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Structure-driven approaches and technologies for drug discovery

Structural knowledge of specific biological targets and their ligands is essential for structure-based drug design and the development, optimization, and characterization of pharmaceutical molecules. Rational design approaches in drug development comprise multiple advantages compared to classical drug discovery efforts. Therefore, there is an urgent need for structure-based techniques to inform researchers about the molecular detail of ligands and their spatiotemporal interactions with a given macromolecular target. Deciphering these interactions is informative for the development and optimization of a wide array of therapeutic molecules.

Recent technological developments opened many more possibilities, but the translation for individual research is often hampered. Partially this is due to the limited availability of expensive equipment, but also the right consultancy to choose the best method available is not easy to achieve. On top, often preliminary work must be provided that is not only timely and cost intensive, but also requires a level of expertize that is not always given without collaborative setups. An early interaction with the structural experts to collaborate with will help to set up the projects right from the start. During grant application writing, colleagues can assist and also help with budgeting the structural technologies correctly so that usage of structural facilities or big equipment is possible. Communities like local Block Allocation Groups (BAGs) that organize the access to large equipment like synchrotrons or the iNEXT Discovery as a European community for access to structural biology infrastructures are good starting points for non-structural experts to find expertize and collaborative partners.

As different macromolecular (protein) targets require discriminative structural elucidation methods to create a basis for drug discovery due to their high/low molecular weight, complexity, stability, enzymatic activity or degree of order/disorder. For instance, transcription factors are largely unstructured and therefore require AI or NMR methods for structural elucidation, whereas kinases are predominantly ordered and therefore X-ray crystallography represents a valid strategy to decipher their respective 3D structures. On the contrary, high molecular weight protein targets and complexes require Cryo-EM techniques.

This special issue is intended to be a guide to researchers and aims to informing about the latest advances in structure elucidation methods and their applications. Specialized structural biologists from academia, manufacturers, and core facilities professionals highlight various perspectives of cutting-edge structure elucidation techniques for drug discovery and medicinal chemistry. With this knowledge, scientists will be able to understand, chose and initiate the right structural elucidations for their project.

Nuclear Magnetic Resonance represents the most traditional structure determination method. *Mesleh* and *LeBlanc* describe classical and advanced NMR techniques to study the behavior of ligands upon target binding which in particular are useful to enable the identification and characterization of truly novel binding interactions of weak binders in a robust manner. In addition to structural information, this technique's yields information about binding dynamics, and interactions of biomolecules and particularly challenging targets based on their solution behavior [1]. X-ray crystallography represented the state-of-the-art structural biology method for decades and aided in the detailed understanding of the interactions between drugs and their targets which is crucial in the structure-based development and optimization of therapeutic agents. *Mazzorana* et al. showcase the technological opportunities and synergistic benefits for researchers in academia and industry provided by the "Diamond Light Source" synchrotron (Oxfortshire, UK) [2]. Access to facilities with highly automated macromolecular crystallography (MX) beamlines ensures fast, efficient and reliable data collection as well as automated downstream data processing which is of utmost importance for a timely progression of drug discovery efforts. Microcrystal electron diffraction (MicroED) has recently been demonstrated to be a promising technique for structure determination in structural biology and pharmaceutical chemistry. *Clabbers* and *Xu* discuss the unique properties of electrons and their use for diffraction experiments. Structure guided approaches in drug discovery will benefit from this technique and it will complement the existing X-ray based methods for structural elucidation in particular for those projects where only (sub-)micron sized crystals are available [3].

X-ray free-electron lasers (XFEL) combined with serial femtosecond crystallography (SFX) are technologies that allow structural access to small and also radiation sensitive crystal samples. *Dr. Nass Kovacs* gives a thorough overview of the technology, including sample preparation, delivery and data analysis [6]. She describes advantages for drug discovery on particular targets such as GPCRs and provides a critical outlook of the status quo.

Wigge et al. illuminate the current and latest technological advances in cryo-electron microscopy (cryo-EM) which has evolved from a limited resolution and throughput technique to a mainstream high-resolution structural biology method over the last decade. The cryo-EM field benefitted from significant technological advances in both hardware and imaging software that

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led to a significant impact in the drug discovery for previously intractable proteins sets a new the state-of-the-art application for structure determination [4].

While computer-based methods to advance drug development approaches were traditionally viewed as an additive and supportive set of tools, the field has dramatically advanced over the last decade and structurally enabled computational methods have become an integral part of small molecule drug discovery programs. In their review, *Frye* et al. cover the most recent developments in the fields of computational chemistry and machine learning as well as their synergies with structural biology to drive hit identification, hit-to-lead, and lead optimization in drug discovery [7].

Small molecule induced targeted protein degradation (TPD) is a powerful tool to expand the druggable space and has created tremendous excitement in drug discovery within recent years. *Leissing* et al. review structural approaches that assisted in the understanding of ternary complex formation of E3 ubiquitin ligase, small molecule degrader, and target protein which is crucial for the success of this novel approach. Structural insights of the underlying conformations and molecular contacts of the trimeric complex advanced the understanding and evolution of small molecule degraders [5].

This Drug Discovery Today: Technologies special issue provides an interdisciplinary, concise overview of current technological advances in structure elucidation methods for medicinal chemists and structural biologists. The editors would like to thank all authors and referees for their valued and insightful contributions. We hope that this special issue will assist to selecting the appropriate structural technology for your research question. Enjoy the read!.

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André Richters received his doctorate degree in Chemical Biology in 2013 (TU Dortmund University, Germany) working on targeting gatekeeper resistance mutations in kinases with reversible and covalent inhibitors using structure-based design approaches. He joined Angela Koehler's group at the Koch Institute for Integrative Cancer Research at MIT (Cambridge, USA) in 2015 on a fellowship from the German Research Foundation to unravel p300/CBP oncogenic signaling using small molecule inhibitors and probes. His research interests cover a wide range of structure based small molecule and probe development approaches to modulate oncogenic transcription factors and their interactome members. He contributed to the development of an ultra-selective CDK9 inhibitor in a collaborative project with KronosBio Inc. (Cambridge, USA). The lead candidate is now progressing to clinical trials. His experience in the development of Proteolysis Targeting Chimeras (PROTACs) led him to explore novel approaches to hijack lysosomal uptake mechanisms for the targeted degradation of macromolecules. To explore this concept of Lysosome Targeting Chimeras – LYTACs – he was awarded two principal investigator career development awards at the Broad Institute of MIT and Harvard (2017 and 2019). He currently works as senior research scientist at Plexium Inc. (San Diego, CA).

Sven Hennig is a biochemist by training and became a structural biologist during his Ph.D. (2008), where he studied human proteins of the circadian rhythm using X-ray crystallography in the group of Dr. Eva Wolf at the Max-Planck Institute of molecular physiology (Dortmund, Germany). Afterwards, he joined the lab of Dr. Christian Ottmann to study the stabilization of protein-protein interactions using high throughput screening and structural biology at the Chemical Genomics Centre (Dortmund, Germany). In 2010 he was awarded a German Academic Exchange Service PostDoc Fellowship to join Dr. Archa H. Fox in her lab in Perth (Western Australia) to study long, non-coding RNA and their protein interactions. In 2012 he returned to the Chemical Genomics Center (Dortmund, Germany), where he started his independent research group on Therapeutic Transcriptome Modulations. Within this area, he uses biochemical approaches, thermodynamics, peptidomimetics, structural biology and protein engineering to understand and modulate biomolecular complexes of the transcriptional machinery. He brought his research and expertize to the Vrije Universiteit Amsterdam in 2017 where he became tenure track assistant professor of structural chemical biology (tenured in 2019) and head of X-ray crystallography at the Department of Chemistry & Pharmaceutical Sciences.

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