***Japan Academy Prize to:***

Yoshiyuki NAGAI

Director, RIKEN Center of Research Network for Infectious Diseases
Professor Emeritus, Nagoya University

for "Elucidation of the Molecular Basis of Paramyxovirus Pathogenicity and Generation of a Novel Class of Expression Vector"

***Outline of the work:***

The major research subjects of Dr. Yoshiyuki Nagai have been Newcastle disease virus (NDV) and Sendai virus (SeV) belonging to the family *Paramixoviridae*, which consists of a variety of important human and animal pathogens. They are enveloped viruses with a linear, nonsegmented, negative (-) sense RNA genome. Dr. Nagai's scientific achievements are itemized into the following four heads.

**(1) Discovery of "Host Protease Dependence of NDV Pathogenicity"**

NDV comprises a wide variety of strains, which differ in virulence for chicken. Virulent strains infect all kinds of tissues in the host, causing a systemic lethal infection, whereas only limited types of tissues are targeted by avirulent ones, resulting in a non-lethal localized infection. Dr. Nagai found that these differences in tissue tropism and pathogenicity depend upon whether the inactive precursor of viral fusion (F) protein is converted to an active (fusion-competent) form by the proteases ubiquitously expressed in all kinds of tissues within the body or by those expressed in limited types of tissues. He then defined the cleavage motifs in the substrate F protein that are responsible for the different cleavability; i.e., the polybasic motif for virulent strains and monobasic motif for avirulent strains, and eventually identified the proteases involved in these two categories of cleavage-activation. This discovery of "NDV paradigm of viral pathogenicity" was a landmark in the history of virology because it represented the first understanding of viral pathogenicity at the molecular level. The paradigm further is making an enormous impact on modern virology because it is applicable to highly pathogenic vs. low pathogenic avian influenza viruses as well as to many other enveloped viruses.

**(2) Advancing Paramyxovirus Research by Reverse Genetics**

It was a new common task with challenge for researchers on paramyxoviruses and other negative strand RNA viruses to establish a system to recover the virus entirely from cDNA and thereby to allow reverse genetics (manipulation of viral genome at will). Dr. Nagai early established the system for SeV with incomparably high efficiency of virus recovery. Making full use of this technology, he resolved a series of long-held questions. In particular, he demonstrated that although dispensable for growth in cells in culture, the two accessory genes play crucial roles in pathogenesis producing fatal pneumonia in mice by counteracting two facets of antiviral state induced, respectively, by interferons and by an IRF3 (interferon regulatory factor 3) dependent but yet unknown effector. These achievements have set a scientific trend that studies on other paramyxoviruses focus on the accessory genes and opened a new common

ground shared with virology and immunology.

**(3) Generation of a Novel Class of Expression Vector**

Dr. Nagai developed the SeV reverse genetics into a novel class of expression vector, SeV vector, a non-genotoxic, cytoplasmic RNA vector with extremely high potential in transgene expression. Engineering toward generation of safer versions progressed rapidly. Diverse, unique and promising applications of the SeV vector to gene therapy, cancer treatment, AIDS prophylaxis and others are now in the pipeline and poised for testing in clinical trials. Particularly worthy of mention are that Dr. Nagai and his coworkers proposed a vaccine protocol regarded as one of the most promising in AIDS vaccine development race of keen competition and that US-Japan collaboration started with the prospect of its clinical trial.

**(4) Comprehensive Analysis of Sugar Chains of AIDS Virus**

Dr. Nagai perceived the facts that an AIDS virus envelope possesses as many as about 25 *N*-glycans, while most other enveloped viruses contain only several glycans. He generated a panel of simian AIDS virus mutants with the individual glycans deleted and assessed the requirement of each glycan for viral infectivity (either essential, down-modulating or neutral). He further demonstrated that the removal of multiple glycans causes striking changes of immune response pattern of monkeys. These results have breathed new life into the research on the structure and function of AIDS virus envelope protein, which tended to focus on the studies of the polypeptide backbone.

In summary, Dr. Nagai has led virus research in the world for over 40 years by promoting the molecular understanding of such a complex issue as viral pathogenicity. Furthermore, he developed SeV reverse genetics hatched out of pure academic need into a world-class biotechnology. Dr. Nagai's achievements in both basic theory and technologic innovation are thus prominent and greatly appreciated.

**Review articles**

[1] NAGAI Y. (1993). Protease-dependent virus tropism and pathogenicity. *Trends Microbiol.* 1, 81-87.

[2] NAGAI Y. (1999). Paramyxovirus replication and pathogenesis. Reverse genetics transforms understanding. *Rev. Med. Virol.* 9, 83-99.

[3] NAGAI Y., Kato A. (2004). Accessory genes of the *Paramyxoviridae*, a large family of nonsegmented negative-strand RNA viruses, as a focus of active investigation by reverse genetics. *Curr. Top. Microbiol. Immunol.* 283, 197-248.

[4] NAGAI Y., *et al.* Sendai virus engineering: From reverse genetics to vector development (2007). In "*Viral Expression Vectors* (KL Hefferon ed.)", pp. 123-146, *Research Signpost, Transworld Research Network*, Karela.