CryoEM for drug discovery, design, understanding and application.

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The importance of structural information in drug discovery has been understood since the mid-80s, and by the early 90s the first success stories started to appear. Nowadays, structure guided drug design is an integral part of the discovery platform in most pharmaceutical industries. Structure guided drug design is a very iterative process, that can last years before a new drug candidate is obtained, and involves many fields of research, from structural and computational chemistry to biology, pharmacology, and medicinal chemistry, just to name a few. The very first (and necessary) step is the determination of the structure of the target of interest. Until now, the major methods utilized for structure determination were x-ray crystallography, and NMR, with homology modeling stepping in when an experimental structure could not be obtained. Nevertheless, structural information for a large portion of targets of interest to the pharmaceutical industry is still unknown, mainly for reasons that include molecular size, complexity, flexibility, and difficulties in production and purification. In addition, structures determined by x-ray crystallography very often represent just one snapshot of one specific conformation of the target protein, which does not necessarily represent the most common conformation present at a cellular level and often cannot provide detailed information about flexibility and conformational motions.

In recent years, cryo electron microscopy (cryoEM) has emerged as a complementary technique to crystallography and NMR, potentially providing several advantages over the more traditional methods: access to larger and/or more complex biological systems, analysis of proteins in solution (albeit vitrified) and, perhaps most importantly, the possibility of characterizing multiple conformational or compositional states from the same sample, hence providing insights into states of the macromolecule theoretically closer to those that are biologically relevant. While there are many relevant biological questions that can be answered by lower resolution structures, the process of structure guided drug design has some specific requirements (resolution being only one of them) that need to be considered when selecting protein targets and techniques. We will discuss here the current state of cryoEM in the area of small molecule structure guided drug discovery, what it can bring to the table, and what can be done (or expected) in the future to move this technique to the forefront of drug discovery.