A cryoEM and microED pipeline for the pharmaceutical and biotechnology industry

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Cryo-electron microscopy (cryoEM) has become an established and viable alternative to X-ray analysis for high resolution protein structure determination. The technique is parsimonious in its material requirements and captures the specimens in their fully hydrated state, close to their native environment. Single particle CryoEM is increasingly used as the method of choice for 3D structure determination of targets that are difficult to crystallize, are available in limited quantity, display conformational variability or suffer from instability. There are significant barriers though to adopting cryoEM in the pharmaceutical and biotech industries, including the high costs and maintenance of the electron microscopes, the shortage of experienced personnel and the demanding computational infrastructure required for data collection and image processing. This presentation provides information on how to access cryoEM through outsourcing some or all aspects of the cryoEM workflow, including sample preparation, data collection and structure determination. As a specific example, the unique offerings provided by NanoImaging Services (NIS) will be described. NIS melds traditional CRO service packages with training and instrument access that is typically only accessible through academic and national laboratory facilities. Since 2017, dozens of pharma and biotech clients have successfully completed their cryoEM projects at NIS with over 60 client protein structures solved at 1.8 – 3.5Å resolution. Microcrystal electron diffraction (microED) is another, emerging cryoEM structure determination technique of high interest to the pharmaceutical and biotechnology industries. MicroED can rapidly determine atomic-resolution structures from microcrystals with minimal sample requirements. NIS has developed robust commercial services for small molecule microED studies to support a variety of industrial chemistry workflows. Details of this workflow and determination of over 20 small molecule structures during our initial testing program will be discussed.