Recipient of the 2003 International Prize for Biology

Dr. Shinya Inoué

Date of Birth: January 5, 1921

Nationality: USA

Position: Distinguished Scientist, Director,
Architectural Dynamics in Living Cells Program,
Marine Biological Laboratory

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Education and Career:

1944	B.S. (Zoology) from Tokyo University, Japan
1951	PhD (Biology) from Princeton University, USA
1951-1953	Instructor in Anatomy, University of Washington, Seattle, USA
1953-1954	Assistant Professor of Biology, Tokyo Metropolitan University, Japan
1954-1959	Research Associate to Associate Professor of Biology, Instructor in Optics, University of Rochester, NY, USA
1959-1966	Professor and Chairman, Department of Cytology, Dartmouth Medical School, Hanover, NH, USA
1966-1982	Professor of Biology and Director, Program in Biophysical Cytology, University of Pennsylvania, Philadelphia, PA, USA
1979-1987	Instructor-in Chief, Analytical and Quantitative Microscopy, Marine Biological Laboratory, Woods Hole, USA
1986-present	Distinguished Scientist, Director, Architectural Dynamics in Living Cells Program, Marine Biological Laboratory, Woods Hole, MA USA

Awards and Distinctions:

1947, 1953, 1975	Lecture and Demonstrations to Emperor Showa
1955-1958	Scholar in Cancer Research, American Cancer Society
1971-1972	Fellow, John Simon Guggenheim Foundation
1971	Fellow, American Academy of Arts and Sciences
1982-1996	MERIT Award, National Institutes of Health, USA
1988	Honorary Fellow, Royal Microscopical Society, UK
1992	E. B. Wilson Award, American Society for Cell Biology
1993	Member, National Academy of Sciences, USA

RESEARCH ACHIEVEMENTS

Dr. Shinya Inoué's research has focused on cell division, one of the central topics of cell biology, and his long career has been dedicated to the direct observation of what happens in living cells. Changes in the macromolecules and their assembly (supramolecular structures) that are active in living cells were formerly considered impossible to observe directly, but Dr. Inoué succeeded in making the dynamics of these structures visible by developing new methods of light microscopy, thereby contributing enormously to fields that include cell division, the cytoskeleton, and cell motility. Dr. Inoué's light microscope, with its many ingenious innovations, has produced an array of revolutionary images and transformed the way that we visualize the cell. It is known and esteemed among the research community as the "Shinya-scope."

Development of a Polarizing Microscope for Biology and Improvement of Light Microscopy

Dr. Inoué has dedicated his long research career to the attempt to understand how cells divide. To this end, using living cells, he developed methods of directly observing the dynamic changes in supramolecular structures that accompany cell division. In particular, he has gained worldwide acclaim as a distinguished pioneer for his major contributions to the development of light microscopy. Dr. Inoué's polarizing microscope made possible the greatest advances in cell biology since the development of the phase-contrast microscope in the 1930s, rendering visible the regular alignment of macromolecules in living cells.

Polarizing microscopes, which observe and measure the birefringence of optically anisotropic materials, were originally used to observe the crystal structure of rock and mineral samples. Biological structures generally have much weaker birefringence than crystals, and this weak birefringence cannot be detected with the polarizing microscopes used by mineralogists. Dr. Inoué made many technical improvements to develop a polarizing microscope suited to biological materials, achieving a major breakthrough with his development of rectified polarization optics. This invention greatly enhanced the sensitivity for detecting weak birefringence and eliminated the image aberration of polarizing microscopy, giving polarizing microscopes the best resolution of any light microscope.

Further, using polarized UV microbeam irradiation and spectrophotometric measurement of birefringence, Dr. Inoué demonstrated the coil-of-a-coil structure of the DNA-protein complex, as well as the tandem arrangement of chromosomes, in the needle-shaped sperm head of certain insects.

In the 1980s, Dr. Inoué made ingenious use of video cameras to enhance the imaging of living cells, and also helped to pioneer technology for obtaining super-high resolution. This technology enables researchers to see a single macromolecule (or, more precisely, its diffraction image. Today, the dynamic imaging technology for cells and cell components that has developed from these beginnings provides cell biologists with unprecedented tools, enabling them, for example, to observe the movements of a single motor molecule.

Dr. Inoué continues today to work at improving the quality of both microscope optics and imaging systems. At the turn of the new century, he invented a centrifuge polarizing microscope that is being used to study the dynamic stratification and alignment of fine structures in living cells. Most recently, he demonstrated the fluorescence anisotropy of Green Fluorescence Protein (which is an invaluable tool for molecular and cell biologists) and the use of parallel polars to vastly increase sensitivity for detecting fluorescence anisotropy.

Research on the Dynamics of Spindle Microtubules

Observing fertilized sea urchin eggs and other living cells with his improved polarizing microscope, in 1953 Dr. Inoué demonstrated that spindles (then widely believed to be an artefact of fixation) are a real structure in living cells and that they are involved in the partition of chromosomes into daughter cells, thus settling a fifty-year-old controversy. At the same time, he predicted that spindles consisted of highly labile linear filaments; it would take ten more years before they were identified as microtubules by electron microscopy. In a series of detailed experiments from the early 1950s to the mid-1970s, Dr. Inoué set out to quantify the dynamics of spindle fiber assembly in living cells by measuring their birefringent retardation. As a result, he demonstrated the dynamic nature of spindle and astral fibers and made two important predictions: (i) that the microtubules that composed these fibers were in a dynamic equilibrium with a cellular pool of subunits, and (ii) that the assembly dynamics of the microtubules were tightly coupled to generation of the forces for spindle morphogenesis and chromosome movement. He also discovered that the microtubules could be reversibly disassembled (depolymerized) by cooling or treating cells with the anti-mitotic drug colchicine. These advances led biochemists to the discovery of tubulin (the main protein subunit of microtubules) using a colchicine-binding assay, and to the development of methods for purifying tubulin that would polymerize when warmed and depolymerize when cooled. Dr. Inoué also established a method of localized control of microtubule polymerization in living cells by submitting cells treated with the anti-mitotic colcemid to 366 nm microbeam irradiation for the localized conversion of colcemid into its inactive isomer lumi-colcemid.

In a now-classic paper written in 1967, Dr. Inoué elaborated the concept of the spindle as a dynamic self-assembly system. It would be no exaggeration to say that the current understanding of the molecular mechanisms that produce and control microtubule assembly during cell division, motility, development, and differentiation is based entirely on Dr. Inoué's dynamic equilibrium concept. With regard to his second prediction, he proposed that the disassembly (depolymerization) of spindle microtubules can generate forces for pulling and their formation (polymerization) can generate forces for pushing chromosomes, centrosomes, and other organelles, and there is now much evidence for this hypothesis.

Dr. Inoué's discoveries transformed the prevailing static image of the cell, which was largely based on electron microscopy, to a dynamic image. These findings led the way to what has now become the accepted view in modern cell biology—the idea that most cell components, including actin fibers and the membrane system, are intrinsically dynamic, undergoing a continuous process of assembly and disassembly.

Dr. Inoué's achievements have produced knowledge that is vital to our understanding of the dynamic structural changes in cells and their component supramolecular structures. He has also made pioneering contributions to the fundamental technologies of modern cell biology, namely, the technologies for imaging living cells and the supramolecular structures that play a role in the life of the cell. Not only have these accomplishments contributed enormously to the progress of cell biology, but, by enhancing the understanding of cells, they have furthered the development of biology as a whole.