Electron Crystallography Methods for Drug Discovery

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X-ray diffraction (XRD) has long been a cornerstone technique in materials science, structural chemistry, and structural biology, providing unparalleled insights into molecular structures. However, despite significant advancements in laboratory X-ray sources and synchrotron technology, a persistent challenge remains: the necessity of growing large, high-quality crystals. This process is often labour-intensive, requiring substantial amounts of purified material, and in many cases, particularly for biological macromolecules and pharmaceutical compounds, it is impractical or even impossible.

Electron crystallography techniques, such as 3D Electron Diffraction (3D ED)/MicroED[1] and Serial Electron Diffraction (SerialED),[2,3] offer transformative solutions to these limitations. These methods enable structural determination from crystals with volumes up to a billion times smaller than those required for traditional single-crystal X-ray diffraction (SCXRD). Since its introduction in 2007, 3D ED has been instrumental in solving structures of challenging samples, initially focusing on inorganic materials that were otherwise inaccessible using conventional X-ray techniques. Over the years, diverse methodologies for data acquisition have been developed, including Automated Diffraction Tomography (ADT, University of Mainz) and Rotation Electron Diffraction (RED, Stockholm University). A pivotal breakthrough came in 2013 when Gonen's lab successfully adapted the MicroED[4] technique for macromolecular crystallography, opening new possibilities in structural biology.

More recently, Serial Electron Diffraction (SerialED)[2,3] has emerged as a powerful advancement, enabling high-resolution structure determination of radiation-sensitive macromolecular crystals while minimizing damage. These breakthroughs have significant implications for structural biology and pharmaceutical research, particularly in the realm of drug discovery. Electron crystallography can facilitate rapid and accurate structure determination of small molecules, peptides, and protein-ligand complexes.[5] This capability is particularly valuable for fragment-based drug design, where high-resolution structures of weakly binding fragments are crucial for optimizing lead compounds. Moreover, electron diffraction techniques can accelerate the characterization of polymorphs[6] and co-crystals, which are key aspects in pharmaceutical development and regulatory approval.

At the 15th International Nanomedicine Conference, I will present our latest findings and discuss future directions in electron crystallography, emphasizing its expanding its role in structural chemistry, macromolecular research, and drug discovery. As the field continues to evolve, these methods promise to bridge critical gaps in molecular structure determination, ultimately contributing to more efficient and targeted therapeutic development.

References:

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