Glacios 3 Cryo-TEM

Outstanding 200 kV performance meets undeniable practicality

thermo scientific

200 kV cryo-EM in modern biology and drug development

Cryo-electron microscopy (cryo-EM) has transformed the landscape of biological research and drug discovery by enabling scientists to visualize biomolecules in their native states, revealing critical structural details. These observations have unlocked new insights into the structure and function of proteins, viruses, and cellular machinery. Among cryo-EM instruments, 200 kV transmission electron microscopes (cryo-TEMs) balance high-performance imaging with broader accessibility.

The Thermo Scientific™ Glacios™ 3 Cryo-TEM is our next major advancement in 200 kV imaging. It continues the outstanding cryo-EM performance of the Glacios product line while adding innovative new features, including optical improvements to enhance usability and increase data yield per sample. A new compact instrument design, with built-in mitigation of external disturbances via the Thermo Scientific™ READY™ System, dramatically reduces infrastructure demands, thereby saving significant time and costs.

The Glacios 3 Cryo-TEM opens the door for more institutions and researchers to harness cryo-EM's full potential, helping them tackle complex biological questions and enhance therapeutic development.

Key Benefits:

- High-performance 200 kV imaging to support high-resolution cryo-EM techniques, including single particle analysis (SPA), cryo-electron tomography (cryo-ET), and microcrystal electron diffraction (microED)
- AI-powered software facilitates cryo-EM workflows with real-time feedback to guide decisions, screen samples, and automate complex tasks
- A more compact size, along with built-in protection against external disturbances with the READY System, substantially lowers renovation costs and shortens installation timelines
- Enhanced 200 kV imaging with optical innovations that improve data yield per sample and reduce data storage demands
- A new comprehensive optical model takes the guesswork out of cryo-EM experimental set-up, making the process faster and easier, particularly for users with less experience

Liposome-encapsulated doxorubicin, a chemotherapy drug formulation, imaged with 200 kV cryo-ET.
Purple shows correctly packaged liposomes for drug delivery while yellow indicates improperly packaged liposomes.
Data segmentation with Thermo Scientific ™ Amira ™ Software. 3D rendering created in Blender.

Cryo-EM for more spaces

The installation of a cryo-TEM system can be complex, requiring a number of tightly controlled environmental parameters such as low vibration and noise, as well as minimal electromagnetic interference (EMI) and stable temperature. To accommodate these requirements, lab spaces are often renovated with specialized HVAC systems, vibration-isolation flooring, and faraday cages, all of which require precise engineering and contribute to overall installation time and costs. To address these challenges, the Glacios 3 Cryo-TEM incorporates the READY System, which has built-in mitigation for external disruptions.

The Glacios 3 Cryo-TEM reduces the renovation costs associated with installation by combining a smaller footprint with the READY System. Additionally, with fewer upgrades required at most sites, installation timelines may drop from a year or longer to only a few months.

Compact design with shorter height

Room size

Previous Glacios systems required ceiling heights that exceed standard US room dimensions in order to accommodate an external maintenance hoist.

The new Glacios 3 Cryo-TEM features an integrated telescopic hoist, allowing all system configurations to fit in rooms with minimum dimensions of 4.2 x 3.8 x 2.7 m (WxLxH). This represents a 22% reduction in size compared to the largest configuration of the previous Glacios system, and helps ensure compatibility with standard US ceiling heights.

Protection with the READY System

Lower cost, faster cryo-TEM installation

The Glacios 3 Cryo-TEM is equipped with the READY System, a built-in series of components that dramatically reduce infrastructure demands and facilitate installation. This integrated protection system would have eliminated the need for facility renovations at 80–95% of sites previously surveyed by Thermo Fisher Scientific for electron microscopy installations over the last decade.

Acoustic

A patent-pending enclosure that includes five layers of acoustic insulation, significantly reducing sound-related interference. This advancement would have eliminated the need for additional acoustic treatments at 95% of locations previously evaluated over the last decade for Thermo Scientific microscope installation.

Temperature

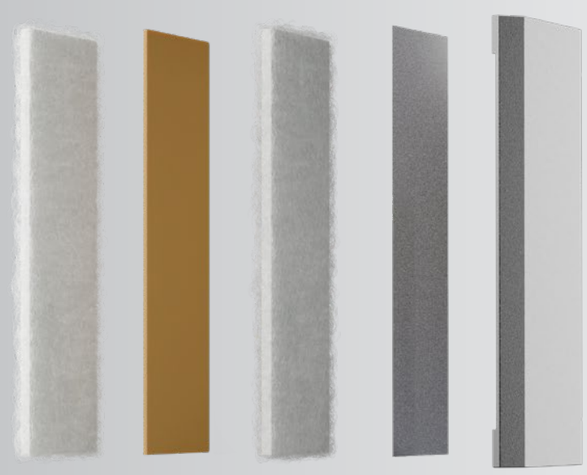
The acoustic isolation layers also protect against temperature variations, allowing for shifts of up to 2°C peak to peak in 24 hours, which can be maintained by standard HVAC systems.

EMI

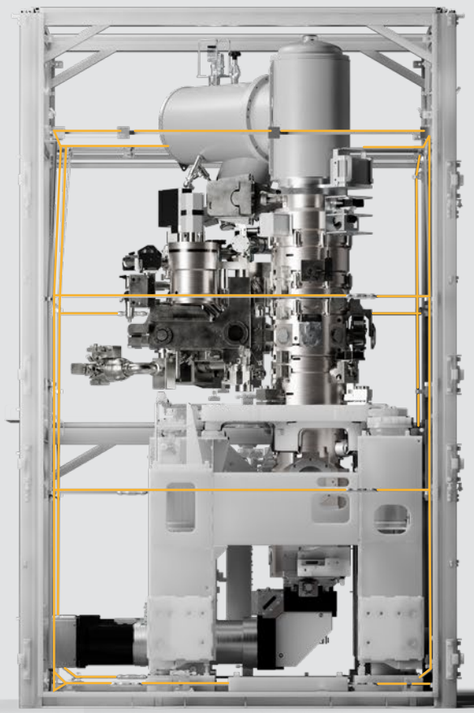
Optional, built-in EMI sensors and an active suppression system directly within the instrument frame reduce the EMI. This would have effectively resolved 80% of previously documented EMI issues assessed during potential installations in the last ten years.

Vibration

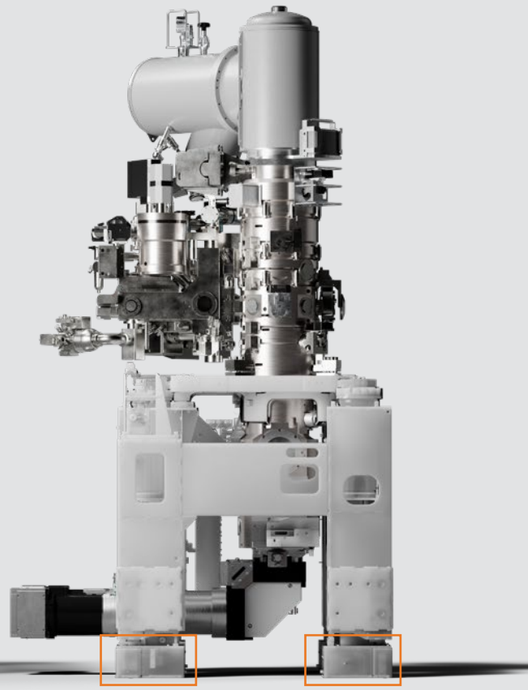
Optional active vibration blocks that are integrated into the system base would have put 95% of previously assessed electron microscopy installation sites within floor-vibration specifications. These blocks also protect against unforeseen new sources of vibration, such as construction.



Five layers of acoustic and temperature insulation



Built-in EMI sensors and suppression system



Active vibration blocks in the system base

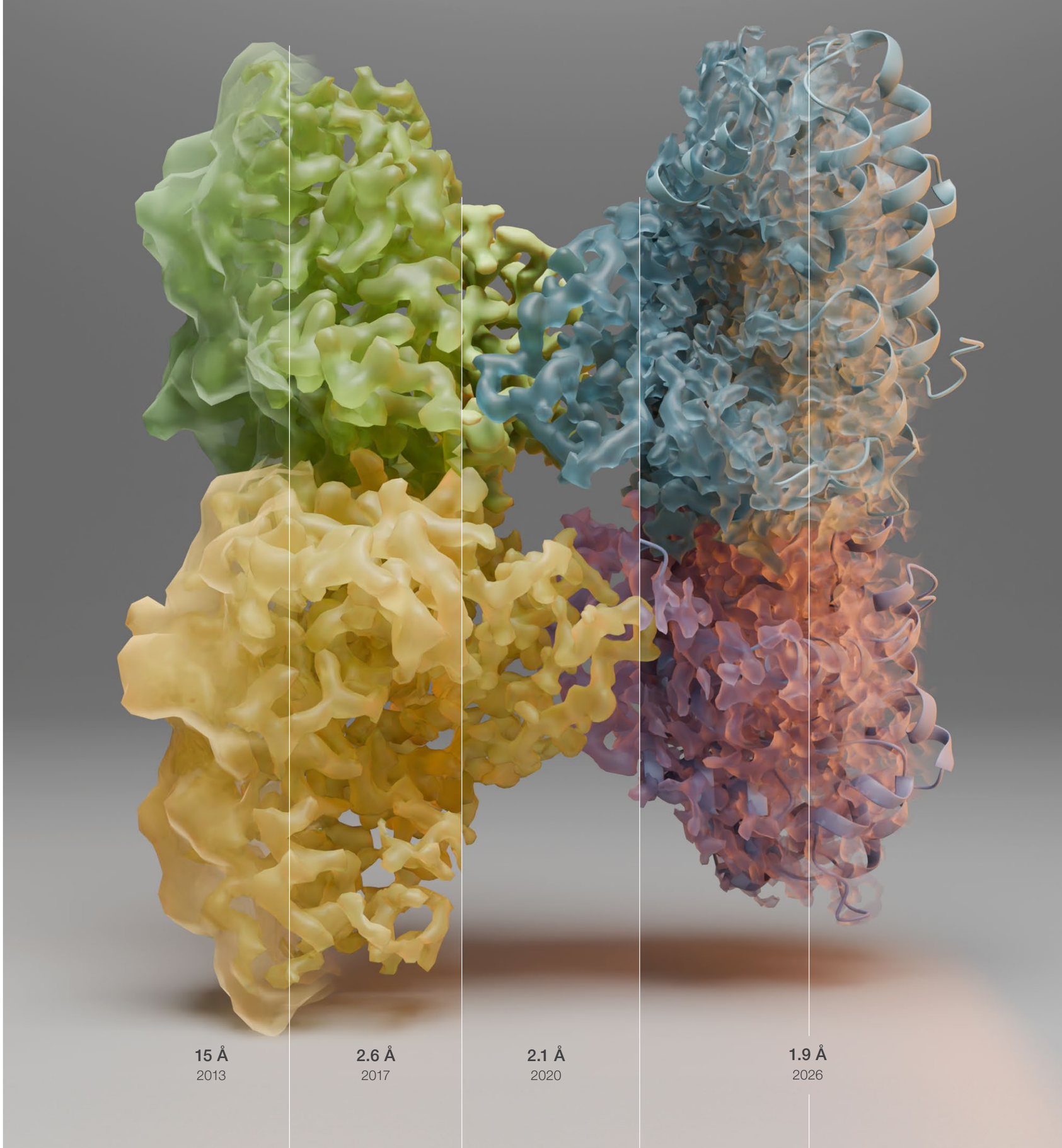
High-performance 200 kV cryo-TEM

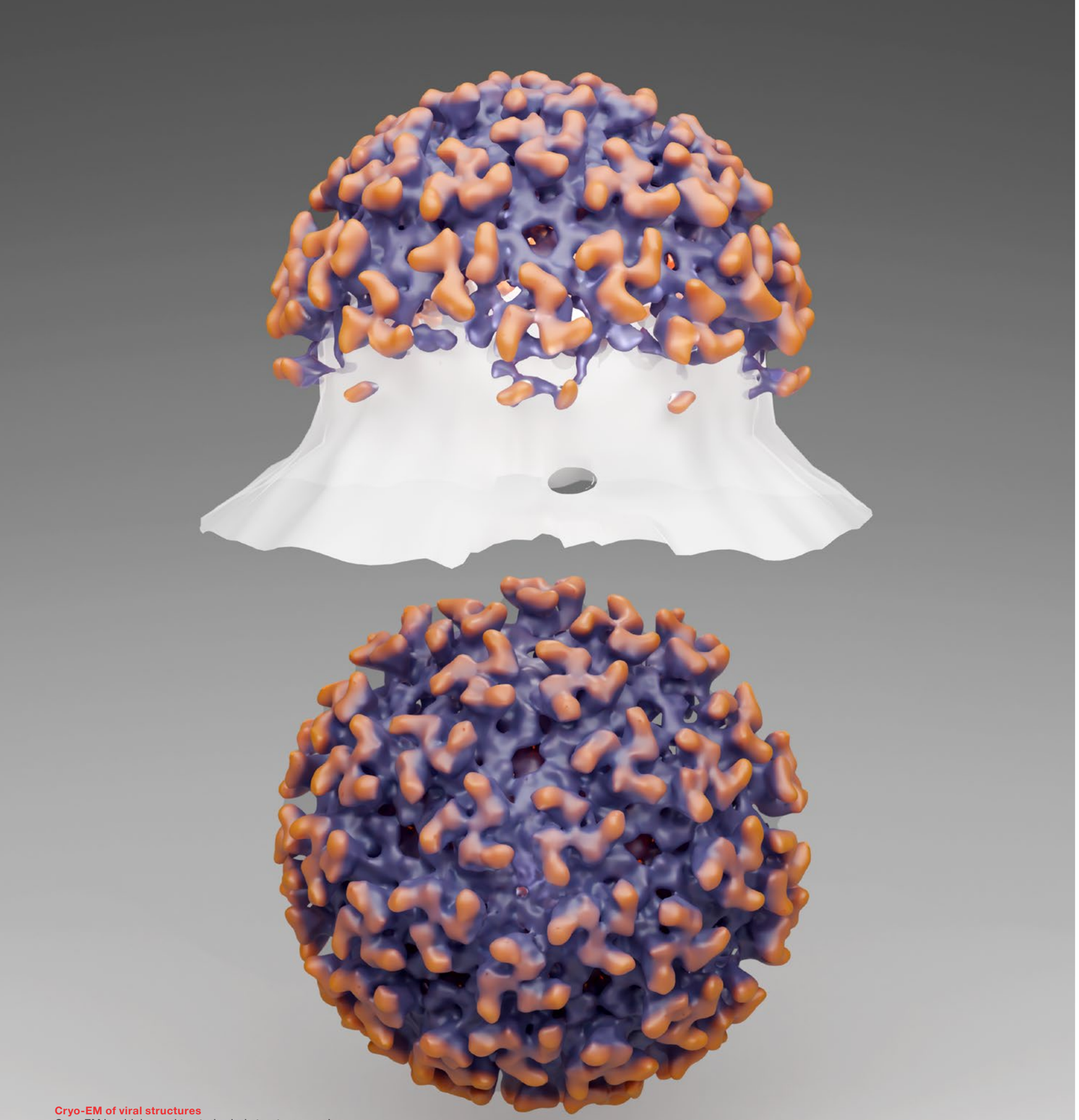
Early 200 kV systems were not widely adopted for high-resolution cryo-EM as they struggled to deliver the throughput and usability needed for detailed structural reconstructions. As a result, previous generations of 200 kV cryo-TEMs were used primarily for sample screening before imaging on 300 kV systems.

The Glacios 3 Cryo-TEM builds on the performance of the established Glacios platform, integrating advanced components and software to provide high resolution, throughput, and usability in 200 kV imaging. This makes the Glacios 3 Cryo-TEM a highly effective system for high-resolution SPA, cryo-ET, and microED across biological discovery, drug design, and more.

From blobology to high-resolution structure determination

With early 200 kV technology, the structure of rabbit muscle aldolase, a 150 kDa protein, was only solved at a resolution of 15 Å. Structure determination with 200 kV cryo-TEM has dramatically improved over the years with advancements in both hardware and software. In 2017, the structure was solved to 2.6 Å (**EMDB: 8743**), and then improved further to 2.1 Å in 2020 (**EMDB: 21023**). Today, the Glacios 3 Cryo-TEM is able to generate a structure at 1.9 Å (**EMDB: 74335**), as shown on the far right. 8,925 images were collected in 12 hours, with an average throughput of more than 700 images/hour. To achieve the previous resolution of 2.1 Å, only 4 hours of data collection would have been needed.

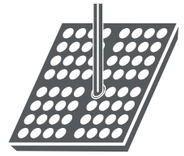




Cryo-EM of viral structures
Cryo-EM is widely used to study viral structures, such as capsids and envelope proteins, and to understand how viruses enter cells, replicate, and interact with the immune system. Here, Chikungunya virus assembly and budding is visualized *in situ* using sub-tomogram averaging with 200 kV cryo-TEM. Recreated from EMD-26448. Original study by Chmielewski *et al.* doi: 10.1038/s41564-022-01164-2

Improved optical features

The latest Glacios Cryo-TEM brings more accurate imaging, reduced data storage demands, and enhanced usability



High accuracy and improved throughput with aberration-free image shift

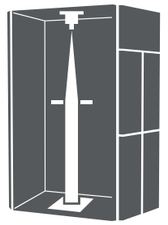
AFIS (aberration-free image shift) is a standard optical mode in Thermo Scientific cryo-TEMs that speeds up data collection by moving the beam instead of the stage when shifting between foil holes. Newly improved with the Glacios 3 Cryo-TEM, AFIS now provides enhanced targeting accuracy (i.e., greater than 100 nm within a 12-micron radius), ultimately accelerating data acquisition with more images that do not contain areas of the film. The result is faster imaging with great accuracy and less images required per sample.

Watch video

Increased data yield with fringe-free imaging

Fringe-free imaging (FFI) is an optical mode that reduces sample damage from the beam in nearby areas, thereby increasing the usable sample area within the grid. New with the Glacios 3 Cryo-TEM, an automated beam centering routine for FFI helps ensure that the beam is always in the center of the field of view, enabling long-term data acquisition and higher data yield per sample. This increase in yield per sample means that less data collection overall is required per experiment for high-resolution protein reconstructions. The reduction of total data collection per experiment brings the additional benefit of lowering long-term data storage demands.

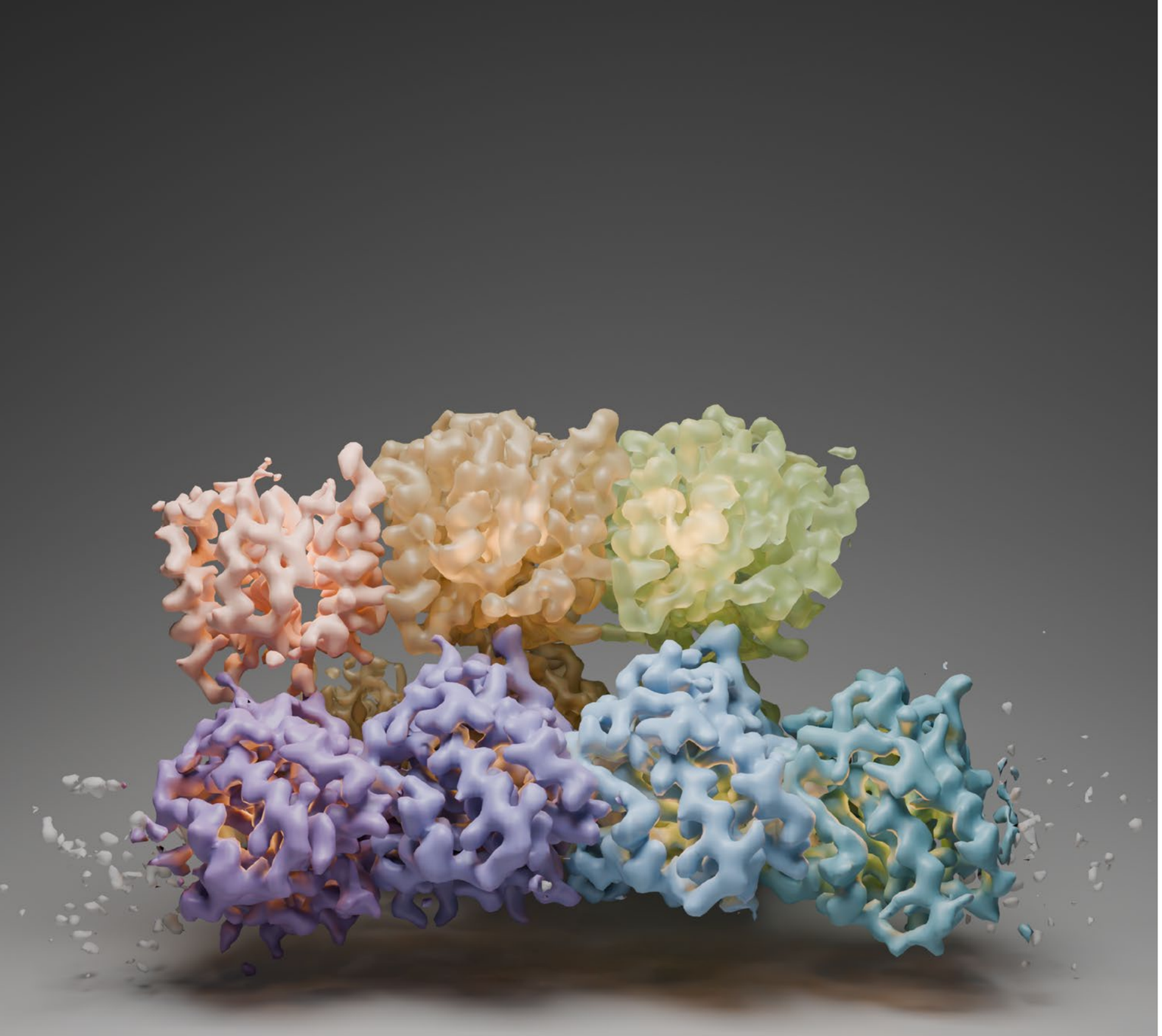
Watch video



Easier instrument set-up with a new optical model

During cryo-TEM experimental set-up, configuration of illumination parameters requires in-depth knowledge of electron optics. The 2-condenser lens system of a cryo-TEM makes the parallel beam illumination have discrete beam diameters and steps in the flux, which increase non-linearly (exponentially). Even for expert users, multiple tries are often needed to optimize the system configuration, and the ideal flux is difficult to achieve.

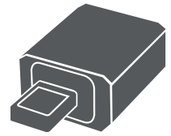
A new optical model in the Glacios 3 Cryo-TEM takes the guesswork out of cryo-EM experimental set-up. In a single click, it calculates all the lens current required along the optical path and sets the electron beam in parallel with the desired flux. As a result, set-up is now faster and easier, particularly for less experienced users. This also shortens the learning curve for new users.



High-resolution visualization of gene editing complexes
Cryo-EM has enabled high-resolution visualization of gene editing complexes, such as the CRISPR-Cas system, revealing the structural basis of target recognition, DNA cleavage, and enzyme regulation, thereby guiding the rational design of next-generation editing technologies.

Single particle analysis of the active SAVED-CHAT protease filament, which is associated with certain type III CRISPR systems, is shown here, generated with 200 kV cryo-TEM. Recreated from EMD-41358. Original study by Steens *et al.* doi: 10.1126/science.adk0378

Performance defining components



Falcon 4i Direct Electron Detector for fast, high-quality imaging

The Thermo Scientific™ Falcon™ 4i Direct Electron Detector helps deliver fast imaging speeds and exceptional image quality, making it an ideal choice for high-throughput cryo-EM workflows. Its fast frame rate and reduced overhead enable efficient data collection, while its high detective quantum efficiency (DQE) helps ensure outstanding image quality across all spatial frequencies. The innovative electron event representation (EER) mode boosts DQE at high resolutions, supporting super-resolution imaging and lossless data compression without up-front fractionation. With output formats that are fully compatible with RELION and CryoSPARC Software, the Falcon 4i Detector integrates seamlessly into automated workflows and supports unattended acquisition through Thermo Scientific software. Flexible scripting also facilitates third-party software integration, accelerating cryo-EM research with excellent data quality.

Selectris and Selectris X Imaging Filters for enhanced image contrast

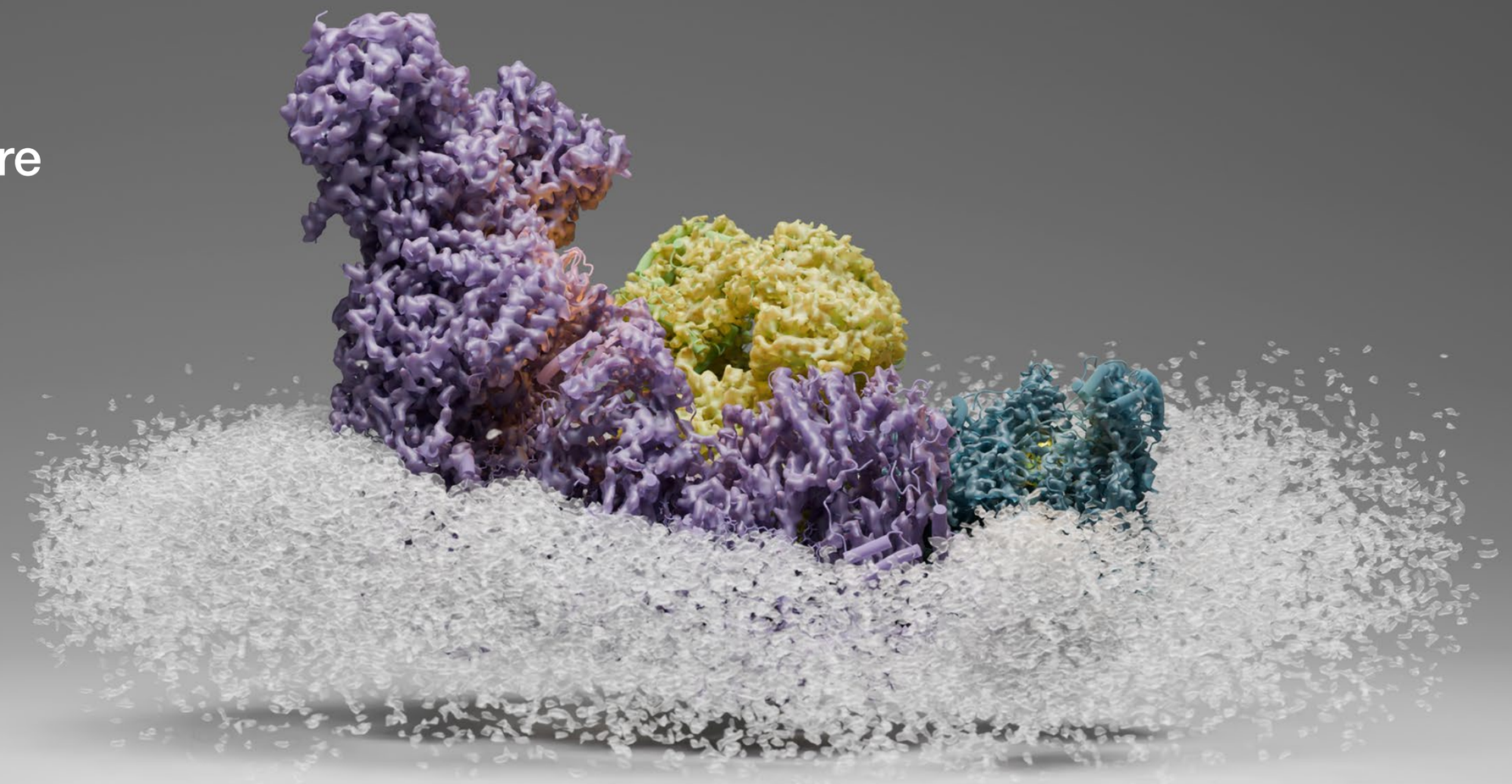
Thermo Scientific™ Selectris™ Imaging Filters are post-column filters with a highly stable energy slit that provides narrow widths (<10 eV) for imaging. By allowing only the zero-loss peak to pass through, inelastically scattered electrons are removed. This improves signal-to-noise ratio and image contrast, enhancing image quality for both single particle analysis and cryo-ET. Additionally, fewer images are needed to achieve high-resolution reconstructions, reducing acquisition time and increasing throughput.

Low-energy-spread cold field emission gun (E-CFEG) for high image contrast and resolution

The low-energy-spread cold FEG (E-CFEG) provides a high-brightness, high-coherence electron source that produces a stable electron beam with very low energy spread. The E-CFEG offers significant benefits for cryo-TEM, including high image contrast and resolution, making it easy to visualize small or low-contrast biological structures. An additional benefit of E-CFEG is its inherently longer lifetime, which reduces service costs and minimizes system downtime.

The importance of software

Software development has transformed both data acquisition and analysis in cryo-EM, driving the field from its early, manual methods to today's high-throughput, high-resolution workflows. Modern, AI-powered Thermo Scientific software enables automated, unattended acquisition, optimizing microscope performance and maximizing efficiency. For analysis, advances in image processing algorithms have significantly improved speed, accuracy, and resolution. Overall, these software innovations have made cryo-EM more accessible, scalable, and powerful, helping to accelerate discoveries in structural biology.



Smart EPU Software

Automated single particle analysis

- Unsupervised, fast grid screening through AI plugins
- Set up high-resolution imaging in about 20 minutes per session, even remotely
- Run multiple grid sessions unattended, minimizing microscope idle time
- Monitor image quality with real-time feedback on imaging parameters and optical status
- Assess sample quality and reduce time to results with embedded CryoSPARC Live Software that generates preliminary 3D models during acquisition

CryoTomo Software Suite

Efficient cryo-ET

- Tomo Multishot acquires multiple tomography series in one sweep, significantly increasing throughput
- Tomo Multisite enables user interaction and search map acquisition in parallel, accelerating session setup
- Tomo Multigrid seamlessly schedules long data acquisitions for multiple grids without interrupting ongoing collection, maximizing microscope usage
- Evaluate sample quality with on-the-fly reconstruction and easy analysis of key parameters such as sample thickness

CryoFlow Software

Integrative cryo-EM data management

An integral part of both Smart EPU Software and the CryoTomo Software Suite, CryoFlow Software unifies image acquisition, processing, and analysis into a connected and collaborative environment.

- Remote visualization of real-time image processing results
- Filter and export raw and pre-processed data in several image formats for analysis with common cryo-EM post-processing programs
- Simultaneously view and work on the same project in real time with collaborators
- Create shareable reports with summaries of key results and microscope settings

Respiratory supercomplexes in mitochondria
In-situ **structure of complex I in the mammalian respiratory supercomplex, acquired with single particle analysis on a 200 kV cryo-TEM. Recreated from EMD-42166.**

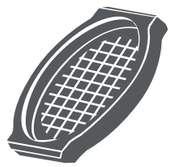
Energy production inside mitochondria occurs via oxidative phosphorylation, which relies on respiratory protein complexes located in the inner mitochondrial membrane. Zheng *et al.* (doi: 10.1038/s41586-024-07488-9) used *in situ* cryo-EM to visualize the building of these respiratory supercomplexes inside the mitochondria.

Connected cryo-EM workflows

Vacuum Capsule facilitates cryogenic sample transfers

Some cryo-EM workflows require samples to be transferred between instruments. For example, in single particle analysis, sample quality may first be assessed on a 200 kV cryo-TEM before it is transferred to a 300 kV cryo-TEM for higher-resolution imaging. In cryo-ET, lamellae prepared using a cryo-focused ion beam (cryo-FIB) are subsequently moved to a cryo-TEM for tomographic data acquisition. These transfers are critical steps that require careful handling to preserve sample integrity and to help ensure successful imaging.

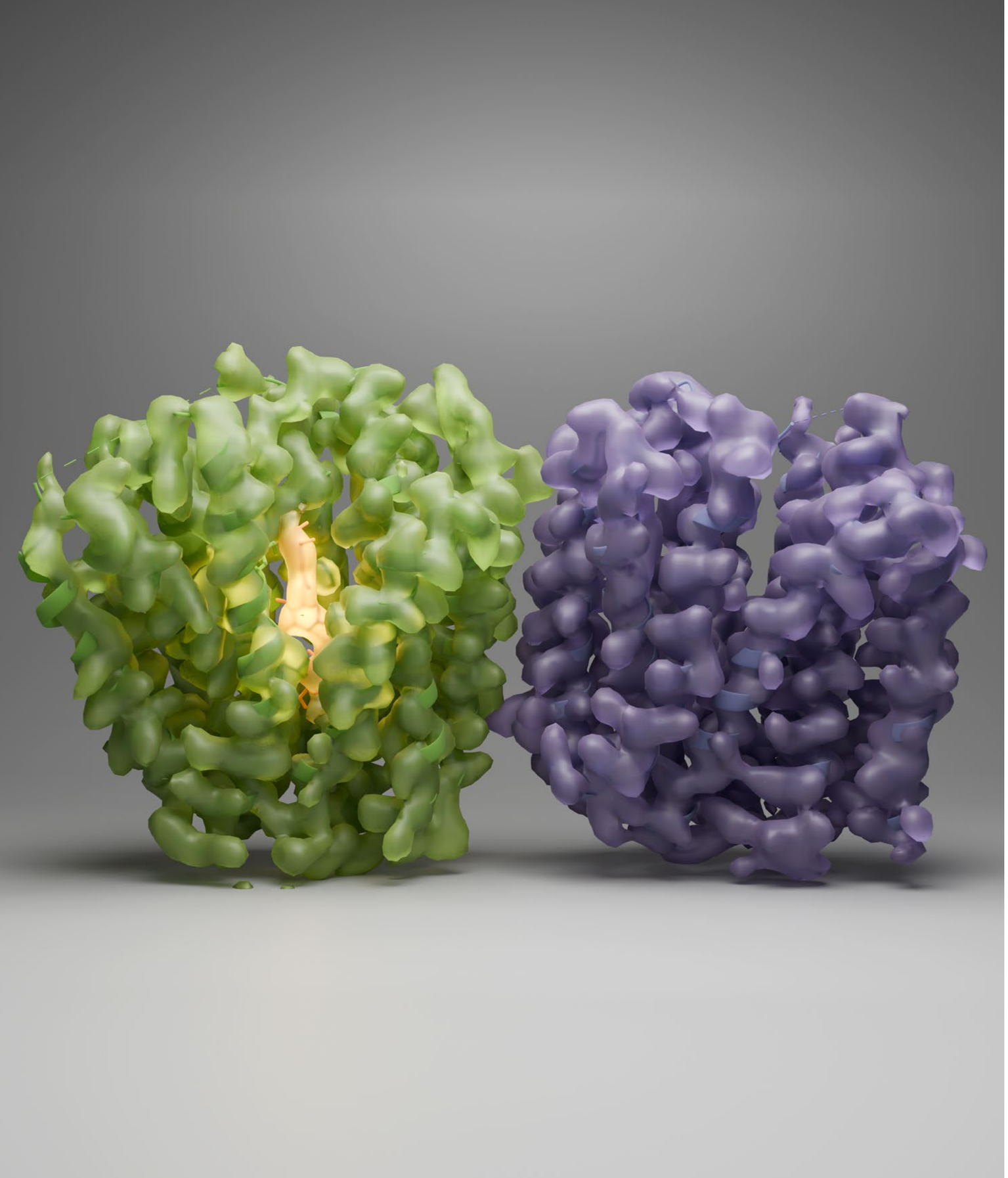
The Thermo Scientific Vacuum Capsule is designed to avoid ice deposition during sample transfer by keeping the cryogenic specimen within an enclosed reservoir. The Vacuum Capsule is fully compatible with Thermo Scientific cryo-TEMs that have an Autoloader system, including the Glacios 3 Cryo-TEM. This enables safe, easy sample transfer, thereby improving the overall success rate of these workflows.



Cryo-ET supported by TomoGrid compatibility

After a delicate cryogenic lamella is prepared with a cryo-FIB, it is essential that it is precisely aligned during sample loading into the cryo-TEM. Proper positioning helps keep the region of interest within the tilt range and field-of-view throughout data collection. The Glacios 3 Cryo-TEM supports TomoGrids, specialized sample carriers designed to maintain the correct orientation of the lamella axis relative to the TEM tilt axis. This alignment minimizes data loss, improves tilt-series quality, reduces mechanical stress on the lamella, and ultimately increases the success rate of high-resolution reconstructions.

Ultrastructural visualization of the nuclear pore complex
3D reconstruction of the nuclear pore complex (green), nuclear membrane (yellow), nucleosomes (purple), and ribosomes (blue) using 200 kV cryo-TEM from a sample that was prepared with the Thermo Scientific™ Arctis™ Cryo-Plasma-FIB. Data segmentation with Amira Software. 3D rendering created in Blender.



Fast-tracking therapeutic discovery

Cryo-EM has become an essential tool in drug design, enabling researchers to directly observe protein-ligand interactions, conformational changes, and dynamic binding pockets at atomic or near-atomic scale.

Cryo-EM can help reduce late-stage trial failures by determining high-resolution drug-target structures and defining the mechanism of action at early discovery stages. From target selection to IND, structure-based drugs have twice the rate of clinical success at 50% of preclinical time and cost, as described in "The cost and value of three-dimensional protein structure," Drug Discovery World.

More and more organizations are adopting 200 kV cryo-EM, with its balance of performance and accessibility, to fast-track the development of biotherapeutic drugs across a range of modalities, including:

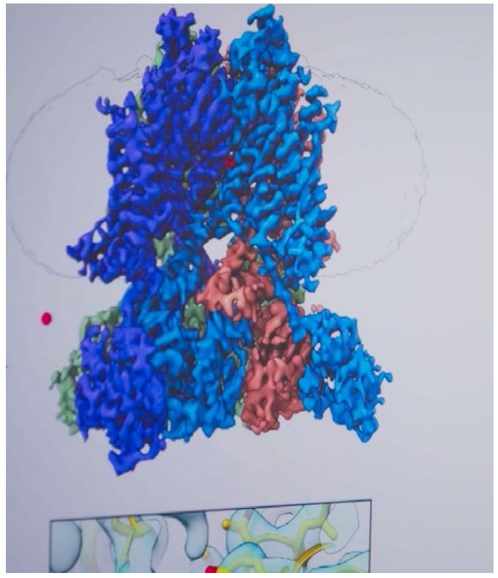
- Antibody candidate selection with fast, accurate epitope information
- Structure-based design of vaccines and CAR-T candidates
- Discovery, engineering, and optimization of novel gene-editing enzymes
- Comprehensive particle characterization of viral and lipidic delivery vehicles

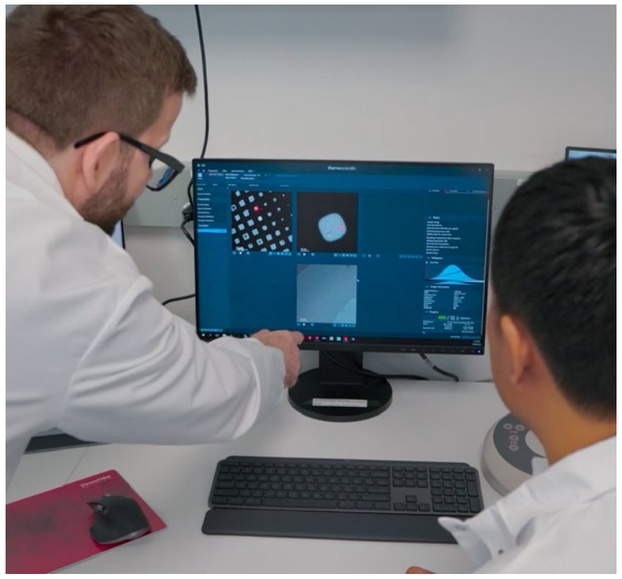
Unlocking the therapeutic opportunities of SLC transporters
Single particle analysis of the VMAT1 dimer complex, both unbound and bound to reserpine, solved with 200 kV cryo-TEM. Recreated from EMDB-41238 Original study by Ye *et al.* doi: 10.1038/s41586-024-07290-7. Vesicular monoamine transporters (VMATs) are members of the SLC transporter family that help control brain, hormone, and immune system functions.

SLC (solute carrier) transporters play a central role in cellular uptake and metabolism, making them key players in many physiological processes and diseases, including cancer, neurological disorders, and metabolic conditions. Targeting of SLC transporters can improve drug efficacy, overcome resistance, and reduce side effects, making them attractive candidates for the development of new therapeutics.

Structure-based drug design

The Therapeutics Group at Schrödinger uses cryo-EM to advance the possibilities of structure-based drug design, particularly for more challenging targets. Members of their leadership team share their thoughts on Thermo Fisher Scientific and their Glacios Cryo-TEM.





"Cryo-EM used to be this bespoke technology that was only available to a few labs around the world. Thermo Fisher [Scientific] has now democratized this, bringing cryo-EM to thousands of lives across the world. "

Karen Akinsanya, President of R&D
Therapeutics Group, Schrödinger

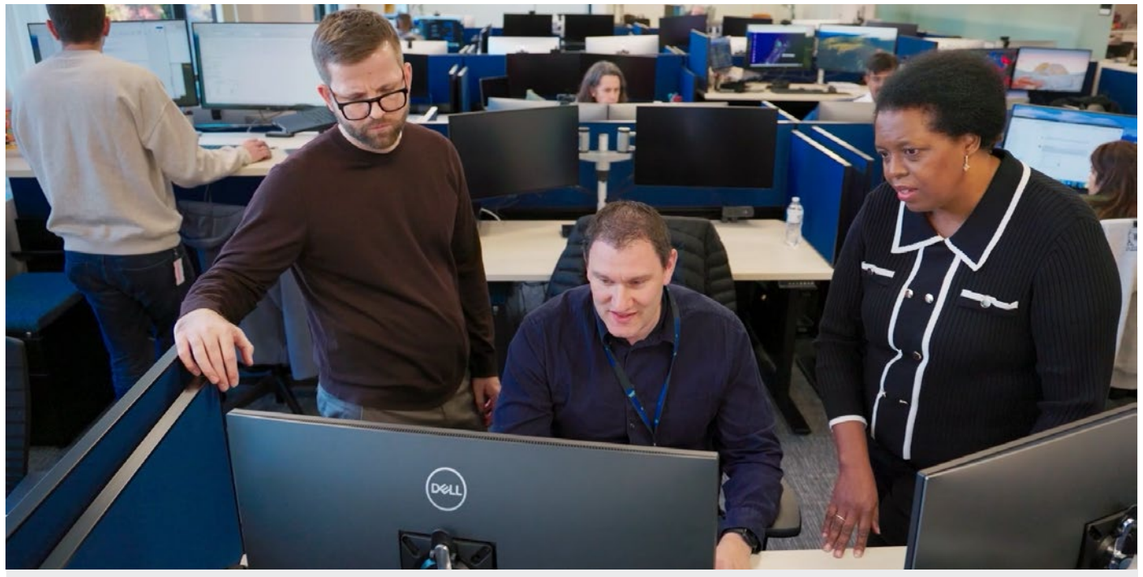
Watch video

Zach Johnson, PhD
Senior Director of Cryo-EM
Therapeutics Group, Schrödinger

"We signed off on our Glacios [Cryo-TEM] on December 7 of 2023, and by the time we got to the holidays on December 22, we had already determined preliminary structures of three different protein targets.

We have now been operational for just over two months and we have solved multiple high-resolution structures of four different targets, ranging in size from 70 kDa to over 400 kDa. Both soluble targets and membrane targets at resolutions better than 3 angstroms across the board."

Watch video



"We're now able to collect enough high-quality data in just a day or two on a 200 kV Glacios [Cryo-TEM] and turn around a sub three angstrom structure in a matter of just days to a few weeks, enabling the confident modeling of small molecules in a surrounding protein environment at a speed that keeps up with drug discovery programs."

-Zach Johnson

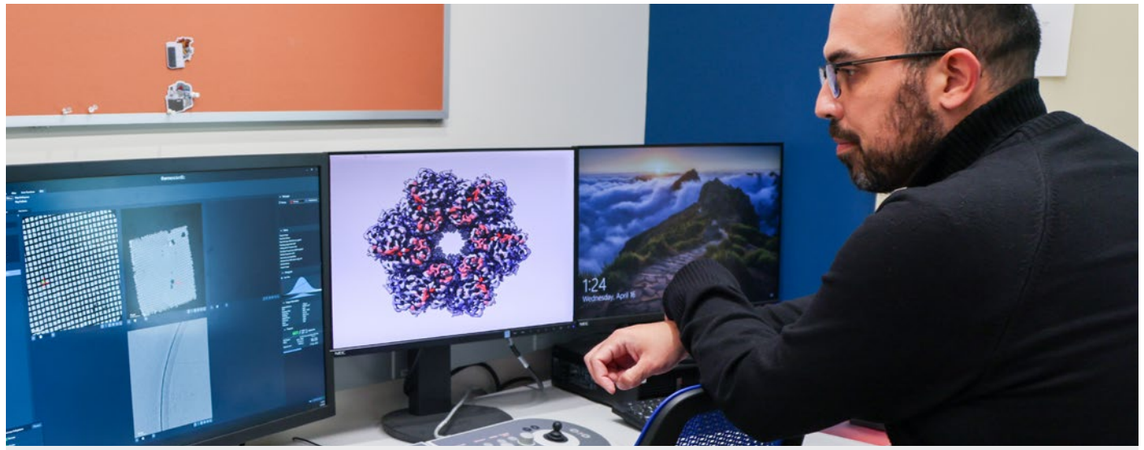
Accelerating the path to an HIV vaccine

Cryo-EM has advanced HIV vaccine research by allowing scientists to visualize the envelope glycoprotein (Env) of the virus in near-atomic detail. These structural insights have helped researchers design stable versions of Env that mimic its conformation during infection, enabling the development of more effective vaccine candidates. Cryo-EM has also shown how broadly neutralizing antibodies (bnAbs) bind to the virus, guiding strategies to elicit similar immune responses through vaccination.

Single particle analysis of the 3G08 Fab in complex with the HIV envelope trimer, solved with 200 kV cryo-TEM. Images here and on the front cover recreated from **EMDB-48286**. Original study by Caniels *et al.* doi: **10.1126/science.adv5572**

Empowering universities to be leaders in structural biology

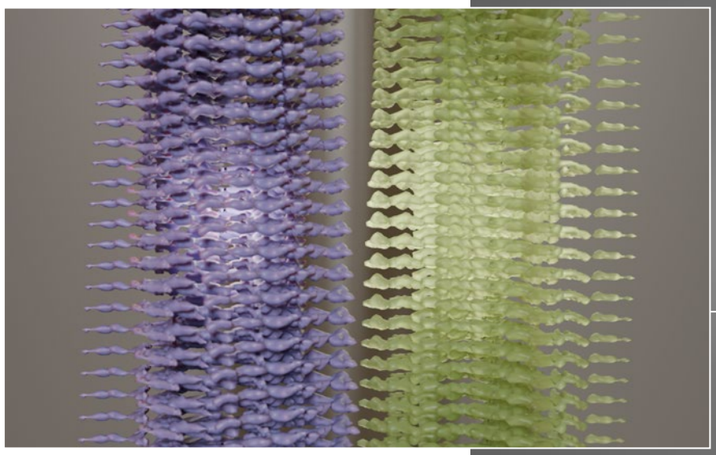
The adoption of the Glacios Cryo-TEM by the University of California, Santa Cruz, demonstrates the extraordinary potential of 200 kV cryo-EM to support centers of excellence in structural biology research. The technology is fostering collaboration and enabling discovery across broad fields of research.

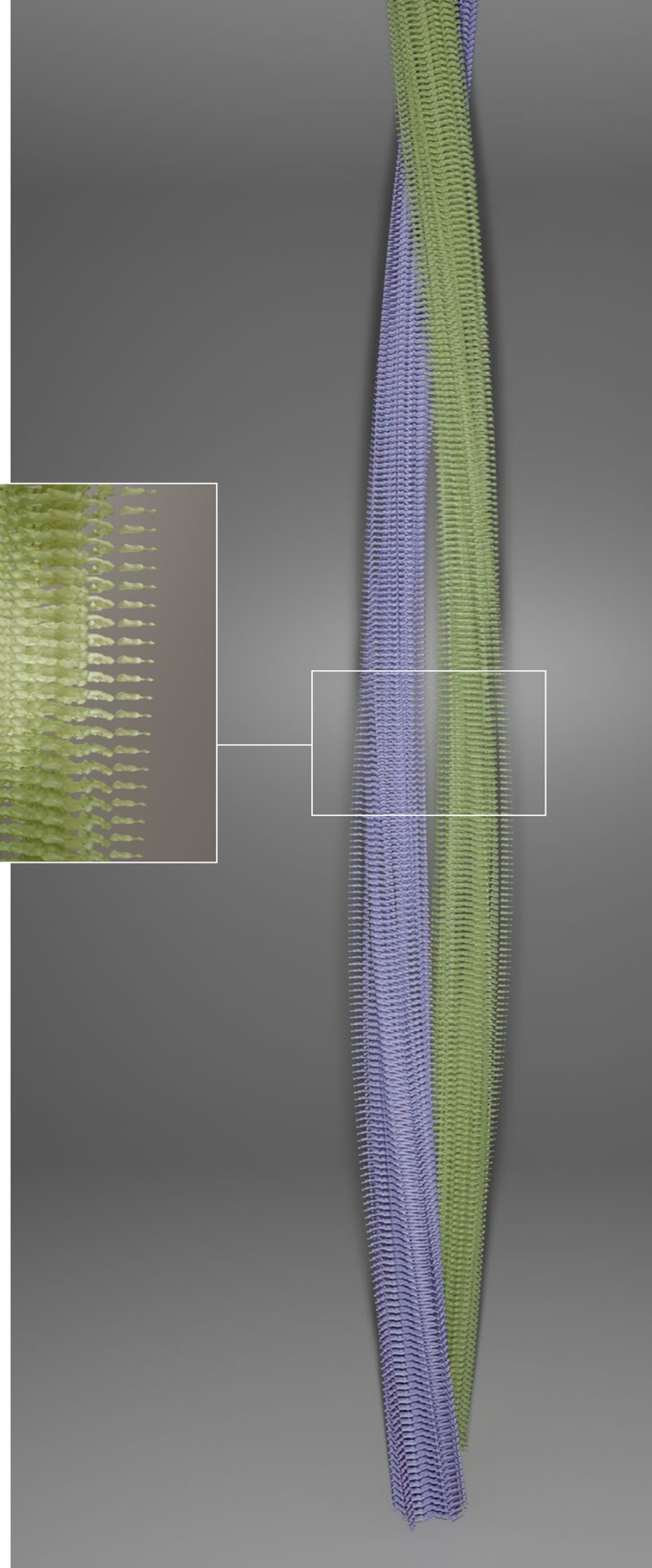


“The Glacios 200 kV [Cryo-TEM] has positioned the UCSC Biomolecular Cryo-EM Facility among the leading centers in structural biology, delivering exceptional performance, stability, and throughput. This equipment reassures the potential of a lower kV microscope in order to obtain near-atomic resolution of multiple targets, with lower cost and incredible high-throughput using different imaging methods.

This cryo-microscope can be widely and easily used for different biological or material samples and has transformed UCSC into an international hub for cryo-EM research and training, attracting collaborations and visiting scientists from institutions worldwide, including South Africa, Canada, and Brazil. The facility’s hands-on support has driven breakthroughs across diverse fields, from cancer research and circadian biology to ribosome function and vaccine development. Through these advances, UCSC has firmly secured its place on the global map of structural biology, fostering innovation, collaboration, and excellence in cryo-EM.”

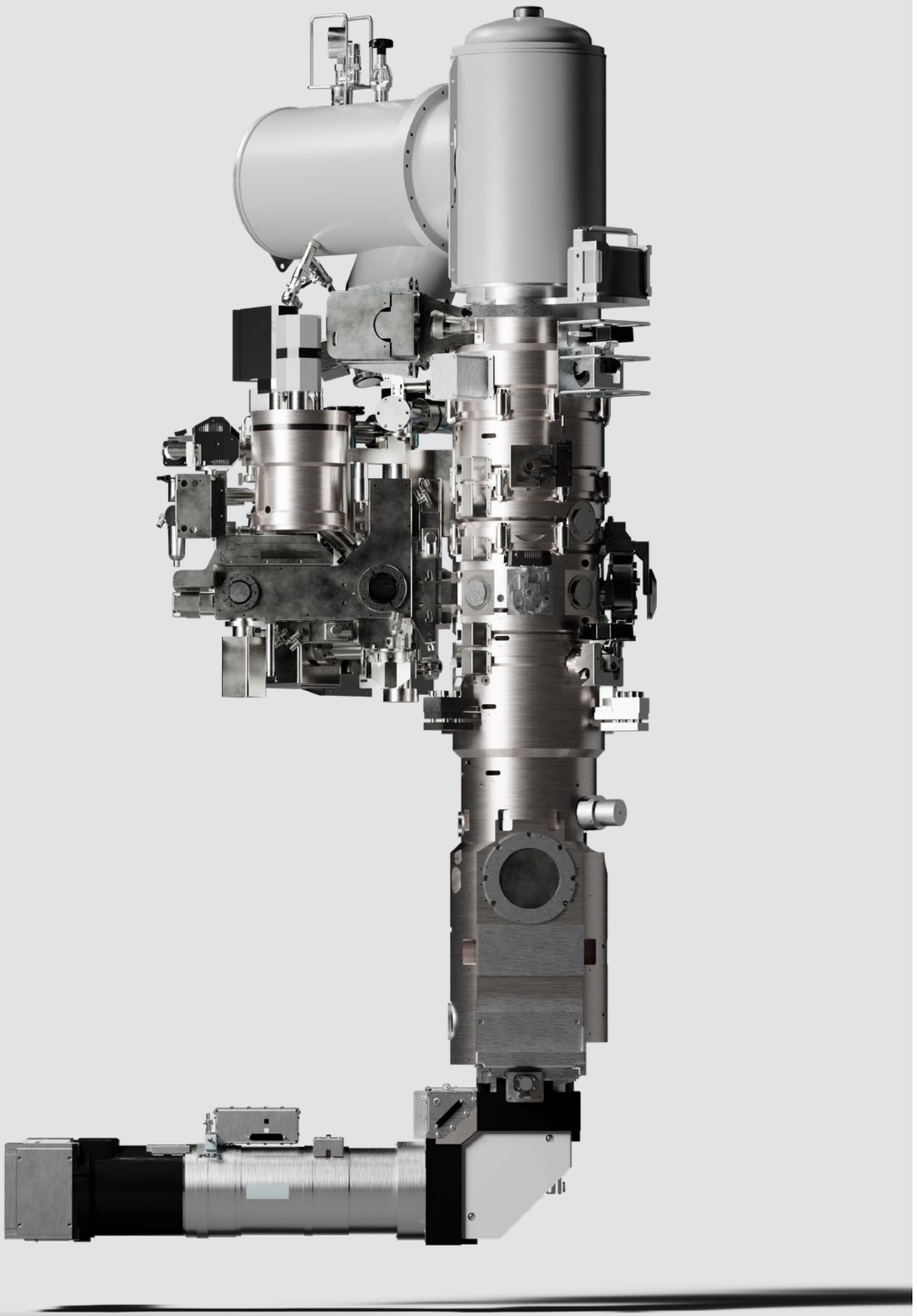
Vitor Hugo Serrão, Director
Biomolecular Cryo-Electron Microscopy Facility
University of California, Santa Cruz





Cryo-EM insights into brain protein structures
Helical reconstruction of mouse alpha-synuclein fibrils. Data acquired with 200 kV cryo-TEM. Recreated from EMD-50023. Original study by Sokratian *et al.* doi: 10.1126/sciadv.adq3539

Cryo-EM can visualize the structures of brain proteins and complexes at near-atomic resolution. It has been especially useful in the study of membrane proteins like ion channels, neurotransmitter receptors, and transporters involved in neural signaling. Insights from cryo-EM have supported the development of targeted therapeutics for conditions such as Alzheimer’s and Parkinson’s disease, as well as epilepsy.



Technical overview

Electron optics and components	
Source options	• X-FEG (extreme high-brightness field emission gun) • E-CFEG (low-energy-spread cold FEG)
Accelerating voltage	Flexible accelerating voltage from 80 - 200 kV, depending on detector choice
Lenses	• Automatic condenser, objective, and SA apertures • Symmetric constant-power objective lens that minimize image aberrations and lens hysteresis during mode switching • Symmetric constant power C-TWIN objective lens with wide-gap pole piece (11 mm)
Imaging	Rotation-free imaging upon magnification changes
Stage	• Computerized 4-axis specimen stage with ±70° alpha tilt • Cryo-stage with single-axis holder
Aberration-free image shift (AFIS)	Fast data collection with improved accuracy
Fringe-free imaging (FFI)	Automated beam centering routine for long-term data acquisition
Energy filters and detectors	
Energy filter (optional)	Selectris or Selectris X Imaging Filters
Detector options	• Falcon 4i Direct Electron Detector • Thermo Scientific™ Ceta™ D Camera • Thermo Scientific™ Ceta™ 16M Camera • HAADF STEM detectors* • On-axis BF/DF detectors* *STEM is not compatible with FFI
Software and data management	
Data management	• CryoFlow Software for integrative data management
Software workflow options	• Smart EPU Software for automated single particle analysis • CryoTomo Software Suite for efficient cryo-ET • MicroED package
Installation	
Installation requirements	• Room temperature: 18-23°C • Temperature stability: within 2°C peak to peak in 24 hours • Door height: 2.3 m (can optionally be reduced to 1.96 m) • Door width: 1.118 m • Room size: 4.2 x 3.8 m • Ceiling height: 2.7 m
READY System for built-in environmental mitigation	• Integrated protection for acoustic noise and temperature variances • Optional protection for electromagnetic interference (EMI) • Optional protection for floor vibrations
Sample considerations	
Cryo-Autoloader	Cryo-Autoloader for automated and contamination-free loading of cassettes containing up to 12 AutoGrids
Vacuum Capsule (optional)	Supports sample transfer between Autoloader cryo-TEM systems and cryo-FIB systems

ACT Ecolabel

Unambiguous documentation of the instrument's environmental footprint is provided by the ACT Ecolabel, as assessed by My Green Lab, an independent non-profit organization.

ThermoFisher SCIENTIFIC

Learn more at **thermofisher.com/glacios**

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