti-inflammatory activity of STAT3 in the hematopoietic system. The overarching goal of Dr. Watowich's work is to discover fundamental immunological mechanisms and use this knowledge to improve human disease outcomes. Dr. Watowich has been recognized with the MD Anderson Faculty Achievement Award in Education, the John P. McGovern Outstanding Teacher Award and induction into the UT Kenneth I. Shine Academy of Health Science Education.



## **Monika Wolkers**

Associate Professor, Department of Hematopoiesis  
Sanquin Landsteiner Laboratory for Blood Cell Research  
Amsterdam, the Netherlands

Monika Wolkers earned her PhD at the Netherlands Cancer Institute, Amsterdam in 2003, mentored by Ton Schumacher. With an Irvington Institute fellowship she joined Stephen Schoenberger's lab at the La Jolla Institute to dissect the molecular imprinting of CD4+ T cell help to CD8+ T cells. She then moved to the Netherlands to the Academic Medical Center, University of Amsterdam to further unravel the role of TRAIL in the effector function of innate immune cells. In 2010, she became an independent group leader at Sanquin. Her research group studies the regulation of T cell effector function in human and mice. Recent highlights include the identification of post-transcriptional mechanisms that govern cytokine production in effector and in memory T cells.

## Boston's 6 must-have foods and where to get them

No matter what city you're traveling to, each one is famous for certain kinds of foods or has a specialty dish that it's known for. Other cities may try and replicate the famous foods, but everyone knows they taste the best when eaten in their native city. Boston is no different. When you travel to the capital of Massachusetts, there are six foods you should sample. But in order to truly enjoy Boston's best, you must taste each of these foods at a specific place.

### 1. Boston Cream Pie

Head on over to Mike's Pastry to eat a sweet slice of Boston cream pie. Located in Boston's North End, this bakery lets you purchase the famous Boston dessert (which is actually a cake) by the slice or the entire cake.



### 2. Samuel Adams

The pub known as Cheers was the inspiration behind the hit TV show and is also one of Boston's biggest attractions. While here, be sure to have a bottle or draft of the smooth Samuel Adams. You can even get a souvenir Cheers mug if you're a big fan of the show.





**Jacob S. Yount, PhD**

Assistant Professor  
The Ohio State University  
Department of Microbial Infection and Immunity  
Columbus, OH, USA

Dr. Jacob Yount is an Assistant Professor in the Department of Microbial Infection and Immunity at the Ohio State University College of Medicine. He completed his doctoral training at the Mount Sinai School of Medicine in the laboratories of Dr. Thomas Moran and Dr. Carolina Lopez, where he studied the role of viral defective interfering genomes in activating interferon and cytokine production by dendritic cells. As a postdoctoral fellow in the laboratory of Dr. Howard Hang at the Rockefeller University, Dr. Yount utilized chemical probes to identify and characterize lipid posttranslational modifications that control the activity of innate immunity proteins. This work identified the palmitoylation-dependent anti-influenza virus activity of the interferon-induced transmembrane proteins (IFITMs). In his independent laboratory, Dr. Yount focuses on the IFITMs and other interferon effector proteins in terms of their mechanisms of action, mechanisms of posttranslational regulation, and physiological roles during infections.

## ICIS MEMBERSHIP APPLICATION

*The role of and effect of cytokines in every aspect of human health will continue to be identified and characterized and the use of cytokines themselves or antibodies to cytokines will become even more important tools in the arsenal of clinicians. Thus, the importance of the ICIS as a focal point for cytokine research will only continue to grow.*

**Become a part of the world-wide community of scientists devoted to research in the fields of interferon, cytokine & chemokine cell biology, molecular biology and biochemistry**

Join ONLINE: [www.cytokinesociety.org](http://www.cytokinesociety.org)

### 3. Clam Chowder

For some of the best Boston clam chowder you'll ever sip (or slurp) from your spoon, go to Neptune Oyster. This restaurant is open every day, giving you plenty of opportunities to try this Boston specialty.



### 4. Fenway Franks

Every baseball fan knows you need to have a delicious hotdog when at the home of the Boston RedSox for a game. Fenway Park provides some of the juiciest you'll ever have with their Fenway Franks.



### 5. Boston Baked Beans

Marliave has been in business since 1875 serving up tasty lunch and dinner options. This restaurant also serves up perfectly seasoned Boston baked beans — another food Boston is famous for that just tastes better when eaten here.



### 6. Lobster

When you go to Neptune Oyster, be sure to arrive hungry. Not only do you need to try the clam chowder, their lobster dishes are also to die for. Go on a Monday because Lobster Spaghetti is usually the featured dish.



# Lab Happiness

## DARN GOOD CHOCOLATE CAKE

What sets this recipe apart from other chocolate cakes is the irresistible chocolate aroma that permeates the kitchen as it bakes. And so with a cold glass of milk, you fork into a warm bite and mutter “This is darn good chocolate cake”...thus confirming its name.

SERVES: 16

PREPARATION TIME: 10 MINUTES

BAKING TIME: 45 TO 50 MINUTES

Vegetable oil spray for misting the pan

Flour for dusting the pan

**1 package** (18.25 ounces) plain devil’s food or dark chocolate fudge cake mix

**1 package** (3.9 ounces) chocolate Instant pudding mix

**4 large** eggs

**1 cup** sour cream

**½ cup** warm water

**½ cup** vegetable oil, such as canola, corn, safflower, soybean, or sunflower

**1 1/2 cups** semisweet chocolate chips

Place a rack in the center of the oven and preheat the oven to 350°F. Lightly mist a 12-cup Bundt pan with vegetable oil spray, then dust with flour. Shake out the excess flour. Set the pan aside.

Place the cake mix + 1/3 cup flour, pudding mix, eggs, sour cream, warm water and oil in a large mixing bowl. Blend with an electric mixer on low speed for 1 minute. Stop the machine and scrape down the sides of the bowl with a rubber spatula. Increase the mixer speed to medium and beat 2 to 3 minutes more, scraping the sides down again if needed. The batter should look thick and well combined. Fold in the chocolate chips, making sure they are well distributed throughout the batter. Pour the batter into the prepared pan, smoothing it out with the rubber spatula. Place the pan in the oven.

Bake the cake until it springs back when lightly pressed with your finger and just starts to pull away from the sides of the pan, 45 to 50 minutes. Remove the pan from the oven and place it on a wire rack to cool for 20 minutes. Run a long sharp knife around the edge of the cake and invert it onto the rack to cool completely, 20 minutes more. Or invert it onto a serving platter to slice and serve while still warm.

Bake two 9” pans or a 9x13” pan 35-40 minutes



## CHOCOLATE GANACHE

Once you make ganache and taste a spoonful, you know you'll never be the same again. It is downright simple in its list of ingredients, and it is pure ecstasy in your mouth. And just wait until you spread it around the edges of a layer cake. It glides on effortlessly, seductively. And then it firms up magically before your eyes. Amazing stuff!

MAKES 2 CUPS, ENOUGH TO THINLY FROST  
A 2- OR 3-LAYER CAKE PREPARATION TIME: 5  
MINUTES

**¾ cup** heavy whipping cream

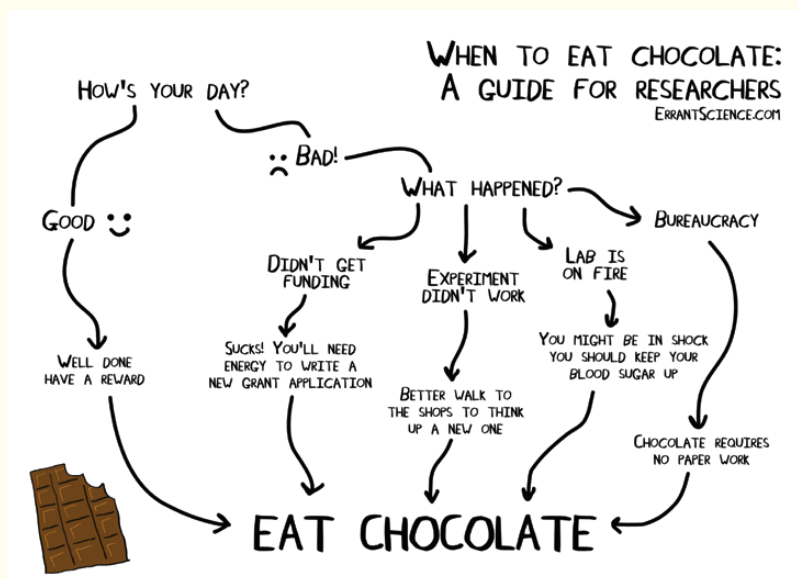
**8 ounces** semisweet chocolate, finely chopped

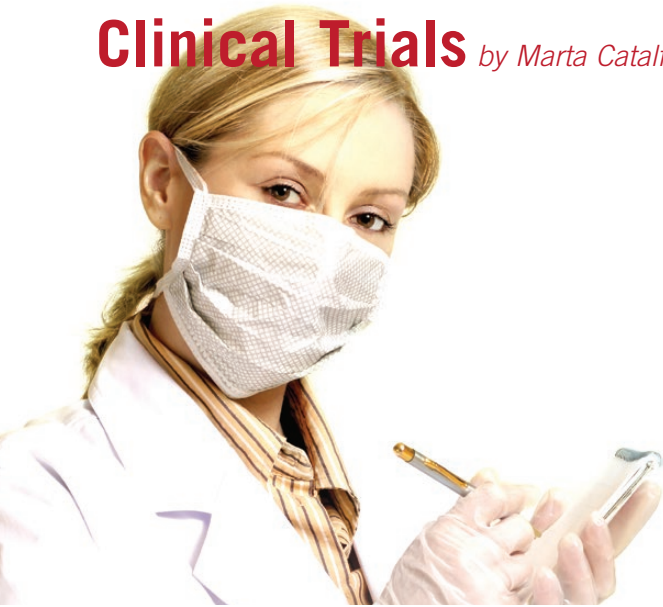
**1 tablespoon** liqueur such as Grand Marnier or  
framboise

If the ganache gets too thick for using as a glaze or frosting, simply set the pan in a larger pan of water that's simmering on the stove (double boilers are perfect for this) and stir until the ganache softens.

**1.** Place the cream in a small heavy saucepan over medium heat. Bring to boil, stirring. Meanwhile, place the chopped chocolate in a large mixing bowl. Remove the pan from the heat and pour the hot cream over the chopped chocolate. Stir until the chocolate is melted. Stir in the liqueur, if desired.

**2.** To use this ganache as a glaze, let it stand at room temperature for 10 minutes before spooning over a cooled cake. To use the ganache as a frosting or a filling, let it stand at room temperature for 4 hours or chill until it thickens and is spreadable.





## **A Study to Target the Type I IFN Receptor by Administering Anifrolumab in RA Patients With a High IFN Signature (TarIFNIRA)**

**Principal Investigators:** Josef Smolen, MD. Medizinische Universität Wien, Innere Medizin III, Abteilung für Rheumatologie Wien, Austria, 1090.

**Contact:** Thomas Karonitsch, MD. Phone: +43 1 40400 ext 43050  
**ClinicalTrials.gov Identifier:** NCT03435601

## **Interferon- $\alpha$ After DLI for the Prevention of Relapse (IDPR-HSCT)**

**Principal Investigators:** Xiaojun Huang, Principal Investigator, Peking University People's Hospital. China.

**Contact:** Xiao-Dong MO, MD. Phone: 86-10-88326001  
**ClinicalTrials.gov Identifier:** NCT02568241

## **Localized Radiation Therapy or Recombinant Interferon Beta and Avelumab With or Without Cellular Adoptive Immunotherapy in Treating Patients With Metastatic Merkel Cell Carcinoma**

**Principal Investigators:** Aude Chapuis, MD. Fred Hutch/University of Washington Cancer Consortium. Seattle, Washington, United States, 98109

**Contact:** Aude Chapuis, MD Phone: 206-667-4369  
**ClinicalTrials.gov Identifier:** NCT02584829

## **HIDIT II - PegIFN- $\alpha$ 2a Plus Tenofovir in Chronic Delta Hepatitis (HIDIT-II)**

**Principal Investigators:** Michael P. Manns, Prof. Dr. Medizinische Hochschule Hannover, Zentrum Innere Medizin. Hannover, Germany, 30625

**Contact:** Michael P. Manns, Prof. Dr.  
**ClinicalTrials.gov Identifier:** NCT00932971

## **Role of Interferon-gamma 1-b (IFN- $\gamma$ ) on Cells of the Innate Immune System: Functional, Biochemical and Gene Expression Studies in Patients with Chronic Granulomatous Disease**

**Principal Investigators:** Daniel R. Ambruso, MD. University of Colorado Anschutz Medical Campus. Aurora, Colorado, United States, 80045

**Contact:** Alison Lakin RN L LLM. Phone: 1+ 303-724-1010  
**ClinicalTrials.gov Identifier:** NCT03548818

## **Interferon-lambda: Novel Biologics for Controlling Neutrophil-mediated Pathology in Rheumatic Diseases? (ILAND)**

**Principal Investigators:** Raashid A Luqmani, DM FRCP. Oxford University Hospitals NHS Foundation Trust. Oxford, United Kingdom, OX3 7HE.

**Contact:** Jana Vaskova. Phone: 01865227971  
**ClinicalTrials.gov Identifier:** NCT02498808

## **Nilotinib $\pm$ Peg-IFN for First Line Chronic Phase CML Patients (PETALS)**

**Principal Investigators:** Franck Nicolini, MD. Hopsices Civils de Lyon. Lyon, France.

**Contact:** Franck Nicolini, MD. Phone: 04 78 86 22 50  
**ClinicalTrials.gov Identifier:** NCT02201459

## **Ruxolitinib and Peg-interferon Alpha-2a Combination in Patients With Primary Myelofibrosis RUXOPeg (RUXOPeg)**

**Principal Investigators:** Jean Jacques Kiladjian, MD, PD. FILO French Innovative Leukemia Organization.

**Contact:** Jean Jacques Kiladjian, MD, PD. Phone: +33142499494  
**ClinicalTrials.gov Identifier:** NCT02742324

## **Proof of Principle Study of Pulse Dosing of IL-15 to Deplete the Reservoir in HIV Infected People (ALT-803)**

**Principal Investigators:** Tim Schacker, MD. University of Minnesota, Minneapolis, Minnesota, United States, 55455.

**Contact:** Anne Thorkelson, RN. Phone: 612-625-7472.  
**ClinicalTrials.gov Identifier:** NCT02191098

## **JAK-inhibition in Recurrent Classical Hodgkin Lymphoma (JeRiCHO)**

**Principal Investigators:** Michael Fuchs, MD. Dept. of Medicine, Cologne University Hospital. Cologne, Germany, 50924.

**Contact:** Michael Fuchs, MD Phone:  
**ClinicalTrials.gov Identifier:** NCT02164500

## **Assessing an Oral Janus Kinase Inhibitor, AZD4205, in Combination With Osimertinib in Patients Who Have Advanced Non-small Cell Lung Cancer**

**Principal Investigators:** Tom John, MD. Austin Hospital. Heidelberg, Victoria, Australia, 3084.

**Contact:** Jiemin Wang, MD, MPH. Phone: 00862161097868  
**ClinicalTrials.gov Identifier:** NCT03450330

## **Phase I-II Study of Interferon-gamma in Patients With HER-2 Positive Breast Cancer**

**Principal Investigators:** (Hyo) Heather S. Han, M.D. H. Lee Moffitt Cancer Center and Research Institute. Tampa, Florida, United States, 33612

**Contact:** Dawn Goodridge. Phone: 813-745-1807  
**ClinicalTrials.gov Identifier:** NCT03112590

## **Pembrolizumab and Interferon Gamma-1b in Treating Patients With Stage IB-IVB Relapsed or Refractory Mycosis Fungoides and Sezary Syndrome**

**Principal Investigators:** Alain H. Rook, MD. University of Pennsylvania/ Abramson Cancer Center. Philadelphia, Pennsylvania, United States, 19104

**Contact:** Alain H. Rook, MD. Phone: 800-474-9892  
**ClinicalTrials.gov Identifier:** NCT03063632

## **A Study of IL-7 to Restore Absolute Lymphocyte Counts in Sepsis Patients (IRIS-7-B)**

**Principal Investigator:** Edward SHERWOOD, MD, PhD Vanderbilt University Medical Center

**ClinicalTrials.gov Identifier:** NCT02640807

## **NM-IL-12 (rHuIL 12) In Relapsed/Refractory Diffuse Large B- Cell Lymphoma (DLBCL) Undergoing Salvage Chemotherapy**

**Principal Investigator:** Yossef Kalish, MD Hadassah Medical Center

**Contact:** Lena A Basile, PhD, JD 626-844-3800  
[basile@neumedicines.com](mailto:basile@neumedicines.com)

**ClinicalTrials.gov Identifier:** NCT02544724

## **Serum IL-21 Levels in Patients with Pemphigus Vulgaris**

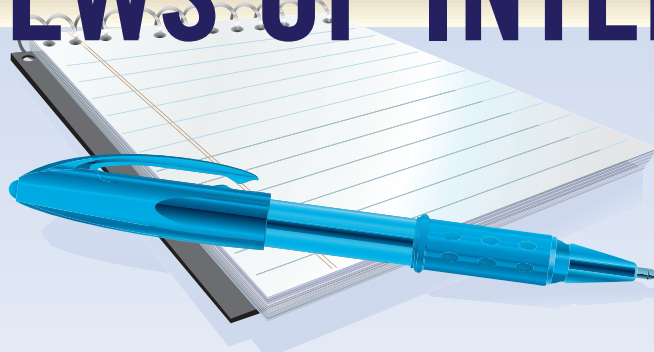
**Responsible Party:** Marwa Kassim, AssiutU, Assiut University

**Contact:** Hatem Zi Mohammed, Professor 01003420217 [zedanzma@aun.edu.eg](mailto:zedanzma@aun.edu.eg)

**ClinicalTrials.gov Identifier:** NCT03177213

# REVIEWS OF INTEREST

by Di Yu



## **Interleukin-6: designing specific therapeutics for a complex cytokine.**

Garbers C, Heink S, Korn T, Rose-John S.  
*Nat Rev Drug Discov.* 2018 Jun;17(6):395-412. doi: 10.1038/nrd.2018.45. PMID:29725131

## **JAK inhibition as therapeutic strategy for immune and inflammatory diseases.**

Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ.  
*Nat Rev Drug Discov.* 2017 Dec 28;17(1):78. doi: 10.1038/nrd.2017.267. PMID:29282366

## **IFN $\gamma$ : signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy.**

Ivashkiv LB.  
*Nat Rev Immunol.* 2018 Jun 19. doi: 10.1038/s41577-018-0029-z. PMID:29921905

## **Targeting cytokines to treat asthma and chronic obstructive pulmonary disease.**

Barnes PJ.  
*Nat Rev Immunol.* 2018 Jul;18(7):454-466. doi: 10.1038/s41577-018-0006-6. PMID:29626211

## **Contextual determinants of TGF $\beta$ action in development, immunity and cancer.**

David CJ, Massagué J.  
*Nat Rev Mol Cell Biol.* 2018 Jul;19(7):419-435. doi: 10.1038/s41580-018-0007-0. PMID:29643418

## **Targeting the IL-6/JAK/STAT3 signalling axis in cancer.**

Johnson DE, O'Keefe RA, Grandis JR.  
*Nat Rev Clin Oncol.* 2018 Apr;15(4):234-248. doi: 10.1038/nrclinonc.2018.8. PMID:29405201

## **Signaling and Function of Interleukin-2 in T Lymphocytes.**

Ross SH, Cantrell DA.  
*Annu Rev Immunol.* 2018 Apr 26;36:411-433. doi: 10.1146/annurev-immunol-042617-053352. PMID:29677473

## **Type I interferon in rheumatic diseases.**

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## **Immune Cytokines and Their Receptors in Inflammatory Pain.**

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*Trends Immunol.* 2018 Mar;39(3):240-255. doi: 10.1016/j.it.2017.12.003. PMID:29338939

## **Do Type I Interferons Link Systemic Autoimmunities and Metabolic Syndrome in a Pathogenetic Continuum?**

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*Trends Immunol.* 2018 Jan;39(1):28-43. doi: 10.1016/j.it.2017.07.001. Epub 2017 Aug 17. Review. PMID: 28826817

## **Host-Intrinsic Interferon Status in Infection and Immunity.**

Liu BC, Sarhan J, Poltorak A.  
*Trends Mol Med.* 2018 Aug;24(8):658-668. doi: 10.1016/j.molmed.2018.06.004. Epub 2018 Jul 7. Review. PMID:30060835

## **The role of cytokines in T-cell memory in health and disease.**

Raeber ME, Zurbuchen Y, Impellizzieri D, Boyman O.  
*Immunol Rev.* 2018 May;283(1):176-193. doi: 10.1111/imr.12644. Review. PMID:29664568

## **Overview of the IL-1 family in innate inflammation and acquired immunity.**

Dinarello CA.  
*Immunol Rev.* 2018 Jan;281(1):8-27. doi: 10.1111/imr.12621. Review. PMID:29247995

## **Interleukin-18: Biological properties and role in disease pathogenesis.**

Kaplanski G.  
*Immunol Rev.* 2018 Jan;281(1):138-153. doi: 10.1111/imr.12616. Review. PMID:29247988

## **Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family.**

Cayrol C, Girard JP.  
*Immunol Rev.* 2018 Jan;281(1):154-168. doi: 10.1111/imr.12619. Review. PMID:2924799

# REVIEWS OF INTEREST

by Di Yu  
Continued



## **Regulation and function of interleukin-36 cytokines.**

Bassoy EY, Towne JE, Gabay C. *Immunol Rev.* 2018 Jan;281(1):169-178. doi: 10.1111/imr.12610. Review. PMID:2924799

## **Suppression of inflammation and acquired immunity by IL-37.**

Cavalli G, Dinarello CA. *Immunol Rev.* 2018 Jan;281(1):179-190. doi: 10.1111/imr.12605. Review. PMID:2924798

## **Biology of IL-38 and its role in disease.**

van de Veerdonk FL, de Graaf DM, Joosten LA, Dinarello CA. *Immunol Rev.* 2018 Jan;281(1):191-196. doi: 10.1111/imr.12612. Review. PMID:29247986

## **Cytokine modulation of atopic itch.**

Trier AM, Kim BS. *Curr Opin Immunol.* 2018 Jun 20;54:7-12. doi: 10.1016/j.coi.2018.05.005. [Epub ahead of print] Review. PMID:29935376

## **Cytokines regulating lymphangiogenesis.**

Sáinz-Jaspeado M, Claesson-Welsh L. *Curr Opin Immunol.* 2018 Apr 19;53:58-63. doi: 10.1016/j.coi.2018.04.003. [Epub ahead of print] Review. PMID:29680577

## **Mucocutaneous IL-17 immunity in mice and humans: host defense vs. excessive inflammation.**

Li J, Casanova JL, Puel A. *Mucosal Immunol.* 2018 May;11(3):581-589. doi: 10.1038/mi.2017.97. Epub 2017 Nov 29. Review. PMID:29186107

## **A Systematic Review of Interleukin-1 $\beta$ in Post-Traumatic Stress Disorder: Evidence from Human and Animal Studies.**

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## **IL-2 and Beyond in Cancer Immunotherapy.**

Wrangle JM, Patterson A, Johnson CB, Neitzke DJ, Mehrotra S, Denlinger CE, Paulos CM, Li Z, Cole DJ, Rubinstein MP. *J Interferon Cytokine Res.* 2018 Feb;38(2):45-68. doi: 10.1089/jir.2017.0101. PMID:29443657

## **Orchestration of epithelial-derived cytokines and innate immune cells in allergic airway inflammation.**

Castillo EF, Zheng H, Yang XO. *Cytokine Growth Factor Rev.* 2018 Feb;39:19-25. doi: 10.1016/j.cytogfr.2017.11.004. Epub 2017 Nov 21. Review. PMID:29169815

## **Cytokines in the pathogenesis of hemophilic arthropathy.**

Wojdasiewicz P, Poniatowski ŁA, Nauman P, Mandat T, Paradowska-Gorycka A, Romanowska-Próchnicka K, Szukiewicz D, Kotela A, Kubaszewski Ł, Kotela I, Kurkowska-Jastrzbska I, Gasik R. *Cytokine Growth Factor Rev.* 2018 Feb;39:71-91. doi: 10.1016/j.cytogfr.2017.11.003. Epub 2017 Nov 13. Review. PMID:29153709

## **Multisystem multitasking by CXCL12 and its receptors CXCR4 and ACKR3.**

Murphy PM, Heusinkveld L. *Cytokine.* 2018 Sep;109:2-10. doi: 10.1016/j.cyto.2017.12.022. Epub 2018 Feb 15. Review. PMID:29398278

## **DAMP-TLR-cytokine axis dictates the fate of tumor.**

Patidar A, Selvaraj S, Sarode A, Chauhan P, Chattopadhyay D, Saha B. *Cytokine.* 2018 Apr;104:114-123. doi: 10.1016/j.cyto.2017.10.004. Epub 2017 Oct 9. Review. PMID:29032985

## **Progress in pharmacological research of chemokine like factor 1 (CKLF1).**

Liu DD, Song XY, Yang PF, Ai QD, Wang YY, Feng XY, He X, Chen NH. *Cytokine.* 2018 Feb;102:41-50. doi: 10.1016/j.cyto.2017.12.002. Epub 2017 Dec 21. Review. PMID:29275012

## **Chemoresistance and targeting of growth factors/cytokines signalling pathways: towards the development of effective therapeutic strategy for endometrial cancer.**

Guo F, Zhang H, Jia Z, Cui M, Tian J. *Am J Cancer Res.* 2018 Jul 1;8(7):1317-1331. eCollection 2018. PMID: 30094104



<http://ucbase.unimore.it/>

### Welcome to theUCbase 2.0

Ultraconserved elements (UCRs), that were first described by Bejerano et al. in 2004 (Science. 2004;304:1321-5), are highly conserved genome regions that share 100% identity among human, mouse and rat. UCRs are 481 sequences longer than 200 bases. UCRs are frequently located at genomic regions involved in cancer, differentially expressed in human leukemias and carcinomas and in some instances regulated by microRNAs. UCRs chromosome coordinates are now updated with the last Human Genome (hg19/ GRCh37) chromosome Information. UCbase 2.0 is directly linked to UCSC Genome Browser.

## miR2Disease Base

<http://www.mir2disease.org/>

miR2Disease, a manually curated database, aims at providing a comprehensive resource of miRNA deregulation in various human diseases. Each entry in the miR2Disease contains detailed information on a miRNA-disease relationship, including miRNA ID, disease name, a brief description of the miRNA-disease relationship, miRNA expression pattern in the disease state, detection method for miRNA expression, experimentally verified miRNA target gene(s), and literature reference

## Expression Atlas

<https://www.ebi.ac.uk/gxa/home>

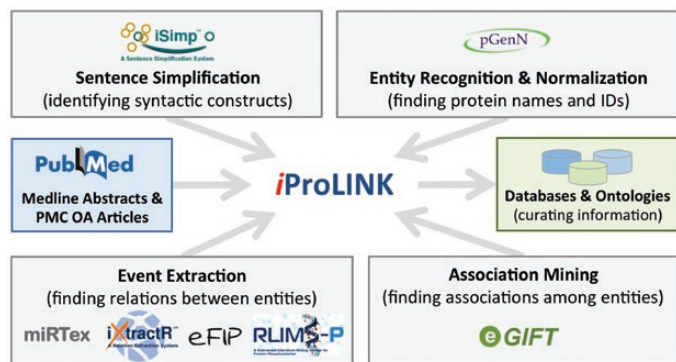
### Exploring gene expression results across species under different biological conditions

Expression Atlas is an open science resource that gives users a powerful way to find information about gene and protein expression across species and biological conditions such as different tissues, cell types, developmental stages and diseases among others. Expression Atlas aims to help answering questions such as 'where is a certain gene expressed?' or 'how does its expression change in a disease?'

## iProLink

<https://research.bioinformatics.udel.edu/iprolink/>

iProLINK (integrated Protein Literature, INformation and Knowledge) is a resource with access to text mining tools and annotated corpora developed in house. The collection of data sources can be utilized by computational and biological researchers to explore literature information on proteins and their features or properties.



## SB CD DB: Sleeping Beauty Cancer Driver Database

<http://sbcddb.moffitt.org/>

This portal provides information on cancer driver genes identified in tumor models generated by *Sleeping Beauty* insertional mutagenesis. Here, insertion data generated by 454 Pyrosequencing from both published and unpublished studies have been independently analyzed to identify cancer drivers using a statistical gene-centric approach. The links in the upper right hand corner of this website provide information about the content and interface of this database.

A query for a specific gene in the search bar will produce a summary of datasets in which the gene is identified as a cancer gene. Transposon data is visualized at the insertion, gene, tumor, and population levels. The sunburst chart summarizes the organ types (inner ring) and the tumor types (outer ring) represented in the database with the number of samples for each.

*Sleeping Beauty* insertional mutagenesis uses a transposable element to disrupt gene function. Transposons randomly insert into the mouse genome at TA dinucleotides; considering the distribution of TA sites across the genome, transposons can in principle alter any gene. Transposition is a continual process until an insertion occurs in a locus that confers a selective advantage to cells. Such events are selected and maintained and the accumulation of selected events leads to tumor formation. Transposons contain both a promoter element coupled with a splice donor element and bi-directional splice acceptor sites and poly-A tail. The transposon activates expression of downstream exons using the internal promoter when inserted in-frame and in the sense direction; alternatively, the transposon acts as a gene-trap, disrupting gene expression by randomly inserting along the coding region.

*Sleeping Beauty* insertional mutagenesis can be controlled in space and time using tissue or lineage-specific Cre inducers and coupled with sensitizing mutation can give rise to specific tumor types.



*Continued*

## HOCOMOCO

<http://hocomoco11.autosome.ru/>

HOmo sapiens COmprehensive MOdel COllection (HOCOMOCO) v11 provides transcription factor (TF) binding models for 680 human and 453 mouse TFs.

Since v11, HOCOMOCO is complemented by MoLoTool, an interactive web tool to mark motif occurrences in a given set of DNA sequences. In addition to basic mononucleotide position weight matrices (PWMs), HOCOMOCO provides dinucleotide position weight matrices based on ChIP-Seq data.

All the models were produced by the ChIPMunk motif discovery tool. Model quality ratings are results of a comprehensive cross-validation benchmark.

ChIP-Seq data for motif discovery was extracted from GTRD database of BioUML platform, that also provides an interface for motif finding (sequence scanning) with HOCOMOCO models.

## SORFS.org

**A repository of small ORFs identified by ribosome profiling**

<http://www.sorfs.org/>

### Introduction

Small open reading frames (sORFs) can be defined as open reading frames smaller than or equal to 300 nucleotides (100 amino acids). These “sORFs”, while inherent to all genomes, are historically ignored in gene annotation studies, stating that these lack any coding potential. Exclusion of these sORFs has emerged as a side effect during the development of different (gene prediction) tools in the field of bioinformatics/genomics/proteomics trying to reduce noise, imposed by technological limitations. However, recent scientific breakthroughs discovered coding potential of several sORFs with clinical significance, indicating their importance. 1, 2, 4. In particular, the advent of ribosome profiling 5 (RIBO-seq), a next generation deep sequencing technique, providing a genome-wide snapshot of the translating machinery in a cell, provided evidence of translation in sORFs. The value and importance of sORFs is becoming widely recognized 6, 7 furthermore ribosome profiling data is becoming more abundant. The creation of a public repository for sORFs, providing information resulting from various tools and metrics, seems a necessity in aiding functional research in the micropeptide field

### What does the database hold:

With this in mind, we like to introduce sORF.org, a public repository for sORFs. The main purpose is to allow researchers to examine individual sORFs or to perform searches based on several criteria for further large-scale studies. Different data sources, both experimental and in silico (based on various bioinformatics tools), are collected. sORF.org currently holds 3594894 sORFs across three different species (human, mouse and fruit fly), derived from multiple RIBO-seq experiments and is expanding as more data becomes available. Available datasets can be inspected [HERE](#).

### Query possibilities

Two query interfaces were developed for sORFs.org. The default query interface excels in the quick lookup of sORFs, however has limited query possibilities. For example the default query interface excels at the lookup of sORFs containing a specific sequence pattern.

## anti-CRISPRdb

<http://cefg.uestc.edu.cn/anti-CRISPRdb/>

CRISPR is a tool that is widely used for gene editing. However, unexpected off-target effects may occur as a result of long-term nuclease activity. Anti-CRISPR proteins, which are powerful molecules that inhibit the CRISPR-Cas system, may have the potential to promote better utilization of the CRISPR system in gene editing, especially for gene therapy. Additionally, more in-depth research on these proteins would help researchers to better understand the co-evolution of bacteria and phages. Therefore, it is necessary to collect and integrate data on various types of anti-CRISPR proteins. Data on these proteins were manually gathered through text mining and data screening of the literatures. We then constructed anti-CRISPRdb: this is the first online resource for organizing these proteins.

Anti-CRISPRdb resource acts as an online resource to organize the anti-CRISPR proteins. It enables easy browsing of the anti-CRISPRs that have been published. It contains the available protein sequences, DNA sequences, coding regions, source organisms, taxonomy, virulence, and protein interactors and the corresponding three-dimensional structures. The first version of anti-CRISPRdb currently contains 432 anti-CRISPR proteins and 106 non-redundant ones tested by experimental and bioinformatics methods. These proteins can be divided into the following five categories: anti-CRISPR proteins with anti-I-F activity, those with anti-I-E activity, those with anti-II-A activity, those with anti-II-C activity, and those with anti-IV-B activity.

Data Update - May 2018:

1. We added two new subtype Acrs: AcrIIA5 (PMID: 28785032), AcrID1 (PMID: 29507349). Please note that data is not contained in our blast database. We will update our blast database in next version
2. Self-targeting of a genome have been used as a maker by investigators to screen potential bacteria that bear Acrs. Therefore, to perform the annotation and classification task of Acrs, it is necessary to confirm the CRISPR-Cas locus and its (sub)type that a bacterium maintain. We proposed a web-based server, CasLocusAnno to annotate Cas locus and (sub)type based on a previous work.

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## Welcome to ICG

### A knowledgebase of Internal Control Genes for RT-qPCR normalization

[http://icg.big.ac.cn/index.php/Main\\_Page](http://icg.big.ac.cn/index.php/Main_Page)

ICG is a wiki-based knowledgebase of internal control genes (or reference genes) for RT-qPCR normalization in a variety of species. Based on community curation, ICG harnesses collective intelligence to integrate a comprehensive collection of internal control genes curated from a large volume of literatures and provides appropriate internal control genes corresponding to specific experimental conditions for both model and non-model organisms.

*Nothing great is ever accomplished in isolation. – Yo-Yo Ma*

**73 Animals • 115 Plants • 12 Fungi • 9 Bacteria**

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## TCSBN (a database of tissue and cancer [specific biological networks](#))

<http://inetmodels.com/>

### About TCSBN

We recently generated tissue and cancer specific biological networks and presented here in TCSBN (a database of tissue and cancer specific biological networks). This database is run by Sysmedicine group, SciLifeLab, KTH, Sweden, as part of recent our studies.

This database contains co-expression networks for 46 normal tissues and 17 cancers, and integrated networks (i.e. protein interaction network and transcriptional regulatory network) of three tissues, liver, muscle and adipose tissue. Here users can explore the functionally or physically associated proteins from given networks and test their biological hypothesis and develop efficient treatment strategies.

We wish that our database will greatly benefit research community in biology and medicine.

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## SCPortalen: Single-cell centric database “A resource for the single-cell research community”

<http://single-cell.clst.riken.jp/>

Single-cell omics recently emerged as powerful tools to investigate heterogeneity of large populations of cells. Among others, improvements in sequencing, microscopy and microfluidic technologies let to a rapid increase of complex datasets with single-cell resolution. However, due to a lack of available platforms to easily share and integrate complex single-cell datasets, the accessibility of such datasets can be a barrier to efficient usage. The number of publication in the area of single-cell increased in the recent years. Still we are lacking public single-cell database to facilitate and enable researchers to access and explore published single-cell datasets.

To address the above issue, we introduced a single-cell data integration platform. The motivation for the development of this database was to enable easy access, integration and collaboration on single-cell datasets generated by the research community worldwide. The current version of the database integrate of single-cell metadata, cell images and sequence information. As an added-value to the raw data, we performed manual curation and annotation of each dataset and conducted single-cell analysis of single-cell RNA-seq. The easy-to-use user interface of the database will enable biologist and computing researchers to search, explore, and download single-cell data and images.

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<https://phenome.jax.org/>

An integrated resource to explore physiology and behavior through genetics and genomics.

The Mouse Phenome Database (MPD, RRID:SCR\_003212) enables the integration of genomic and phenomic data by providing access to primary experimental data, well-documented data collection protocols and analysis tools. Data are contributed by investigators from around the world and represent a broad scope of behavioral, morphological and physiological disease-related characteristics in naive mice and those exposed to drugs, environmental agents or other treatments.

Data in MPD include per mouse and per strain data from genetic reference populations for which data are cumulative over time and across laboratories. Strain types include inbred, recombinant inbred, Collaborative Cross, chromosome substitution, mutants, and others. In addition, there are data from heterogeneous mice in mapping populations including Diversity Outbred and other inbred mouse strain crosses in the QTL Archive.

MPD provides a venue for compliance with data sharing policies and facilitates data reuse and data integration to provide a means of analyzing trait relations, discovering the biological basis of complex traits, and assessing replicability and reproducibility across experimental conditions and protocols.

MPD is a grant-funded research resource headquartered at The Jackson Laboratory.

# SIGNALS



[www.cytokinesociety.org](http://www.cytokinesociety.org)



**Signals** is a new online journal owned by the ICIS that will be published by Springer Nature BMC. Our aim is to develop a scholarly journal with a significant impact, publishing cutting edge research and clinical studies, and comprehensive reviews related to cytokines. It will be open access, available to anyone from any institution. We believe **Signals** will distinguish itself from other cytokine-related publications and will be of great benefit for both ICIS and the international scientific community interested in cytokine research.

Why would we want (yet another) new journal? Many discussions held between the leadership of ICIS and society members highlighted the pressing need for a broadly accessible, open-access publication. Currently, the existing journals affiliated with ICIS are owned by the publishers and, being subscription-based, are not accessible to most of our members. ICIS' first priorities for the new journal **Signals** are that it be available to all, and that it promotes the advancement of the field of cytokine biology and their clinical application. The new journal will place itself at the front-line of cytokine research, providing the cytokine community and ICIS members a platform for the publication of high-quality original articles and editorial opinions. **Signals** will feature definitive reviews on individual cytokines (IL-2, TNF etc), written by experts, and will cover genetics, biology and clinical aspects.

Finally, **Signals** will be owned by ICIS. Societies that own their journals can derive considerable revenue to be used for conferences, society scholarship, awards and other society functions. Together with publishing and legal experts we reached an agreement with Springer Nature BMC that we believe will be good for the field and the ICIS. The ICIS council has carefully examined this contract and enthusiastically endorsed it. Initially the ICIS will be investing some funds, part of which were generously donated by Jan Vilcek for this purpose. It will take a few years before significant income for the ICIS is achieved. Income will be derived from publishing fees for authors in the open access model. There will be discounts for ICIS members and for those in need.

It may take a few years for **Signals** to attract many papers that are at the level we are aiming for, but we intend to be quite selective. **Signals** will have several advantages over competing journals. One, it will be an official ICIS journal which will give it credibility. Two, it will be open access which will greatly increase readership relative to subscription journals. Three, online publishing will offer immediate visibility for accepted articles. Fourth, we will initially publish definitive reviews on individual cytokines which should attract wide attention.

We are excited about this and extremely grateful to the many enthusiastic ICIS supporters who have contributed to its development. An outstanding editorial board has been assembled and is listed at the end of this article. We welcome submissions of work that advances the field of cytokine biology and medicine, and we promise timely review by experts. Suggestions are welcome. **Signals** website is nearly ready and will open soon.

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Boston is a city full of history, most of which is pretty common knowledge you learned about in elementary school. But there's a lot about this city that's not so well known. Below are 20 fun facts you most likely didn't know about Boston.

**1. Boston is actually named after a town in England**

It's true! The city that's an icon of the American Spirit is named after a town in England. Many of Boston's early settlers were from Boston, England, and decided to keep the name.

**2. The first American lighthouse was built in Boston Harbor in 1716**

Little Brewster Island is where the first lighthouse was ever built in what is now the United States. While that lighthouse is long gone, the current island resident pictured above is actually the second-oldest working lighthouse in the United States, dating back to 1783.

**3. Boston is home to the oldest public park in the U.S.**

Boston Common is stretch of green sanctuary within the city of Boston dates back to 1634. It's the oldest public park in the United States and continues to welcome residents and tourists alike.

**4. "Happy Hours" are against the law**

You won't find any "Happy Hour" signs in the local Boston pub. The typical post-work drink deals have been banned since 1984.

**5. The Fig Newton is named after a Boston sub**

A favorite American sweet snack for decades, the Fig Newton is actually named after the Boston suburb of Newton, Massachusetts.

**6. The Red Sox have a patent on a color**

Fenway Park is another American icon found in Boston. It's Green Monster is so renowned, The Red Sox have actually patented the shade "Fenway Green."

**7. Boston was home to the first U.S. chocolate factory**

Rejoice, chocolate lovers! The very first chocolate factory in the United States was built in the Lower Mills section in the Dorchester neighborhood of Boston.

**8. A deadly wave of molasses once flooded the North End**

In January 15, 1919, a storage tank holding more than 2 million gallons of molasses burst, sending a giant wave of the hot syrupy substance through the North End of Boston. It killed 21 people and several horses and injured more than 100 others, making it the worst molasses-related accident in history.

**9. In turn-of-the-century Boston, you didn't need to take a test to receive a driver's license**

Massachusetts started issuing driver's licenses and registration plates in 1903, but didn't make people take a driving test beforehand. In 1920, Boston began requiring a driving test before issuing someone a license.

**10. The first U.S. subway was built here**

Boston built America's first subway, the Tremont Street Subway, back in 1897.

**11. The Boston University Bridge is the location of a globally-unique phenomenon**

The Boston University Bridge's claim to fame is that it's the only place anywhere in the world where a boat can sail under a train going under a vehicle driving under an airplane.

**12. Beantown really is about baked beans**

The city's nickname is Beantown due to the popularity of the baked beans in molasses among it's early residents.

**13. You can drive 90 feet below the earth's surface in Boston**

Boston's Ted Williams Tunnel is the deepest in North America, running nearly 90 feet underneath the earth's surface.

**14. Christmas was once banned**

Bostonians couldn't celebrate Christmas between 1659-1681. It was against the law because the Pilgrims believed it to be a corrupted holiday.

**15. Boston is home to the first U.S. public beach**

Who doesn't love a day at the beach? The United States' first public beach was Revere Beach in Boston (and now home to the International Sand Sculpting Festival).

**16. Boston gave us candlepin bowling**

In 1880, candlepin bowling was invented in Boston. Candlepin bowling is similar to the tenpin bowling most are familiar with, with a few key differences in equipment.

**17. \$100 million in paintings was stolen from a Boston museum**

The biggest art theft to date occurred in Boston on March 18, 1990. Two thieves posing as cops stole 12 paintings worth a total of \$100 million from the Isabella Stewart Gardner Museum.

**18. Some of Hollywood's most recognizable stars are Bostonians**

Celebrities Mark Wahlberg, James Spader, Jasmine Guy, Uma Thurman, Chris Evans, Madeline Kahn, Matt Damon, Connie Britton, Leonard Nimoy, Taylor Schilling, Uzo Aduba, Eliza Dushku and Barbara Walters are all born in Boston.

**19. Bostonians get the weather from a skyscraper**

Colored lights on top of the old John Hancock Tower (now called 200 Clarendon) tell Bostonians the daily weather forecast. The options are solid blue, meaning it's a clear day; flashing blue, signifying a cloudy day or clouds are coming; solid red, saying there's rain coming; and flashing red, meaning snow is coming. In the summer, flashing red means the Red Sox game is rained out.

**20. The city is full of walkers**

As of 2012 and according to U.S. Census Bureau data, 15.1% of Bostonians walked to work — the highest percentage among the major U.S. cities.



Chair of the Meeting: **Georg Schett**

University of Erlangen-Nuremberg Institute for Clinical Immunology Germany

The 7th Annual Meeting of the International Cytokine & Interferon Society will be held at the Hofburg Conference Centre, an international conference and event centre in the heart of the capital city of Vienna.



### Plenary Sessions Room: **Zeremoniensaal**

Against the inspired setting of the Habsburg Throne Room, Napoleon asked Marie Louise, the Emperor's daughter, for her hand in marriage.

The Plenary Sessions, one Parallel Session and all exhibits, posters and coffee breaks will be on the Mezzanine Level of the Hofburg Conference Center. One Parallel Session room, the Forum, will be one floor below, but worth the short walk.



## Parallel Session Room: **The Forum**

With its ultramodern glass architecture and high-tech-standard features, the Forum satisfies the most exacting visual and technical expectations.



## Conference Dinner: **Vienna City Hall**

Tuesday 22 October, 2019

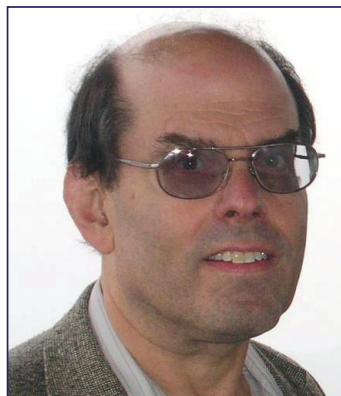
The Festive Hall (Festsaal) of Vienna City Hall is provided free of rental charge by the Mayor of Vienna in appreciation for bringing Cytokines 2019 to Vienna.

Deadline for Abstract Submission, Young Investigator Award Applications/Nominations, Travel Award Applications & Early Bird Registration: **3 June 2019**

## MEMBERS IN THE NEWS



**Professor Bryan Williams**, BSc (Hons), PhD, (Hon) FRSNZ, FAA, Emeritus Director and Distinguished Scientist Hudson Institute of Medical Research will be spending 3 months at the US National Cancer Institute as an NCI Scholar. Dr. Williams will be associated with the Cancer and Inflammation Program in Frederick, MD and will be interacting with laboratories in both Frederick and Bethesda.



**Howard A. Young** has been selected to receive the 2018 NIH Director's Award. He is receiving this award "For exemplary performance while demonstrating significant leadership, skill and ability in serving as a mentor".

## Future Annual Meetings



7th Annual Meeting  
20 – 23 October, 2019  
Hofburg Kongresszentrum, Vienna, Austria



8th Annual Meeting  
1 - 4 November, 2020  
Hyatt Regency Seattle, Seattle, USA