Japan Academy Prize to:

Yoshinori FUJIYOSHI

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for "Structure Determination of Membrane Proteins based on the Development of an Innovative Cryo-Electron Microscope"

Outline of the work:

Knowing the structure of a protein is widely recognised as crucial to understanding its biological function. The number of structures of soluble proteins that have been determined has thus increased dramatically over the last decade. Despite the importance of membrane proteins in many physiological processes, in particular as targets for many pharmaceutical drugs, their structural elucidation has remained a difficult task, mainly because their native environment is a lipid bilayer. Dr. Fujiyoshi has made many significant contributions to the structural determination of membrane proteins. He developed an innovative cryo-electron microscope featuring a helium-cooled specimen stage and used it to produce atomic models for a number of biologically and physiologically important membrane proteins.

Taking a molecular image of chlorinated copper phthalocyanine, Dr. Fujiyoshi showed that by minimising radiation damage to the specimen, electron microscopy could be given high enough resolution to detect individual atoms in an organic molecule. Turning to a structural analysis of proteins, as much larger molecules, he designed and manufactured a new type of electron microscope. This instrument made it possible to observe biological specimens at liquid helium temperature (4.2 K), which he showed to reduce radiation damage of biological molecules to 1/20 of that incurred at room temperature. Dr. Fujiyoshi continued to improve the design of his cryo-electron microscope, overcoming operational difficulties and attaining images at ever higher resolutions. This improved instrument allowed him to analyse the structures of several membrane proteins at atomic resolution in rapid succession, leading to a deep understanding of the molecular mechanisms underlying their physiological functions.

The structural and functional study of the human water channel aquaporin-1 is a typical example of Dr. Fujiyoshi's contributions to membrane protein biology. Driven by osmotic gradients, one aquaporin-1 channel allows passage of 2×10^9 water molecules per second, while completely preventing the permeation of all kinds of ions, even protons. Dr. Fujiyoshi and his co-workers analysed the structure of aquaporin-1 by electron crystallography; and based on their atomic model, proposed a molecular mechanism that explains how the channel can maintain strict water selectivity despite its very fast water permeation. They also determined the structure of another water channel, aquaporin-0, which plays important roles in lens fibre cells and has been implicated in cataract formation. A density map they produced at a resolution of 1.9 Å not only visualised the water molecules in the channel but also allowed the modelling of all the lipid molecules surrounding aquaporin-0 tetramers, visualising for the first time the structure of a complete lipid bilayer. Dr. Fujiyoshi also succeeded in growing two-dimensional crystals; and in analysing the structure of aquaporin-4, a water channel that is expressed in glial cells in the brain. Further studies have revealed the mechanism underlying the formation and disassembly of orthogonal arrays by aquaporin-

4. They have also elucidated another function of this water channel, namely in promoting cell adhesion, which may be related to osmo-sensing and other physiological processes in the brain.

Dr. Fujiyoshi's group analysed the structure of the gap junction channel formed by Connexin 26, leading to a new model for gap junction gating, the plug gating model. Gap junction channels are known to regulate fast signal transduction at the electric synapse and to permeate peptides up to 1.8 kDa. Although the large pore size needed for peptide permeation was difficult to reconcile with the rapid gating of the ion channel, the plug gating model convincingly explains these complex permeation characteristics of gap junction channels. The plug gating model is certain to change the current text book explanation for the gating mechanism of gap junctions, which postulated that the central channel closes upon rotation and inclination of the individual subunits. Dr. Fujiyoshi also contributed to the elucidation of the gating mechanism of the acetylcholine receptor, providing deep insights into how the same type of receptors can be regulated by alcohol or anaesthetics. As stated above, Dr. Fujiyoshi's cryo-electron microscopic studies not only focus on elucidating the structure of membrane proteins but also seek to understand the mechanisms underlying their physiological functions.

Dr. Fujiyoshi and his collaborators used single particle electron microscopy to analyse the structures of the voltage-gated Na^+ channel, the IP_3 receptor and the TRP channel, a temperature and/or pungency sensor. This single particle method has recently gained much attention, as it makes it possible to analyse the three-dimensional structure of proteins without needing to crystallise them. Through his structural and functional studies of biologically important ion channels and receptors conducted using both single particle electron microscopy and electron crystallography, Dr. Fujiyoshi is in the process of establishing a new research field, "Structural Physiology," a discipline in which he is the undisputed world leader.

The cryo-electron microscopes developed by Dr. Fujiyoshi have attracted much attention throughout the world, and he has engaged in many long-standing international collaborations. All high-resolution structures of membrane proteins determined by electron crystallography have been analysed using data collected on a Fujiyoshi-type electron microscope. Cryo-electron microscopes developed by Dr. Fujiyoshi have now been installed in laboratories in the United States, Germany and Sweden. These instruments will continue to contribute to the analysis of membrane proteins structures.

Dr. Fujiyoshi and his group have been and will continue to be a world-famous centre in the structural analysis of membrane proteins. As such, he has been honoured for his accomplishments with many awards and prizes, which include the Setoh Prize of the Japanese Society of Electron Microscopy, the Minister of Science and Technology Policy Award for the Industry-Academia-Government Collaboration Contributor Awards, the Yamazaki-Teiichi Prize, the Keio Medical Science Prize, the Shimadzu Prize and Medal with Purple Ribbon. As Dr. Fujiyoshi has made epochal contributions to cryo-electron microscopy and to establishing the field of Structural Physiology, he is eminently qualified to receive the Japan Academy Prize.