

ISICR 2008 Seymour and Vivian Milstein Award Winner



Dr. Giorgio Trinchieri

**Director, Cancer and Inflammation Program
Chief, Laboratory of Experimental Immunology
Center for Cancer Research
National Cancer Institute
Frederick, Maryland 21702-1201**

Giorgio Trinchieri received his medical degree from the University of Torino, Italy, in 1973. He was a member of the Basel Institute for Immunology (Basel, Switzerland) and an investigator at the Swiss Institute for Experimental Cancer Research (Epalanges sur Lausanne, Switzerland). From 1979 to 1999 he was at Wistar Institute in Philadelphia and became Hilary Koprowski Professor and Chairman of the Immunology Program; he was also Wistar Professor of Medicine at the University of Pennsylvania. He was then director of the Schering Plough Laboratory for Immunological Research in Dardilly, France, and an NIH Fogarty Scholar at the Laboratory for Parasitic Diseases, NIAID, before becoming director of the Cancer and Inflammation Program (CIP) and chief of the Laboratory of Experimental Immunology at NCI in August 2006. As CIP director, he oversees the operations of two major NCI intramural laboratories, the Laboratory of Experimental Immunology and the Laboratory of Molecular Immunoregulation. These two laboratories constitute the major immunologic component of the CCR's inflammation and cancer initiative, which spans the NCI's campuses in Frederick and Bethesda and seeks to partner NCI's expertise in inflammation and immunology with its cutting-edge cancer etiology and carcinogenesis program. He has been interested for many years in the interplay between inflammation/innate resistance and adaptive immunity, and in the role of pro-inflammatory cytokines and interferons in the regulation of haematopoiesis, innate resistance and immunity. In 1989, his group at the Wistar Institute discovered Interleukin-12, and he has spent many years characterizing the molecular mechanisms of IL-12 production and action, and the role of this molecule in tumour immunity, infections and autoimmunity. His main focus of research is now the role of inflammation, innate resistance, and immunity in carcinogenesis, cancer progression, and prevention or destruction of cancer.

2008 ISICR Honorary Member Awards



George John Galasso, Ph.D., Sc.D.

George Galasso was born in New York City. He graduated from Cardinal Hayes High School in 1950 and Manhattan College in 1954. He then served in the US Army 1954-56 and subsequently went to the University of North Carolina where he obtained a Ph.D. degree in Microbiology from in 1960. Following a Post-Doctoral fellowship he became Research Assistant Professor at the UNC Medical School.

In 1964 he became Associate Professor of Microbiology in the University of Virginia Medical School where he did research and taught Virology. In 1968 he was accepted into the Grants Associates Program of the NIH a highly selective training program of the NIH for Health Science Administrators and began his career as an administrator of scientific programs. In 1969 he was asked to initiate an Antiviral Research Program for the National Institute of Allergy and Infectious Diseases. This was a period of skepticism for the efficacy of antiviral agents to combat viral diseases. The initial goal was to determine whether interferon had a role in treating disease and to determine whether chemical agents could be used to treat viral diseases. Due to his efforts adenine arabinoside was shown effective against herpes encephalitis, the first time an antiviral agent was successfully used to treat an ongoing serious viral disease. This showed that antiviral agents could indeed prove effective and paved the way for other antiviral agents. He also was a leader in interferon clinical trials and was instrumental in showing the role of interferon in zoster, laryngeal papilloma and the efficacy of interferon in hepatitis and contributed to its use against cancer. His efforts in this field of antiviral research have been internationally recognized. He served on the US-USSR science exchange program and headed delegations to the then USSR in the 70s. He served as Director of the World Health Organization (WHO) Collaborating Center for Interferon Reference and Research, and as a member on the WHO Expert Panel on Viral Diseases (Interferon and Antivirals). He was made an honorary faculty member of the Hubei Medical School, Wuhan, Peoples Republic of China where he participated in a virology course for representatives of all the provinces of China in 1983.

In 1973 he became Chief of the Infectious Diseases Branch with responsibility for development of vaccines and antivirals to combat all infectious diseases. In 1983 he became Associate Director for Extramural Programs of the NIH, with responsibility for NIH policies involving grants and contracts. He developed the first set of Conflict of Interest Rules in conjunction with the other research agencies of the government. He is the author of nearly 100 scientific articles and reviews. He has served on the editorial board of several scientific journals and as Review Editor for *Antiviral Research*. He edited several texts notably four

editions of, *Antiviral Agents and Viral Diseases of Man*, *Practical Diagnosis of Viral Infections* and *Practical Guidelines in Antiviral Therapy*.

He was active in the early stages of the formation of the Interferon Research Society and the founder of the International Society for Antiviral Research (ISAR) in 1985 and was active in this Society even after retirement.



Dr. Paula Pitha-Rowe

Professor

The Sidney Kimmel Comprehensive Cancer Center

Johns Hopkins School of Medicine

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Paula Pitha-Rowe has been interested in the effects viral infection on the expression of cellular genes and in the novel approaches to modulation of the antiviral and anti-inflammatory responses. She received her PhD from the Academy of Sciences, Prague, Czech Republic and did postgraduate training in the Institute of Organic Chemistry and Biochemistry, Prague and at the Johns Hopkins University School of Medicine. The overall goal of her group is to understand the molecular mechanisms that govern the innate immune response to infectious agents. There is growing evidence which indicates that the inflammatory response plays an important role in autoimmune disease and triggers carcinogenesis. Thus, identification of the critical cellular elements involved in the innate immune recognition of infectious pathogens may provide a lead to our understanding of the role of inflammatory responses in cancer and provide a new therapeutic target.

The long-term goal of Dr. Pitha-Rowe's research is to understand the cellular responses to infection and the relationship between viral pathogenicity and oncogenicity. Over the past several years, her group has identified three novel transcription factors, IRF-3, IRF-5, and IRF-7, and has shown that these factors serve as direct transporters of virus-mediated signaling. The research advances of her group have revealed a critical role of these factors in expression of the early inflammatory genes in infected cells. Her laboratory, together with other laboratories, has shown that these factors are also activated in response to bacterial infection upon binding of ligands to Toll receptors. In their recent studies, her group has shown that over-expression of IRF-5 in B cells induces p21^{waf} and proapoptotic genes in a p53-independent manner. Altogether, these data indicate that the genes of the IRF family play a critical role in the differentiation and maturation of lymphoid cells, apoptosis and activation of early inflammatory cytokines. Whether IRFs play a role in the innate response to HIV-1 infection also is being examined. The importance of IRFs in innate immunity has been recently demonstrated by the observation that many viruses target their function as a part of viral mimicry. The Kaposi's sarcoma virus (KSHV) that is associated with Kaposi's

sarcoma and B cell lymphoma encodes four IRF homologues that associate with cellular IRFs and modulate their function, as well as the functions of other cellular proteins. Recent data from Dr. Pitha-Rowe's group show that one of these KSHV-encoded IRFs—vIRF-3—is a nuclear protein that associates with the c-myc suppressor and thus may contribute to KSHV- AIDS-associated tumorigenicity.

Clinical Research

The recent findings of Dr. Pitha-Rowe's laboratory have potential clinical application. First, Dr. Pitha-Rowe has shown that IRFs can serve as an effective adjuvant of DNA-stimulated immune responses to a DNA-encoded viral antigen. These adjuvants will be eventually tested in clinical settings, both for viral infection (HIV-1, HCV) and tumor vaccines. Second, she has shown that IRF-5 has proapoptotic activity that is independent of p53. Thus, IRF-5 expression may increase sensitivity of p53-defective tumors to proapoptotic drugs. Finally, she has recently shown that an IFN-induced protein (ISG) is an effective inhibitor of HIV-1 replication and enhances the virus-mediated antiviral response.

(Adapted from the Johns Hopkins University School of Medicine and the Sidney Kimmel Cancer Center websites).

Seymour & Vivian Milstein Young Investigator Award Winners

Dr Toby Lawrence

Senior Lecturer, MRC New Investigator
Centre for Cancer & Inflammation
Institute of Cancer and CRUK Clinical Centre
Barts and The London School of Medicine and Dentistry
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London EC1M 6BQ, UK



Dr Lawrence gained his PhD in experimental pathology from the University of London at the William Harvey Research Institute under the mentorship of the late Prof Derek Willoughby during which time he developed research interests in endogenous anti-inflammatory mechanisms and the resolution of inflammation. During his early post-

doctoral studies Dr Lawrence identified an important role for the NFkappaB pathway in the resolution of acute inflammation. With the award of post-doctoral fellowships from the Arthritis Research Campaign and the Wellcome Trust Dr Lawrence continued his studies at the University of California San Diego, in the Laboratory of Signal Transduction and Gene Regulation under Prof Michael Karin, where he gained training in the use of molecular genetics to study the role of cell signalling pathways in the regulation of inflammation and immunity. These studies focussed on the role of the IkappaB kinase (IKK) in the biology of inflammation; using tissue specific gene targeting to establish the specific role of IKK in the inflammatory response. In 2004 he returned to London as a Lecturer at Imperial College London in the Kennedy Institute of Rheumatology. Dr Lawrence joined the Institute of Cancer in 2006 as a Senior Lecturer and established the Inflammation Biology group in the [Centre for Cancer & Inflammation](#). The major research focus of the group is to understand the fundamental mechanisms by which inflammation promotes cancer. With particular reference to the role of stromal and inflammatory cells in carcinogenesis.

Dr. Tao Lu

Project Staff

Cleveland Clinic Foundation

Cleveland, OH USA



Dr. Tao Lu received her Ph.D. degree in Molecular Cellular Biology from the Medical University of Ohio at Toledo, Ohio, USA, in 2001. Since then, she has been working with Dr. George Stark at the Cleveland Clinic Foundation. Her current position is Project Staff in the Dept. of Molecular Genetics. Dr. Lu's major research interest is NFkB, cancer cell signaling and cytokines. In the Stark lab, she has demonstrated that constitutive activation of NFkB in cancer is almost always caused by the constitutive secretion of one or more factors that activate NFkB in an autocrine fashion from outside the cell. She found that TGF-beta activates NFkB in a subset of tumors and mutant cell lines, and that the basis of increased secretion is an increased steady state level of the mRNA. In addition she found that TGF-beta activates NFkB by recruiting the IL-1 receptor and, conversely, that IL-1 activates SMADs by recruiting the TGF-beta receptor. This unusual crosstalk is argued to be especially important in the immediate vicinity of tumors or at sites of inflammation, where the concentrations of TGF-beta or IL-1 are likely to be high. Her current work focuses on how NFkB may be regulated by negative

feedback mechanisms and she has employed a novel method in which retroviral vectors are used to insert strong promoters more or less randomly into the genomes of mammalian cells as a method for identifying genes that regulate NF κ B.

Dr. Lu is a recipient of 2 “Innovator Awards” from the Cleveland Clinic Foundation and is a past recipient of an ISICR Travel Award.

Dr. Cesar Munoz-Fontela

Postdoctoral Fellow
Mt. Sinai School of Medicine
New York, NY USA



Dr. Cesar Munoz-Fontela obtained his Ph. D. in viral oncology under the supervision of Dr. Carmen Rivas, at the Complutense University of Madrid (Spain). His research was focused on understanding the mechanisms by which human herpesvirus 8 (HHV-8/KSHV) counteracted the host immune response and its relationship with cancer development. In KSHV-dependent lymphomas only a small subset of latent viral genes are expressed, suggesting that the transforming potential of the virus relies on the expression of such genes. His work revealed that one of these KSHV latent genes, K10.5, encoded a multifunctional protein, LANA2/v-IRF3, with the ability to target several cellular pathways such as p53, the double-stranded RNA-dependent protein kinase (PKR), the Rb family of pocket proteins, 14-3-3 and FOXO3a. Furthermore, he discovered that LANA2/v-IRF3 is the only Interferon (IFN)-antagonist protein known so far with the ability to directly bind tubulin and prevent taxol-dependent microtubule stabilization. These findings, helped to explain why patients undergoing KSHV-derived lymphomas fail to respond to taxol chemotherapy. As part of his graduate training, he was also involved in research related to the antiviral activity of IFN-inducible tumor suppressor genes. In collaboration with Dr. Manuel Serrano (CNIO, Spain) he and his laboratory established that mice that harbor an extra copy of the p53 gene are more protected from infection with VSV and Vaccinia virus due to an enhanced apoptotic response. Moreover, in collaboration with Dr. Serrano and Dr. Mariano Esteban (CNB, Spain), his laboratory demonstrated for the first time that ARF, another IFN-inducible tumor suppressor, had a strong antiviral effect due to its ability to directly bind to Nucleophosmin. By doing so, ARF prevents nucleophosmin-dependent inactivation of PKR. He joined Dr. Stuart Aaronson’s lab at Mount Sinai School of Medicine (New

York) in 2006 as a postdoctoral fellow, where he is investigating the role of tumor suppressor genes on IFN-dependent antiviral immunity. In collaboration with Dr. Adolfo Garcia-Sastre (MSSM, New York), he discovered that IRF9 is a novel p53 direct transcriptional target. Through direct up-regulation of IRF9, p53 enhances IFN-dependent activation of antiviral genes in response to viral infection. Moreover, p53 participates in a positive feed back loop between IFN signaling and production, helping to establish an IFN-dependent antiviral state in bystander cells undergoing viral infection. His ongoing projects also indicate that tumor suppressor genes, such as p53 and Rb, are frequent targets not only for oncoproteins from DNA viruses, but also for IFN-antagonist proteins from RNA viruses such as Influenza NS1 or Ebola VP35. These findings, further point to the role of tumor suppressor genes in innate antiviral immunity.

Dr. Takeshi Saito

Senior Fellow

Department of Immunology

University of Washington School of Medicine

Seattle, WA USA



Dr. Takeshi Saito received his medical and scientific training at training at Showa University, School of Medicine, Tokyo (2004). His Ph.D. training was conducted in the Division of Internal Medicine, Department of Gastroenterology under Prof. Keiji Mitamura, and focused on defining the viral genetic determinants conferring resistance or sensitivity of hepatitis C virus to interferon therapy. After completing his doctoral studies, he received further training as a clinical hepatologist/general gastroenterologist, and practiced medicine under the mentorship of Professor Michio Imawari, during which time he became interested in the basic mechanisms of liver diseases. Dr. Saito has pursued this interest during his post-doctoral training in the laboratory of Dr. Michael Gale Jr. where he is currently a Senior Fellow in the Department of Immunology at the University of Washington School of Medicine. Dr. Saito's career goal is to become a physician-scientist and conduct translational research of liver-related diseases. While in Dr. Gale's laboratory, Dr. Saito has been working to understand how host innate immune receptors sense HCV infection and initiate the innate immune response that involves type I interferons and proinflammatory cytokines that regulate hepatic immunity. Dr. Saito's

research has revealed how hepatitis C virus triggers innate immunity through processes of pathogen recognition receptor (PRR) sensing of pathogen associated molecular patterns (PAMPs) during infection. His work has defined 1) Retinoic acid inducible gene I (RIG-I) is the major PRR that senses HCV RNA in the host cell; 2) the C-terminal repressor domain of RIG-I as the off/on switch of innate immunity against hepatitis C virus and other RNA viruses; 3) the specific RNA PAMP signature recognized by RIG-I and encoded in the HCV genome; 5) Conserved PAMP motifs within the genome of RNA viruses that trigger RIG-I-dependent signaling of innate immunity. Dr. Saito's studies have shown that antiviral immunity is triggered by sequence-specific RNA recognition by RIG-I, and provides novel insights into the immune-stimulatory processes induced by the RIG-I/PAMP interaction. His current interest is to apply his research toward improving adjuvant and vaccine designs to drive protective immune responses against pathogenic viruses.

Seymour & Vivian Milstein Travel Award Winners

Through the generosity of the Seymour and Vivian Milstein Foundation, the ISICR is pleased to designate almost \$50,000 for the 2008 Travel Awards. Winners come from more than 10 countries, clearly demonstrating the international focus of our society.

Sabrina Brzostek
Daniel Burke
Arindam Chakrabarti
Mounira Chelbi-Alix
Hui-Chen Chen
Venugopalan Cheriya
George Christophi
Ahmet Civas
Silvia Correia
Ana Costa-Pereira
Brian Doehle
Beihua Dong
Jennifer Drahos
Eugene Friedman
Carole Galligan
Ana Gamero
Yunfei Gao
FuiGoon Goh
Jennifer Gommerman
Geetanjali Gupta

Deborah Hodge
Wei-Chun Huang-Fu
Katharine Irvine
Brendan Jenkins
Danlin Jia
Sven Klaschik
Thomas Krausgruber
Malathi Krishnamurthy
Helle Kristiansen
Thomas Kuri
Virginia Maina
Atsuko Masumi
Zora Melkova
Eliane Meurs
Reem Mohammed
Markus Mordstein
Anna Överby
Zulema Antonia Percario
Courtney Plumlee
Maya Poffenberger
Zoran Popmihajlov
Chiara Porta
Tracy Putoczki
M R Sandhya Rani
Giovanna Romeo
Shamith Samarajiwa
Ayca Sayi
Emmanuel Thomas
Scott Thomson
Chafia Touil-Boukoffa
Deborah Vestal
Angela Walker
Ajay Wanchu
Wei-Bei Wang
Joanna Wegrzyn
Christine White
Mumtaz Yaseen
Ying Zheng

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Vivian Milstein Foundation and the**

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Christina Fleischmann Award Winner

Special thanks to the Fleischmann Foundation for the continuing support of this award

Dr. Yueh-Ming (Ming) Loo

Acting Instructor
Dept. of Immunology
University of Washington
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Dr. Yueh-Ming Loo is an Acting Instructor in the Department of Immunology at the University of Washington School of Medicine. Her research in the laboratory of Dr. Michael Gale Jr. is focused on understanding the mechanisms by which RNA viruses trigger and control innate immune signaling through the cellular RIG-I/IPS-1 pathway. A major focus of her studies is to define the role of IPS-1 and the nature of the IPS-1 signalosome that mediates interferon production and innate immunity during RNA virus infection.

Ming received her Ph.D. in Microbiology and Immunology from the State University of New York at Buffalo where her training with Dr. Thomas Melendy focused on virus-host interactions required for papillomavirus DNA replication. She pursued her post-doctoral training with Dr. Michael Gale, Jr. at the University of Texas Southwestern Medical Center at Dallas where she independently identified IPS-1, otherwise known as Cardif, VISA or MAVS as a novel adaptor required for signaling interferon production by the RIG-I-like helicases RIG-I and MDA5 during RNA virus infection. Her studies showed that Hepatitis C virus (HCV), a human pathogen of global public health concern expresses a protease NS3/4A that specifically targets and cleaves IPS-1 to release it from the outer membrane of the mitochondria. HCV is thus able to efficiently abrogate interferon production and evade the host innate immune response to establish chronic infections. Confocal microscopy and biochemical analyses of patient liver biopsies

showed that NS3/4A cleavage of IPS-1 occurs in vivo in the human patient, and can vary from patient to patient such that those who exhibit little or partial IPS-1 cleavage were correspondingly able to mount a more robust innate immune response during infection, thus promoting viral clearance. NS3/4A-specific protease inhibitors not only rescued IPS-1 from cleavage, but further restored interferon production and the innate antiviral response in infected cells, thus providing strong evidence identifying IPS-1 as a potential therapeutic target for HCV infection. Additionally, she has shown that IPS-1 is essential for establishing innate immunity to many RNA viruses that are also significant human pathogens. The viruses, which were derived from different virus families and whose RNA genomes harbor distinct PAMP features were shown to differentially engage RIG-I and MDA5 to trigger innate immunity. In addition, her collaborative studies have shown that RIG-I regulates cell permissiveness to HCV infection, and that RIG-I signaling is regulated by protein antagonists encoded by the Ebola virus and influenza viruses. Overall, her research has revealed IPS-1 as an essential signaling adaptor of the RIG-I pathway regulated by HCV infection in vivo, and has revealed distinct mechanisms by which different RNA viruses trigger and control RIG-I signaling.

Dr. Loo has co-authored several scientific publications and commentaries, and has published a book chapter describing the mechanisms by which RNA viruses regulate host innate immune defenses. She is a member of the International Society for Interferon and Cytokine Research and the American Society for Virology, and serves as an ad-hoc manuscript reviewer for various scientific journals.

Ludwig Boltzmann Award

The Boltzmann Award, established by Austrian scientists, is meant to encourage international scientific cooperation in the field of cytokines. One award is granted to a pair of scientists from two countries selected jointly by ICS, ISICR and ECS Awards Committees for an outstanding scientific presentation (oral, poster) at the joint meeting of the societies.



Josef Schwarzmeier with Boltzmann Award winners Bryan Williams, Ganes Sen and Saurabh Chattopadhyay (Joao Marques not shown).