Imperial Prize and Japan Academy Prize to:

Keiichi NAMBA
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for "Structural and Functional Analyses of Biological Macromolecular Nanomachines"

Outline of the work:

All the functions of living organisms are realized by biological macromolecules, such as proteins and nucleic acids, and their assemblies. They are literally nanomachines that form dynamic networks of material transfer, energy conversion and information processing in the cells. Biological nanomachines are distinct from man-made machines in that they are flexible, well regulated and highly energy efficient, working properly even at an extremely low energy level close to thermal noise. Understanding how they assemble and interact with one another to carry out highly well-regulated energy transduction and information processing is important in understanding how all the intricate cellular functions are achieved. Prof. Keiichi Namba has focused on nanomachines, such as tobacco mosaic virus, the bacterial flagellar motor and muscle actin filament, and has revealed the mechanisms of self-assembly and sophisticated functions with extremely high-energy efficiency by developing and applying techniques of X-ray diffraction and electron microscopy to carry out three-dimensional (3D) structural analyses of these nanomachines at atomic resolution.

In early to mid 1980s, Prof. Namba devised and developed a new method of X-ray fiber diffraction analysis and applied it to the structural analysis of tobacco mosaic virus, a rod-shaped plant virus. The atomic resolution structural analysis of a non-crystalline specimen was itself unprecedented, but this structure also provided an atomic-level mechanistic understanding of virus assembly and disassembly regulated by the association and dissociation of protons to their specific binding sites made of carboxyl groups of neighboring molecules of the virus coat protein. Prof. Namba also developed state-of-the-art computer graphic programs at that time to produce beautiful figures for comprehensible explanations of the virus assembly/disassembly mechanism, aimed not only to scientific fields but also to the general public.

In the late 1980s, Prof. Namba initiated studies on the bacterial flagellum, a motile organelle made of a rotary motor and a helical propeller used by many bacteria to swim through liquid environments. The bacterial flagellum is a huge macromolecular complex composed of about 30 different proteins, each of which self-assembles to form sub-structures with a few to a few tens of thousand copies of subunits. Prof. Namba and his group analyzed the structures of different parts of the flagellum and revealed an extremely precise, sub-angstrom level mechanical switch in the structure of flagellin that is essential for polymorphic supercoiling of the filament to build the helical propeller and make it switch between left- and right-handed forms for bacterial behaviors called taxis. Based on the 3D structures, one after another he unraveled various mechanisms of the flagellum, such as the promotion of flagellar protein assembly by the distal cap, the universal joint motion of the hook that connects the motor and helical propeller, the left-right handedness switch of the filament, and the translocation of flagellar proteins by the type 3 protein export apparatus in the flagellar basal body. Such studies also revealed the mechanism of type 3 protein export in which the energy is not provided by ATP hydrolysis as had long been thought but by proton motive force across the cytoplasmic membrane. This unexpected result advanced the mechanistic understanding of type 3 virulence protein secretion by bacterial pathogens, such as Salmonella and Shigella. He also developed various methods of electron cryomicroscopy and image analysis and succeeded in

solving the atomic structure of the flagellar filament. This achievement marked an important milestone in structural biology, demonstrating for the first time that it is possible to solve the atomic structures of biological macromolecular assemblies without crystallizing the target specimen. This is potentially a very powerful method in that there is no need for crystallization and even a solution specimen as little as 0.1 ml can be used to visualize the structure. This technological development stimulated the interest of molecular biologists all over the world by demonstrating the potential power of electron cryomicroscopy and image analysis as a basic technique for future biological sciences.

The biggest problem in the structural analysis of biological macromolecular complexes by electron cryomicroscopy is that it takes months or even years to collect many high-quality images and carry out precise image analysis to reconstruct high-resolution 3D images. Prof. Namba and his group made key technical advances to shorten this period to several days, turning the once-slow method into a remarkably high-throughput one. High-resolution structure of muscle actin filament, for example, had been elusive despite intensive efforts made by many groups over a few decades because of its thin, flexible structure. Now, the newly developed method allows the secondary structures of actin in the filament structure to be visualized within a week from data collection to the 3D image reconstruction. This has moved the field of structural biology into a completely new era.

Prof. Namba has been highly recognized within the international community as indicated, for example, by the many keynote lectures he has delivered at international meetings. There is no doubt that he will continue to be a leading figure well into the future. Many of his achievements have been highly recognized as news topics, not only in international research journals but also in magazines and the TV media, for the public in the US and Europe as well as in Japan. He has been awarded many prizes, such as the Osaka Science Prize and the Biophysical Society Founders Award as the first Japanese to receive it, as well as honors such as Associate Member of the European Molecular Biology Organization and Fellow of American Academy of Microbiology. These achievements and international recognitions undoubtedly qualify him for the Japan Academy Prize.

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