

An Interview with the 2007 Milstein Award Winner, Dr. Shizuo Akira

Thomas Tan



Dr. Shizuo Akira is a Professor at the Research Institute for Microbial Diseases at Osaka University, Japan (since 1999), and also a project director of AKIRA Innate Immunity, ERATO (Exploratory Research for Advanced Technology) of Japan Science and Technology Corporation (JST) (since 2002). He received his M.D. in 1977, and Ph.D. in 1984 from Osaka University. After two years of postdoctoral working in Department of Immunology, University of California at Berkeley, he started to investigate IL-6 gene regulation and signaling in the Institute for Molecular and Cellular Biology, Osaka University, and cloned the transcription factors, NF-IL6 and STAT3. He was a Professor in Department of Biochemistry, Hyogo College of Medicine from 1996 to 1999, where he became involved in Toll-like receptor (TLR) research. His current research interests are molecular mechanisms of host defense and innate immunity, and as part of these studies, he has generated many important knockout mice. In 2006 and 2007 he was recognized as the hottest scientist who had published the greatest number of 'Hot Papers' (11 papers) over the preceding two years. He is the recipient of several international awards, including the Robert Koch Prize and the William B. Coley Award.

ISICR: Congratulations on receiving the Milstein Award. Where were you when you first learned that you have been selected by ISICR to receive the prestigious Award?

SA: In my office. Professor Paula Pitha-Rowe called to inform me that I have been selected as the winner of the Milstein Award 2007.

ISICR: What does the Award mean to you?

SA: Interferon research was and now is very strong in Japan. Indeed, we already have famous Japanese researchers as Milstein Awardees. I am very honored to be included in

such prominent list, and proud of the internationally high standard of interferon research in Japan.

ISICR: What do you feel are your most important contribution to the field of cytokine research?

SA: Identification of TLR9 as CpG DNA receptor.

ISICR: And if you have to pick one TLR member or pathway, which one would you target for therapy?

SA: Of course, TLR9. I have high hopes for TLR9 stimulating molecules in vaccine development, allergy treatment, and cancer immunotherapy.

ISICR: You also made seminal discoveries on IL-6 and STAT3. Which disease indications do you think would best benefit from therapies targeting IL-6 and STAT3 pathways?

SA: IL-6 is now found to be an essential cytokine which drives Th17 response. Blockade of IL-6 action or STAT3 signaling will be useful for treatment of chronic inflammatory diseases and autoimmune diseases.

ISICR: What ignited the fire in you to become a scientist? Who was your mentor or role model in your scientific career?

SA: I was initially trained as a medical doctor, and practiced two years in a municipal hospital after graduation. I wanted to do research, and decided to pursue graduate studies at Osaka University, Medical School. My mentor was Professor Tadimitsu Kishimoto, who was studying B cell differentiation and discovered IL-6. In order to learn molecular technology, I was sent to the lab of Professor Tasuku Honjo, who was a professor in the Department of Genetics at Osaka University. The encounter with both superb scientists determined my fate to become a scientist.

ISICR: Thinking back, how has the trajectory of your Ph.D. pursuit influenced your career choices and present position?

SA: I think two things during my PhD course influenced my career choices and present position. One is that I could publish my experimental results in Cell and EMBO journal as the first author and Nature as the second author. The other is I met two distinguished immunologists, Professors Kishimoto and Honjo, and I was much influenced by their personalities and their achievements.

ISICR: You were a postdoctoral fellow at the University of California-Berkeley. Was this your first trip to the US? Any cultural shock?

SA: That was my first trip to the US. I had not experienced cultural shock much because Japan was already immersed with American culture. But I had difficulty in communicating in English.

ISICR: You have authored and co-authored over 500 papers, and you're one of the most cited immunologists. How did you do it?

SA: For one, the generation of various knockout mice increased the number of papers because the mice are utilized in other laboratories in a collaborative manner. And I always searched the next target from the results obtained by knockout mice. For instance, we found by chance that MyD88 knockout mice are unresponsive to LPS. This got me involved in innate immunity research. Then, we started to knock out all receptors which might use MyD88 as adaptor, including IL-1 receptors family and Toll-like receptors. Once it was shown that TLR4 is an LPS receptor, the next question became what was the role of other TLRs. We searched for many immunostimulants which activate immune cells to produce cytokines. Step by step we identified the ligand recognized by individual TLRs. We then noticed that LPS still activates NF- κ B in the absence of MyD88. We searched for the genes which are induced in response to LPS in MyD88 knockout mice and found interferon-inducible genes. We also expected the presence of MyD88-related molecules, and mined for such molecules in database, and found several genes, and started knocking them out as well in mice, and uncovered their role. Our main strategy is to find out the next research target from the phenotype of knockout mice before embarking on the *in vitro* experiments.

ISICR: If you weren't a scientist, what would you be?

SA: Medical doctor. Perhaps a novelist, but I know I will not become a good writer.

ISICR: What's your idea of relaxation?

SA: I like to read novels.

ISICR: Can you describe the research environment at Osaka University?

SA: The building is old, and the space of my lab is small. The University is constructing a new building, which is scheduled to be completed by April, 2009, and my lab will move to the new building.

ISICR: What are your current priorities?

SA: To continue the high quality of our publications, but it does not mean to simply publish papers in high-impact journals.

ISICR: What are you most looking forward to at this year's ISICR Annual Meeting in Oxford?

SA: New findings regarding the DNA sensors.

ISICR: And that's why you're a highly cited immunologist--always working and always on the lookout for the next target! Thank you for your time, Dr. Akira.

SA: My pleasure.

Past Awardees

1988---Tadatsugu Taniguchi (Japan)

1989---Michel Aguet (Switzerland)

**1990---Ara G. Hovanessian (France)
Bryan R. G. Williams (Canada)**

**1992---Jordan Gutterman (U.S.A.)
Hans Strander (Sweden)**

**1993---Ian Kerr (U.K.)
Robert H. Silverman (U.S.A.)**

**1994---Charles E. Bugg (U.S.A.)
Yokio Mitsui (Japan)
Tattanahalli L. Nagabhushan (U.S.A.)**

**1995---Susan E. Krown (U.S.A.)
R. Michael Roberts (U.S.A.)**

**1996---Paula Pitha-Rowe (U.S.A.)
Robert D. Schreiber (U.S.A.)**

**1997---James Darnell (U.S.A.)
Ian Kerr (U.K.)
George Stark (U.S.A.)**

1998---Otto Haller (Germany)

**1999---Michael Katze (U.S.A.)-
Adi Kimchi (Israel)**

**2000---John Kirkwood (U.S.A.)
Moshe Talpaz (U.S.A.)**

2001---Sidney Pestka (U.S.A.)

**2002---David Levy (U.S.A.)
Ganes Sen (U.S.A.)**

**2003---John Hiscott (Canada)
Tom Maniatis (U.S.A.)**

**2004--- Ernest Borden (U.S.A.)
Keiko Ozato (U.S.A.)**

**2005---Nancy Reich (U.S.A.)
Menachem Rubinstein/Daniela Novick (Joint Award) (Israel)**

**2006---Michael Gale, Jr. (U.S.A.)
Takashi Fujita (Japan)**

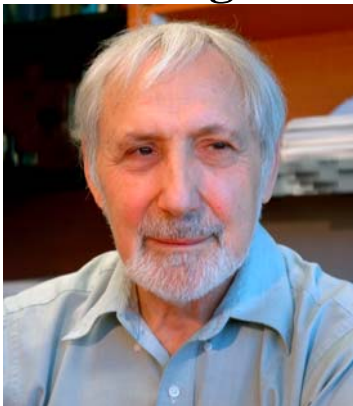
2007 ISICR Honorary Members

Dr. Ian Kerr



Dr. Ian Kerr has had a long and very distinguished career studying the mechanism of action of the interferons. Obtaining his PhD in 1963, he did postdoctoral work at Stanford and MIT, and was a group leader at the MRC National Institute of Medical Research for many years before moving to Lincoln's Inn Fields in 1980. Dr. Kerr has made numerous ground breaking contributions to our understanding of how interferons alter cellular behaviour. These include the discovery of 2-5A, the 2'-5' oligoadenylates which activate RNA degrading enzymes as part of the interferon response; the identification and characterization of interferon-responsive genes; and the application of somatic cell genetic approaches to elucidate signal transduction pathways controlling interferon-induced genes. Dr. Kerr was made a Fellow of the Royal Society in 1985, and amongst other awards has twice received the ISICR Milstein Award. Dr. Kerr retired in 2005 as a senior group leader at Lincoln's Inn Fields, London Research Institute. (Info copied from the 2005 London Research Institute Annual Report).

Dr. George Stark



Dr. George Stark graduated in Chemistry from Columbia University and became a postdoctoral fellow at the Rockefeller University. He then went to Stanford University and eventually became a Professor of Biochemistry. In 1983 he moved to the Imperial Cancer Research Fund in London as Associate Director of Research. Dr. Stark joined The Cleveland Clinic Foundation in 1992, as Chairman of the Lerner Research Institute, a position he held until August 2002. He currently holds the title of Distinguished Scientist and runs a busy laboratory in the Lerner Research Institute. Dr. Stark was elected to the National Academy of Sciences (USA) in 1987 and became a Fellow of the Royal Society (London) in 1990. In October 2002, he was elected to the Institute of Medicine of the National Academy of Sciences. Dr. Stark is also a winner of the ISICR Milstein Award.

Major objects of research conducted by Dr. Stark include the interferons (IFNs), pathways that activate or repress the transcription factor NF κ B and stress-induced pathways that activate the tumor suppressor protein p53 and pathways that respond to activated p53.

Past Honorary Members

- 1984 - Jean Lindenmann (Switzerland)**
 Yasuiti Nagano (Japan)+
- 1985 - Piet DeSomer (Belgium)+**
- 1986 - Gertrude Henle (U.S.A.)**
 Werner Henle (U.S.A.)+
- 1988 - Karl Fantès (U.K.)**
- 1989 - Yoshimi Kawade (Japan)**
- 1990 - Norman B. Finter (U.K.)**
- 1991 - Charles Chany (France)**
- 1993 - David Tyrrell (U.K.)**
 Julius Youngner (U.S.A.)
- 1994 - Kari Cantell (Finland)**
 Ferdinando Dianzani (Italy)
- 1995 - Jaqueline DeMaeyer-Guignard (France)**
 Earle F. Wheelock (U.S.A.)
- 1996 - Lois Epstein (U.S.A.)**
- 1997 - Gerhard Bodo (Austria)**
 Ion Gresser (France)
- 1998 - Samuel Baron (U.S.A.)**
 Ernest Knight (U.S.A.)
- 1999- Derek Burke (U.K.)**
 Edward DeMaeyer (France)+
- 2000 - Peter Lengyel (U.S.A.)**
- 2001 - Thomas Merigan (U.S.A.)**
- 2002 - Michel Revel (Israel)**
- 2003 - Robert Friedman (U.S.A.)**
 Jan Vilcek (U.S.A.)

2004 - No award given
2005 - Phillip Marcus (U.S.A.)
Kathryn Zoon (U.S.A.)
2006 - Wolfgang K. Joklik (U.S.A.)
Sidney Pestka (U.S.A.)
+ Deceased Honorary Members

2007 Seymour and Vivian Milstein **Young Investigator Award Winners**

Andrea Erickson
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I received my Bachelor of Science Degree in Biochemistry from The University of Texas at Austin in 2001. I am currently completing my Ph.D. at the University of Texas Southwestern Medical Center in Dallas. My dissertation research is focused on defining the biological actions of α/β IFNs against HCV.

Brenda Fredericksen
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My laboratory is interested in defining the molecular mechanism(s) by which flaviviruses evade and/or block the innate antiviral response. The ability of viruses to control and/or evade the host antiviral response is critical to the establishment of a productive infection. As eukaryotic anti-viral programs evolved to combat invading pathogens, viruses evolved processes to escape the anti-viral effects of these programs. Using West Nile virus (WNV) as a model system, we have begun to identify the molecular mechanisms by which this virus overcomes the host cell antiviral response. Pathogenic strains of West Nile virus utilize multiple strategies to both evade and circumvent the innate antiviral response. I have demonstrated that WNV evades detection by the host cells at early times post-infection, allowing the virus to replicate to high levels early in infection. However, once a productive infection has been established, the antiviral pathways become activated and WNV must then utilize a second mechanism to control the cellular environment. Several WNV proteins have been shown to impede signaling through the JAK/STAT pathway. Therefore, expression of high levels of these proteins late in infection would presumably attenuate JAK/STAT signaling and thereby prevent the induction of a robust antiviral response. By combining multiple mechanisms WNV is able to successfully control both the kinetics of induction and the overall gene expression profile of the innate antiviral response, thus, enabling the virus to establish a productive infection.

Vladimir Hurgin
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In 1999 I started my Ph.D under the supervision of Prof. Menachem Rubinstein shortly after IL-18 Binding Protein (IL-18BP) was isolated by a member of the lab, Dr. Daniela Novick. IL-18BP is a unique high affinity binding protein of IL-18 (IFN- γ inducing factor) and is distinct from a classical soluble receptor. IL-18BP neutralizes IL-18 biological activities and is induced by IFN- γ , suggesting that it serves as a negative feedback inhibitor of the IL-18-mediated immune response. In my Ph.D., I characterized the promoter of IL-18BP. I demonstrated that the rapid IFN- γ -induced JAK-STAT signaling pathway did not mediate IL-18BP induction but rather the induction required *de novo* synthesis of the transcription factor IRF-1, which together with C/EBP β activates the IL-18BP promoter, thus providing a time window for IL-18 activity. I found that the gene coding for IL-18BP, which seems to have a rather limited role as an inhibitor of IL-18, is regulated by very complex mechanism which is required for maintaining specificity and enabling more precise control of gene activity.

In view of these results pointing to a tight regulation of IFN- γ expression, I hypothesized that it is cytokines interplay that responsible for the prevention of an excessive hazardous IFN- γ activity. Indeed, in our research we describe such safety mechanism where the signaling by IFN- γ is dependent on expression of IL-1 α to allow its full array of signaling to occur. IFN- γ binding to its cognate receptor results in two separate events that occur in concert. One is rapid IRF-1 expression followed by its translocation to the nucleus, and the second is activation of membrane-associated IL-1 α . Membrane IL-1 α activates neighboring cells that harbor the type I IL-1 receptor to cause rapid translocation of NF- κ B to the nucleus. When IRF-1 and NF- κ B are activated in unison, a 10-fold enhancement in IFN- γ 's ability to induce an antiviral state is seen. Indeed, blocking IL-1 α causes a 90% reduction in the IFN- γ -induced antiviral state. It is remarkable that the dependence of the antiviral state on basal IL-1 was unique to IFN- γ and was not observed with type I IFNs (α and β) who are less pleotropic and less potentially toxic. The critical role of IL-1 α in IFN- γ action combined with the ability of IFN- γ to induce further production of IL-1 α raises the possibility that infiltrating macrophages or dendritic cells bearing surface-expressed IL-1 α interact with keratinocytes, rendering them more responsive to T cell-derived IFN- γ . Such a cascade of events may be the underlying mechanism of chronic skin inflammation. In summary we showed that what was considered to be intrinsic IFN- γ activities in fact depend on constitutively expressed IL-1 α .

Luis Martinez-Sobrido
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I received my Ph.D. in the field of virology under the supervision of Dr. Jose Antonio Melero at Madrid, Spain. After my Ph.D., I joined Dr. Adolfo García-Sastre's laboratory at Mount Sinai School of Medicine (2000), New York. My work has focused on reverse genetics systems for DNA and RNA viruses as it relates to the characterization of interferon antagonist proteins encoded by several viruses. I developed recombinant DNA and RNA viruses to study virus-cell interactions. These viruses have been an essential tool in our laboratories for the discovery and characterization of interferon antagonist proteins. I was involved in studies to more fully understand the underlying mechanisms used by negative strand RNA viruses (Ebola viruses, influenza viruses, Thogoto virus, arenaviruses) as well as positive-strand RNA viruses (mouse hepatitis virus, severe acute respiratory syndrome (SARS) coronavirus, and flaviviruses) to counteract the type I IFN response. In collaboration with Dr. Basler, we have found that Ebola virus VP35 binds double-stranded RNA and inhibits interferon production induced by RIG-I signaling. I also found that the influenza NS1 protein inhibits the RIG-I mediated induction of beta interferon and, recently, I characterized multiple anti-interferon actions of this viral protein. In collaboration with Dr. Kochs, we found that the interferon antagonist protein encoded by Thogoto virus (ML) inhibits type I interferon production by inhibiting the transcriptional activity of IRF-3. In collaboration with Dr. Weber and Dr. Palese we found inhibition of beta interferon induction by SARS coronavirus and the viral proteins that counteract the host response, respectively. Inhibition of the interferon response by mouse hepatitis virus at multiple levels was initiated in collaboration with Dr. Weiss. Together with Dr. Munoz-Jordan we identified the inhibition of interferon signaling by the NS4B protein of flaviviruses. Recently, in collaboration with Dr. de la Torre, we have found for the first time an interferon antagonist activity associated with the nucleoprotein of arenaviruses.

My current interests include the development of new state-of-art techniques to identify and characterize viral proteins that counteract the interferon response as well as the development of new anti-viral drugs that target the anti-IFN function of these interferon antagonist proteins.

I became a faculty member in the department of Microbiology at Mount Sinai in 2007. Additionally, I am a technology-development-component co-Investigator at CIVIA (an NIAID sponsored Center for Investigating Viral Immunity and Antagonism) as well a member of the Emerging Pathogens Institute at Mount Sinai School of Medicine, New York

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I received my Cand. Scient. degree in Molecular Biology in 2003 from the laboratory of Dr. Just Justesen at the University of Aarhus, Denmark. My pre-doctoral work (1999-2003) focused on the 2-5A system as a mediator of interferon action. My thesis work demonstrated a novel role for the OAS-like protein, p59 OASL, through a protein-protein interaction with the transcriptional repressor Methyl-CpG Binding Protein 1, MBD1.

I joined Dr. Bret Hassel's laboratory at the University of Maryland, Baltimore, Marlene & Stewart Greenebaum Cancer Center in 2003 for my Ph.D. research where I discovered a novel role for RNase-L in senescence. In collaboration with Dr. Robert H. Silverman at the Cleveland Clinic, I was able to demonstrate the *in vivo* role for RNase-L in longevity. In another study, in collaboration with Dr. Torben F. Orntoft at the University Hospital, Skejby, Denmark, I conducted the first detailed study of ISG15 expression in a human cancer which revealed a stage-specific expression of ISG15 in bladder cancer. I received my Ph.D. based on these studies from the University of Aarhus, Denmark in 2006.

I am currently a post-doctoral fellow at the National Cancer Institute, NIH. In February 2007 I joined Dr. Snorri S. Thorgeirsson's Laboratory of Experimental Carcinogenesis. My current research involves several aspects of liver tumorigenesis and I am currently studying the epigenetics and transcriptome of cholangiocarcinoma, a rare and lethal subtype of liver cancer of the biliary tree. Moreover, I am involved in the characterization of novel cancer stem cells in hepatocellular carcinoma.

I have been a member of the ISICR since 2000, at the very early beginning of my career, and since then actively participated in five of the past meetings. It is my opinion that ISICR gives its younger members, students and post-doc, a unique chance to "*show their flag*".

2007 Christina Fleischmann Memorial Award Winner

Dedicated to the memory of outstanding IFN research scientist, Dr. Christina Fleischmann

Dr. Nancy Jewell



I am currently a postdoctoral fellow in Dr. Joan Durbin's lab in the Center for Vaccines and Immunity at Columbus Children's Research Institute. I was trained as a molecular virologist in the laboratory of Dr. Louis Mansky where I studied the RNA packaging, infectivity and drug susceptibility of bovine leukemia virus (BLV) and human T-cell leukemia virus types 1 and 2 (HTLV-1 and HTLV-2). I am now completing my post-doctoral studies in Dr. Durbin's laboratory where I am investigating the innate immune response to respiratory viruses, specifically respiratory syncytial virus (RSV) and influenza A virus. I have shown that while the infected epithelial cells are a major source of IFN- α/β production following influenza A virus or RSV infection in the BALB/c mouse, only influenza A virus induces significant IFN- α/β production by plasmacytoid dendritic cells (pDCs). Moreover, while type I IFN levels decreased by > 60% in pDC-depleted, influenza virus-infected animals, no such decrease was seen in RSV infected mice. This observation is consistent with the specificity of TLR-ligand interactions and suggests that mechanisms of pathogenesis and host response will be specific to each virus and cannot be inferred from the study of other pathogens.

I am a member of the ISICR, the International Cytokine Society and the American Society for Investigative Pathology.

Seymour and Vivian Milstein Travel Awards

Betsy Barnes – USA
Danielle Brabant – Canada
Daniel Burke – Canada
Venugopalan Cheriyaath – USA
Troy Cline – USA
Eliana Coccia – Italy
Ana Costa-Pereira – UK
Blossom Damania – USA
Raymond Donnelly – USA
Deborah Hodge – USA
Markus Hofer – Australia
Xiaoyu Hu – USA
Cynthia Johnson – USA
Ricardo Khouri – Brazil
Yi-Ling Lin – China
Yueh-Ming Loo – USA
Barbora Lubyova – Czech Republic
Giorgio Mangino – Italy
Zora Melkova – Czech Republic
Susie-Jane Noppert – Australia
Yann Percherancier – France
Ramtin Rahbar - Canada
M R Sandhya Rani – USA
Maria Bena Remoli – Italy
Giovana Romeo – USA
Shamith Samarajiwa – Australia
Saumendra Sarkar – USA
Chafia Touil-Boukof – Algeria
Anette Van Boxel-Dezaire – USA
Johan Van Weyenbergh - Brazil
Deborah Vestal – USA
Mark Walter – USA
Christine White – USA
Dakang Xu – Australia
Jae-Kwang Yoo - Canada