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SCIENTIFIC REVIEW

Insights into HIV Research

Using structural biology to gain a deeper understanding of HIV

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Why cryo-EM is beneficial in structural biology?

- The rapid freeze treatment of the sample maintains its closer-to-native state.
- It requires only a small amount of sample material.
- It does not require the protein to crystalize.

Learn more about various disease areas, such as cancer, HIV, malaria, and neurodegenerative diseases, that are being investigated by your peers, who are benefitting from cryo-EM.

On-demand webinars

Cryo-EM has become a routine technology for determining the three-dimensional structure of biological macromolecules to understand their activities and interactions as the molecular basis of life's processes. Structure is the key to understanding function. Recent structural biology developments that have been made possible by cryo-electron microscopy (cryo-EM) have enabled researchers to better understand complex biological molecules with unprecedented ease and efficiency.

These developments have tremendous implications for the field of HIV research. Cryo-EM has provided deeper insights into all facets of HIV research, ranging from anti-viral drug development to vaccine development approaches. For example, understanding the HIV capsid structure from intact virions and its interactions with the host cells, visualizing the mode of action of the advanced HIV integrase (IN) strand transfer inhibitors (INSTIs at near-atomic resolution (Cook, N.J. et al., 2020), and finding new ways for the development and preclinical validation of germline-targeting immunogens to stimulate precursors for HCDR3-dependent antibodies (Steichen, J. M. et al., 2020).

Following is an overview of recent scientific publications on how cryo-EM methods have been advancing HIV vaccine development and structure-based drug design research.

The open access review by B. Mak, J. & de Marco, A., 2018, is an excellent starting point to learn about using cryo-EM for the study of retroviruses. It includes sections on cryo-EM sample preparation, the microscopes, and two cryo-EM techniques, single particle analysis and cryo-electron tomography. HIV research is a particular focus of this review, as it discusses the analysis of HIV-1 glycoproteins, its capsid assembly and maturation, as well as the integration of the viral genome into the host via the intasome.

A string of recent publications used cryo-EM in the specific context of research aimed at preventing or treating HIV infections by vaccines and antivirals.

While HIV has been investigated for decades, developing a vaccine against HIV-1 has not been successful so far due to the immense genetic diversity underlying the different strains of HIV. A vaccine aiming to prevent infection with HIV would have to induce broadly neutralizing antibodies (bnAbs) against multiple HIV strains. The bnAbs' antigen is the HIV-1 envelope (Env) trimer on the surface of the virion. The perspective article written by Agazio, A. & Torres, R.M., 2019 explains past research characterizing bnAbs isolated from infected individuals and the engineering of immunogens aimed at triggering the neutralization of HIV. It specifically focuses on work by Saunders et al. and Steichen et al., who designed custom Env proteins as immunogens and validated their vaccination strategy in animal models of the disease. Both studies utilized cryo-EM to gain a structural understanding of the interaction between vaccine-elicited neutralizing antibody and HIV-1 antigen.

Using antiretroviral drugs such as integrase strand transfer inhibitors (INSTIs) is a crucial component for treating patients infected with HIV. The intasome, a nucleoprotein complex formed by the viral integrase and viral DNA, drives the integration of the viral genome into that of the host. Given their importance for HIV therapy, there is a keen interest in understanding the structural basis for the efficacy of INSTIs and the drug resistance exhibited by some HIV strains to guide future drug development. Two recent publications by Cook, N.J. et al., 2020 and Passos, D. O. et al., 2020 detail how single particle cryo-EM was used to determine the structure of the intasome and its interaction with several commercialized and experimental INSTIs to gain a mechanistic understanding of the drugs' function.

The above studies used state-of-the-art, fully automated cryo-electron microscopes designed for rapid, stable, and high-resolution data collection on frozen-hydrated samples: the Thermo Scientific™ Talos™ Arctica™ and Krios™ Cryo-TEMs.

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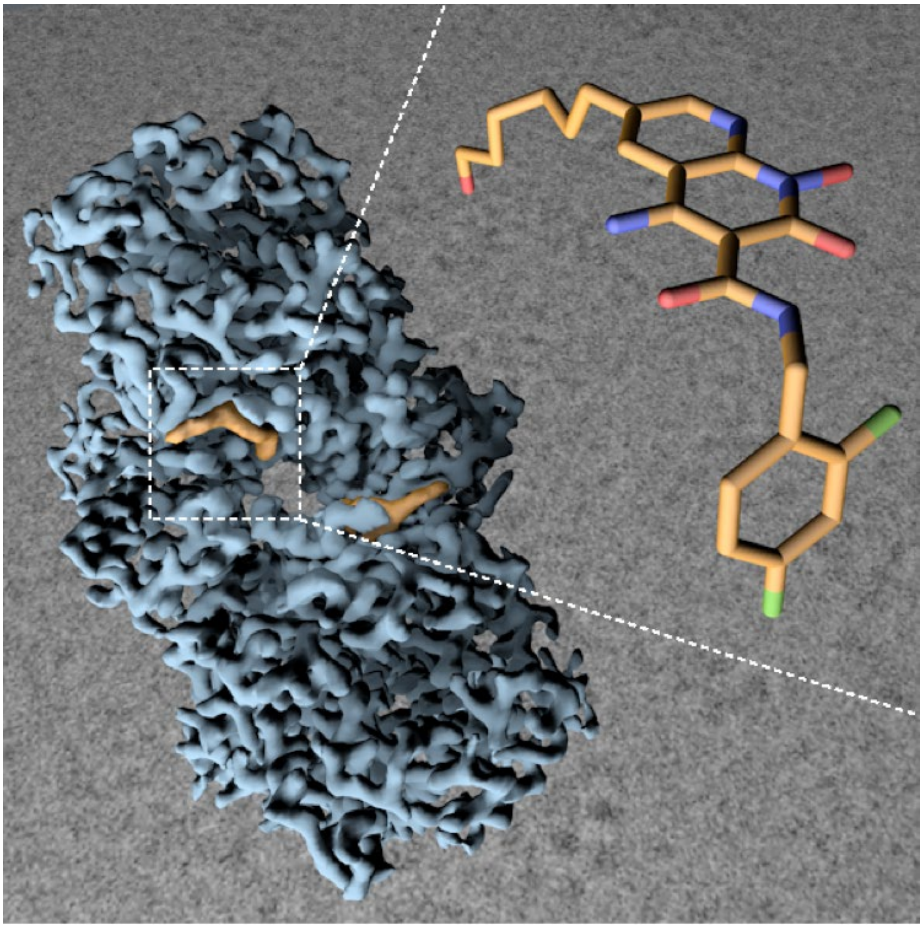

High-resolution cryo-EM enables visualization of the binding modes of small molecule drugs that inhibit HIV integration into target cells. In this image, a leading preclinical compound is bound to an HIV nucleoprotein complex that catalyzes the insertion of the viral genome into host chromatin. Modern single-particle cryo-EM methods enabled visualization of the ligand binding mode, providing insights into drug potency. The tools are now being used for structure-based drug design. *Image Courtesy of Dr. Dmitry Lyumkis, Salk Institute*

Learn more about the impact of cryo-EM in HIV research:

- Blog post: Cryo-EM Reveals How Antibodies Can Combat HIV
- HIV webinar from the Salk Institute: Using cryo-EM for designing next-gen therapeutics against HIV

Agazio, A. & Torres, R. M. Ushering along B cells to neutralize HIV. Science (2019). doi:10.1126/science.aaz8647

Cook, N. J. et al. Structural basis of second-generation HIV integrase inhibitor action and viral resistance. Science (2020). doi:10.1126/science.aay4919

Mak, J. & de Marco, A. Recent advances in retroviruses via cryo-electron microscopy. Retrovirology (2018). doi:10.1186/s12977-018-0405-6

Passos, D. O. et al. Structural basis for strand transfer inhibitor binding to HIV intasomes. Science (2020). doi:10.1126/science.aay8015

Saunders, K. O. et al. Targeted selection of HIV-specific antibody mutations by engineering B cell maturation. Science (2019). doi:10.1126/science.aay7199

Steichen, J. M. et al. A generalized HIV vaccine design strategy for priming of broadly neutralizing antibody responses. Science (2019). doi:10.1126/science.aax4380

Learn more about Thermo Fisher Scientific's **cryo-EM workflow solutions.**

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