



GIOVANNI ARMENISE- HARVARD FOUNDATION DEAN'S BASIC SCIENCE GRANT

STEWARDSHIP REPORT | OCTOBER 2018

ARMENISE-HARVARD DEAN'S BASIC SCIENCE GRANT

Since it was established more than two decades ago, the Giovanni Armenise-Harvard Foundation has provided Harvard Medical School's dean with unrestricted funding through the Armenise-Harvard Dean's Basic Science Grant. This crucial support has allowed the dean to fund the School's most strategic priorities. Thanks to Count Giovanni Auletta Armenise's vision and generosity in supporting HMS, and to the dedication of his son, Count Giampiero Auletta Armenise, in continuing his father's exceptional work, the School is educating future leaders in biomedical research while advancing science for the benefit of people worldwide.

During the 2017–2018 fiscal year, \$1.6 million was made available to Dean George Q. Daley through the Armenise-Harvard Dean's Basic Science Grant. At the dean's direction, these funds were used to support **cryo-electron microscopy (cryo-EM)**—specifically, the new Harvard Cryo-Electron Microscopy Center for Structural Biology.

Dean Daley has said that the School's first priority is innovation: focusing on finding therapies and cures for the diseases that still plague humanity. When it comes to the new center, he says he has no doubt the facility will have “an enormous impact on our ability to advance fundamental science and the development of therapeutics.”

Harvard Cryo-Electron Microscopy Center for Structural Biology

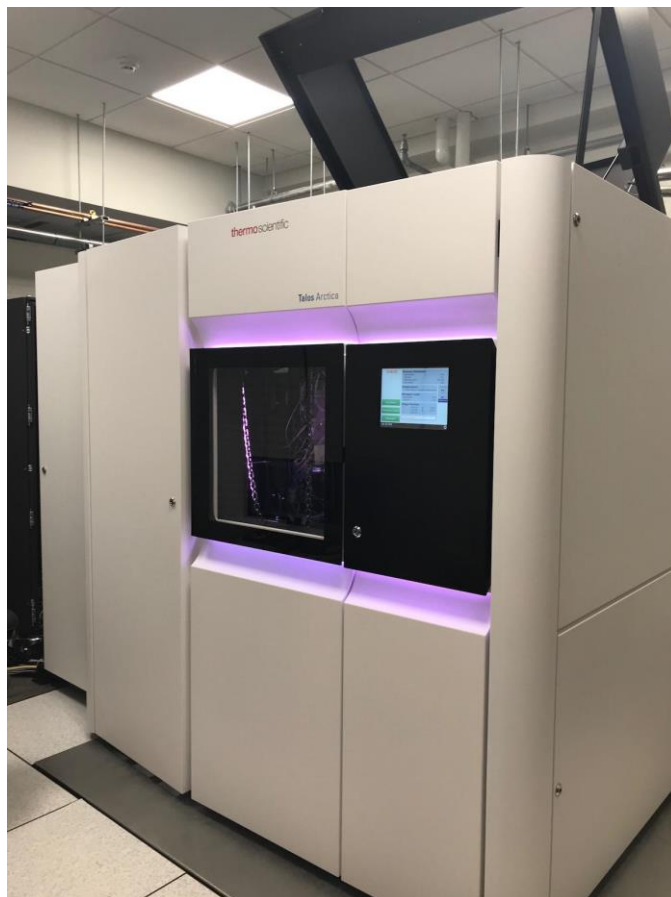
Cryo-EM is cutting-edge technology that allows scientists to visualize molecules at near-atomic resolution, enabling in-depth understanding of molecular mechanisms in both normal and disease states.

Overview

A consortium formed by Harvard Medical School, Harvard University's Office of the Provost, Boston Children's Hospital, Dana-Farber Cancer Institute, and Massachusetts General Hospital established the new Harvard Cryo-EM Center on the HMS Quad. The center promises to catalyze biological discovery by bringing together the community of structural biologists in the Longwood Medical Area.

Headed by renowned structural biologist Stephen Harrison, PhD, the HMS Giovanni Armenise-Harvard Professor of Basic Biomedical Science, the Harvard Cryo-EM Center houses three state-of-the-art microscopes—with space for a fourth long term—along with sample preparation areas and tools to support their use. The facility, which opened in September on a staged basis, will be operated by full-time staff who will provide training, supervision, and user support. It will greatly expand access to cryo-EM for researchers working to answer important basic and clinical science questions.

“This new center demonstrates how Harvard and its affiliated institutions can partner to establish leading-edge facilities and resources that accelerate biomedical discoveries,” says Alan Garber, AB '77, PhD '82, provost of Harvard University.



The Thermo Scientific Talos Arctica transmission and scanning electron microscope inside the new Harvard Cryo-EM Center for Structural Biology.

The Rise of Cryo-EM

Structural biology is a discipline focused on visualizing life at its most fundamental level. Discoveries of the atomic structures of important proteins and biological molecules have been among the most celebrated in science. Despite their successes, structural biologists have struggled to keep pace as technology transforms the study of biology. Every day, researchers reveal more of the molecular processes that underpin life, but the tools that structural biologists have relied upon were developed decades ago, meaning the functional mechanisms of these myriad new molecules often remained invisible. So, when researchers began publishing near-atomic resolution structures of complex proteins using cryo-EM in the early 2010s, structural biologists around the world declared that a revolution had begun.

Cryo-EM, which involves flash-freezing molecules and imaging them with an electron microscope to deduce their structure, was still being derided a few years ago as “blobology” because of the low-resolution, blob-like structures it produced. Its improvement spun from a new generation of image sensors developed in response to consumer demand for better cellphone cameras. A number of key players worked with manufacturers to leverage new sensor technology into greatly improved, direct-electron detectors for cryo-EM. These new detectors could even take movies. Movies allowed for the computational rectification of movement, induced by the energy of the electron beam, which occurred in a sample. The result: blur-corrected images. Combined with dramatic increases in



The inaugural symposium in May for the Harvard Cryo-Electron Microscopy Center for Structural Biology hosted some of the world's leading structural biologists, including (top row, from left): Axel Brunger, Professor of Molecular and Cellular Physiology at Stanford University; Nikolaus Grigorieff, Group Leader at Howard Hughes Medical Institute's Janelia Research Campus; Thomas Walz, Professor and head of the Laboratory of Molecular Electron Microscopy at Rockefeller University; Bridget Garragher, Co-director of the Simons Electron Microscopy Center at the New York Structural Biology Center; (bottom row, from left) Roderick MacKinnon, recipient of the 2003 Nobel Prize in Chemistry; John Kuriyan, Chancellor's Professor at the University of California, Berkeley in the Department of Molecular and Cell Biology and the Department of Chemistry; Richard Henderson, recipient of the 2017 Nobel Prize in Chemistry; Stephen Harrison, the HMS Giovanni Armenise-Harvard Professor of Basic Biomedical Science; Jue Chen, William E. Ford Professor and head of the Laboratory of Membrane Biology and Biophysics at Rockefeller University; and Sir John Skehel, Emeritus Scientist at the Francis Crick Institute in London and former director of the National Institute of Medical Research.

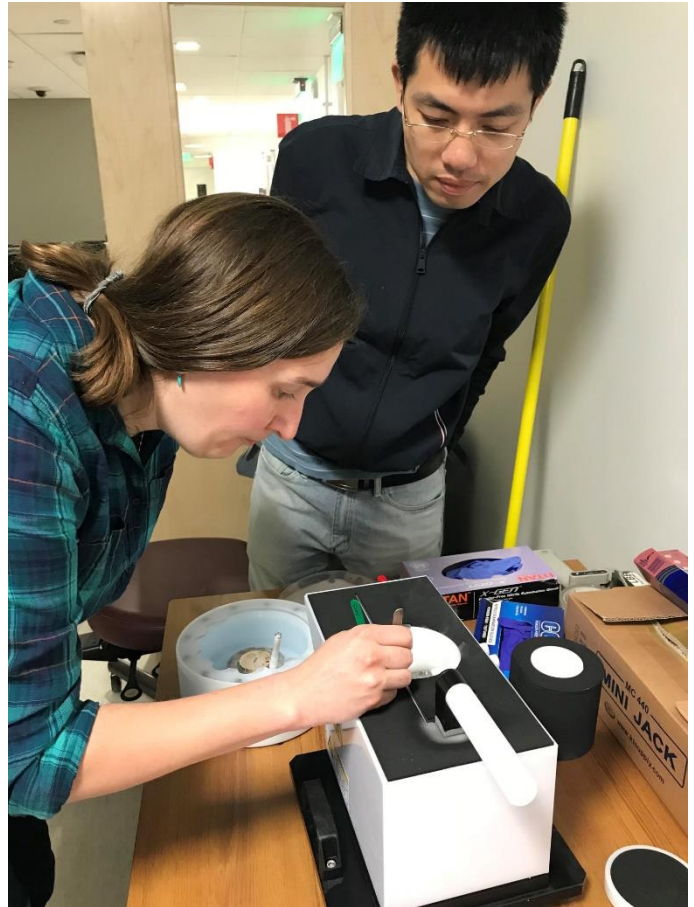
computational power and improved algorithms, cryo-EM specialists could now generate hundreds of thousands, even millions, of blur-corrected images of a protein and use them to calculate 3D atomic models relatively quickly. Formerly blurry models soon revealed functionally important side chains.

The Future of Cryo-EM

Biological scientists around the world have embraced cryo-EM for the myriad possibilities it offers to advance the rational design and evaluation of therapeutics. At an inaugural symposium in May to celebrate the new Harvard Cryo-EM Center for Structural Biology, which marks a new era of structural biology research and discovery at Harvard, some of the world's most esteemed structural biologists reflected on Harvard's distinguished history of leadership in the field. It's the future of this field, however, that is generating so much excitement, as researchers are now using advanced cryo-EM methods to reveal the structures of proteins and protein complexes at a level of detail unfathomable just a few years ago. A door to a new world of biological insight has opened, and the Harvard research community is eager to enter via the new Harvard Cryo-EM Center, whose potential impact will travel well beyond the University.

"Harvard will be giving science a new pair of eyes," says Rick McCullough, PhD, professor of materials science and engineering and vice provost for research at Harvard University. "Cryo-EM is a revolutionary tool that is allowing scientists to see, for the first time, the structures of very large bio-molecules. This could help us understand the causes of some diseases and support the development of new drugs that benefit human health."

Structural biologist Richard Henderson, PhD, who shared the 2017 Nobel Prize in Chemistry for his contributions to cryo-EM, told Harvard Medicine Magazine: "Cryo-EM is already the dominant technology in structural biology. The goal now is to make it cheaper, faster, and more reliable, so that anybody can use it. I think it will someday become a common technique like measuring pH or sequencing DNA. It will only get more dominant."



Training on the new Talos Arctica microscope at Harvard Medical School.