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From concept to reality: cryoEM as an integral part of drug discovery and development

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Cryoelectron Microscopy (cryoEM) has become an integral part of drug discovery and development. In drug discovery, it is a powerful tool for structure-based design across modalities, including small molecules, peptides and biologics (References 1,2 & 3). The impact of cryoEM has been especially felt for complex targets, such as membrane proteins and multi-protein complexes. In particular, cryoEM has transformed the ability for structure-based design on ion channels and active GPCR complexes. In addition to structure-based design, the high-resolution structures from cryoEM provide insights into the mechanism of action of compounds/biologics and a deeper understanding of the biology surrounding their use. In some cases, the cryoEM structures even help to establish the chemical structure of the small molecule itself.

In drug development, cryoEM helps to better understand the potential therapeutics. cryoEM coupled with gold labeling is been used to characterize chemical reactivity and viral protein expression (Reference 4). It is a high-resolution analytical technique employed to look at the structure, size and variability of lipid nanoparticles, which are used for drug delivery. Similar to lipid nanoparticles, cryoEM is also used to look at the virus-like particles from vaccines to measure particle size distribution and other physical parameters. In favorable situations, cryoEM is used to determine high resolution structures of virus-like particles, to help understand their stability and assembly (Reference 5).

In this presentation I will show how cryoEM was built from the ground up within a large pharmaceutical company. I will describe our experience from developing the business case, through the construction and installation, up to the current state. Finally, I will show several of the ways cryoEM has impacted drug discovery and development projects. Throughout the process there were plenty of surprises, and hopefully the lessons learned will be useful for others interested in cryoEM.

References

1. Jean-Paul Renaud, Ashwin Chari, Claudio Ciferri, Wen-ti Liu, Hervé-William Rémigy, Holger Stark & Christian Wiesmann. Cryo-EM in drug discovery: achievements, limitations and prospects. *Nature Reviews Drug Discovery* **Vol. 17** (2018)

2. John H Van Drie & Liang Tong. Cryo-EM as a powerful tool for drug discovery. *Bioorganic & medicinal chemistry letters* **Vol. 30** (2020)

3. Giovanna Scapin, Clinton S. Potter, & Bridget Carragher. CryoEM for small molecules discovery, design, understanding and application. *Cell Chemical Biology* **Vol. 25** (2018)

4. James F. Hainfeld & Richard D. Powell. New Frontiers in Gold Labeling. *Journal of Histochemistry & Cytochemistry* **Vol. 48** (2000)

5. Daniel J. Goetschius, Samantha R. Hartmann, Suriyasri Subramanian, Carol M. Bator, Neil D. Christensen & Susan L. Hafenstein. High resolution cryo EM analysis of HPV16 identifies minor structural protein L2 and describes capsid flexibility *Scientific Reports* **Vol. 11** (2021)