THE FRANKLIN INSTITUTE

PHILADELPHIA, PENNSYLVANIA

Hall of the Institute
Philadelphia, 24 April 2014

Report No. 3922

Investigating the work of

JOACHIM FRANK, PH.D.

of

COLUMBIA UNIVERSITY
NEW YORK, NEW YORK, USA

THE FRANKLIN INSTITUTE

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Hall of the Institute
Philadelphia, 24 April 2014

Committee on Science and the Arts
Report No. 3922

The Franklin Institute, acting through its Committee on Science and the Arts, has considered carefully those workers in Cryo-Electron Microscopy for High Resolution Structural Biology, without regard to country, whose efforts have done the most to advance the field of Cryo-Electron Microscopy, and has selected as the recipient of the award of the Benjamin Franklin Medal in Life Science for 2014:

JOACHIM FRANK, PH.D.

of

COLUMBIA UNIVERSITY
NEW YORK, NEW YORK, USA

For the development of Cryo-Electron Microscopy, for using this technology to investigate the structure of large organic molecules at high resolution, and for discoveries regarding the mechanism of protein synthesis in cells.

ABSTRACT

Detailed structure of macromolecular assemblies, such as proteins, protein complexes, and nucleic acid-protein complexes is essential for understanding the function and mechanism of these cellular components. High resolution structures of many smaller macromolecules have been obtained by x-ray crystallography, but these are static snapshots, are sometimes difficult to obtain and sample only a subset of the full complement of functional states. Dr. Joachim Frank set out to use an alternative method, electron microscopy (EM), to solve the structures of these biological machines. He developed the requisite image processing procedures on low-contrast cryo-electron micrographs, repeatedly refined the methods and algorithms, and made the technology available to the scientific community.

In the paradigm of molecular biology, DNA replication, transcription into messenger RNA, and translation into polypeptide sequences, the final step, translation, is carried out in all cells by a nucleoprotein complex, the ribosome. Using the new cryo-electron microscopy techniques, Dr. Frank solved the structure of the prokaryotic ribosome and discovered many features of the mechanism used by the ribosome to translate the genetic code into amino acid sequences during synthesis of proteins. Cryo-electron microscopy and single-particle reconstructions of macromolecular complexes have been applied to hundreds of biological systems, enabling their functions to be understood and enabling further structure-based research.

REPORT

Much of the information in the genomes of all organisms ultimately codes for proteins that provide the structural makeup of the cell or enzymatically conduct the chemical and physiological functions that characterize life. DNA is transcribed into an intermediate code, termed messenger RNA (mRNA), which is then translated by the ribosome into polypeptide sequences that make up the proteins. The three-dimensional structures of all of these components are pre-requisites to understanding how they interact with each other and carry out these essential functions. All characteristics of life—cellular organization, energy utilization, response and adjustment to the environment, growth, and reproduction—require structural proteins and enzymes to operate. Disorders of protein expression or function are causative of virtually all diseases and recovery processes and are myriad therapeutic targets. Thus, the ribosome and the mechanism of translation are fundamental in development and maintenance of cells in all normal species and pathogenic organisms.

Dr. Joachim Frank trained as a physicist and became an expert in image processing and manipulation. Working at the Wadsworth Center of the New York State Department of Health and the State University of New York in Albany, he developed the concept of three-dimensional reconstruction of macromolecular structures by electron microscopy. The electron microscope (EM) intrinsically has the spatial resolution to observe and distinguish objects much smaller than a light microscope, as small as the distance between individual atoms. However, many factors limited the practical resolution of this technique in biological samples to thousands of times worse than the theoretical limit. Specimens need to be stabilized and dehydrated to be imaged in the vacuum of the EM. Biological macromolecules absorb and scatter electrons very weakly leading to the requirement for staining to increase contrast. These procedures alter the target structures. Radiation with the electron beam destroys the details of the structure after only a few snapshots. Thus, in the 1970s and early 1980s, there was widespread pessimism about electron microscopy achieving its potential.

Yet Dr. Frank persisted with the vision that by combining thousands of very low-contrast images of unstained macromolecules in random orientations, an average representation of the

macromolecule could be obtained that would faithfully represent the original specimen. This required imaging the sample in conditions that would not perturb the original structure and under very low doses of electrons. Rapidly freezing suspensions of sample molecules in a very thin droplet of water, trapping them in a sheet of vitreous ice, provided these conditions, but still the barely visible, noisy images presented an onerous starting point for determining the structures. Dr. Frank persistently and successively developed methods to automatically select appropriate particles in the images, center and align them, classify them into different orientations and functional states, average the classes to reduce random noise, and then to use the class averages to calculate the structure of the original molecule. Different techniques for performing the final reconstruction were developed that traded among various advantages and disadvantages. Many other adjustments to the imaging were essential to account for imperfections in the instrumentation and data processing. Others joined into this development as it came to be viewed as a feasible undertaking, but it was Dr. Frank who led on many of the innovations and it was his grand view of the possible success that inspired the community of microscopists. Early cryo-EM ribosome structures were used by x-ray crystallographers to analyze (phase) their diffraction patterns in solving the atomic structure of the ribosome, which led to the Nobel Prize in 2009. The spatial resolution of structural reconstructions by cryo-electron microscopy has steadily improved and even accelerated within the past 5 years. Improvements in computing power, algorithms, and faster high-sensitivity direct electron detecting cameras have enabled achievement of the present resolution value of about 0.4 nm, enabling these structures to resolve the side chains and atomic details of proteins and nucleic acids. The method carries the advantage that sample preparation is much less cumbersome and more widely applicable than crystallizing molecules for x-ray diffraction, so many more functional states can be visualized. Cryo-EM and x-ray diffraction are complementary structural biology techniques, each carrying advantages and trade-offs.

Dr. Frank applied the evolving structural biological power of cryo-electron microscopy toward the solution of the mechanism of protein synthesis by determining the structure of the ribosome in the many functional states during elongation of poly-peptides and in complexes with its many protein and RNA accessory factors. The cryo-EM reconstructions give a movie-like sequence of images that document the successive steps in initiating, elongating, and terminating the synthesis

of a protein. One of the major original contributions was the discovery that the two major subunits of the ribosome rotate back and forth relative to each other during each amino acid elongation cycle, enabling the ribosome to translocate accurately along the mRNA by exactly the right amount to maintain the framing of successive triplet mRNA bases (called codons). Likewise, distortions of the smaller RNA subunits that carry the amino acids into the ribosome (termed transfer RNAs or tRNAs) helped to show how the correct amino acid is selected among all 20 possibilities in each elongation step, protecting the important fidelity of translation. These features and many other aspects are pertinent to all organisms in all kingdoms of life.

These basic studies of how the ribosome rapidly and accurately translates the genetic code may be applicable to the discovery of improved pharmaceuticals for treatment of human diseases. The structure of ribosomes from the parasitic organism that causes African sleeping sickness published by Dr. Frank's group may lead to new drugs specific for suppressing protein synthesis in the parasite. A 2013 paper elucidated viral mechanisms that hijack the host's ribosomes during viral replication.

Dr. Frank has been the intellectual and implementation leader in bringing cryo-electron microscopy into standard practice in biomedical sciences and he has made use of these tools to discover many aspects of protein synthesis ubiquitous in biological cells. Dr. Frank has been recognized for these contributions to cryo-electon microscopy methods and the mechanism of protein synthesis by many awards. Among others, he is a Howard Hughes Medical Institute Investigator. He is an elected Member of the National Academy of Sciences and the American Academy of Arts & Sciences, a Fellow of the American Association for the Advancement of Science and of the Biophysical Society, and he gave the National Lecture of the Biophysical Society in 2005, that Society's highest accolade.

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Joachim Frank obtained his pre-diploma from Universität Freiburg in chemistry, physics and mathematics in 1963, his diploma from Universität München in physics in 1967, and Doktor der Naturwissenschaften from Technische Universität München in physics in 1970. He performed

post-doctoral research at the Jet Propulsion Laboratory in Pasadena, CA, at University of California, Berkeley and at Cornell University in Ithaca, NY. He was a visiting scientist at the Max-Planck Institute in Munich, Germany, a Senior Research Assistant at University of Cambridge, England. He moved to the Wadsworth Center, New York State Department of Health in Albany in 1976 and became Professor in the Biology Department at SUNY, Albany in 1986. He was appointed as a Howard Hughes Professor in 1998 and moved to Columbia University in 2008, where he is Professor in the Department of Biological Sciences and the Department of Biochemistry and Molecular Biophysics. He been instrumental in developing the methods for high resolution structural determination of large macromolecules, made these methods available to the scientific community, and, using these techniques, made major discoveries about the mechanism of protein synthesis by the ribosome. He has published more than 200 refereed research publications, more than 20 book chapters, and has written or edited 7 books.

Major Previous Awards

1963 Studienstiftung des Deutschen Volkes

1970 The Harkness Fellowship

1987 Fogarty Senior International Fellowship

1991 Chairman of the Gordon Conference on Three-dimensional Electron Microscopy of Macromolecules

1993 Elizabeth Roberts Cole Award of the Biophysical Society (jointly with David DeRosier)

1994 Humboldt Fellowship for Senior U.S. Scientists

1995 Annual Lecture and Outstanding Scientist Citation by the Max Gruber Foundation, Groningen, The Netherlands

1997 Elected Fellow of the American Association for the Advancement of Science.

1998 Howard Hughes Medical Institute Investigator Award; initial appointment 7 years, twice renewed for 5 years each

2001 Recipient of the 2000-2001 University at Albany Award for Excellence in Research

2001 Distinguished Lecturer at the 29th Peter A. Leermakers Symposium, Wesleyan University.

2001 Elected Fellow of the Biophysical Society

2001 Scientific Merit Award, as "Scientist of the Fourth Quarter Century" by the New York State Department of Health

2003 Recognized as "Distinguished Scientist for Biological Sciences for 2003" by the Microscopy Society of America

2003 Chancellor's Research Recognition Award from the University at Albany, SUNY

2005 National Lecturer of the Biophysical Society 2005 Annual Meeting

2006 Elected Fellow of the American Academy of Arts and Sciences

2006 Elected Member of the National Academy of Sciences

2006 Named Wadsworth Distinguished Scientist in Structural Biology

2006 Elected Fellow of the American Academy of Microbiology

2007 Appointed Distinguished Professor, State University of New York

2008 George E. Palade Distinguished Lecture and Gold Medal (with Ada Yonath and Thomas Steitz), Wayne State University

2009 Elected Fellow of the Microscopy Society of America

2014 BENJAMIN FRANKLIN MEDAL IN LIFE SCIENCE

Citation: The 2014 Benjamin Franklin Medal in Life Science is awarded to Joachim Frank for the development of Cryo-Electron Microscopy, for using this technology to investigate the structure of large organic molecules at high resolution, and for discoveries regarding the mechanism of protein synthesis in cells.

The Benjamin Franklin Medal in Life Science Medal Legacy

Previous laureates who, like Dr. Frank, have made important contributions to macromolecules, structural biology, and protein synthesis:

1913 Emil Fischer (Cresson Medal)
Organic and biological chemistry

1949 Theodor Svedberg (Franklin Medal)
Development of the ultracentrifuge and its use in determining molecular weights of proteins

1966 Britton Chance (Franklin Medal)
Understanding of chain of enzyme reactions in respiratory process of living cells

1968 Marshall Warren Nirenberg (Franklin Medal)
For breaking the genetic code

1975 Mildred Cohn (Cresson Medal)
Nuclear magnetic resonance analysis of enzymatic complexes

1982 Cesar Milstein (Franklin Medal)
Discovery of the hybridoma for use in production of monoclonal antibodies

1987 Stanley Cohen (Franklin Medal)
For discovery, characterization, and elucidation of the biological roles of epidermal growth factors and subsequent work on its cellular receptors

1990 Hugh E. Huxley (Franklin Medal)
For the application of x-ray diffraction to study muscle contraction

1994 Marvin Caruthers (Cresson Medal)
For his contributions in automating the synthesis of DNA oligonucleotides

2000 Alexander Rich (Bower Award and Prize for Achievement in Science)

For key discoveries that underlie our understanding of three-dimensional structures and function of RNA and DNA molecules

Report prepared by the Sponsor

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Now, therefore, for Cryo-Electron Microscopy for High Resolution Structural Biology, THE FRANKLIN INSTITUTE AWARDS ITS BENJAMIN FRANKLIN MEDAL IN LIFE SCIENCE TO DR. JOACHIM FRANK OF COLUMBIA UNIVERSITY IN NEW YORK, NEW YORK, USA.

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Dennis M. Wint, Ph.D.
President and Chief Executive Officer
The Franklin Institute

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Larry Dubinski, Esq.
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The Board of Trustees

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Pamela J. Green, Ph.D.
Chair
The Committee on Science and the Arts