Invited Speakers

The evolving role of structural biology and biophysics in drug discovery

Jean-Paul Renaud
Urania Therapeutics, Ostwald, France
Email: jprenaud@uraniatx.com

The use of structural biology and biophysics has become pervasive in drug discovery, allowing not only to accelerate the hit-to-lead process as in the beginning, but also to discover new biology, to identify low-affinity binders at the screening stage and to obtain detailed information on target / compound interactions [1]. This is perfectly illustrated by the success of FBDD (fragment-based drug design), where the progress of biophysical techniques in terms of sensitivity, speed, and automation has been instrumental [2,3]. Indeed, FBDD is now widely adopted in both academia and the pharmaceutical industry and has led to 2 approved drugs and around 40 compounds being evaluated in clinical trials. Recent progress in cryo-EM has been spectacular and has led to the determination of numerous high-resolution structures of highly interesting macromolecular assemblies, including large dynamical complexes and membrane proteins [4]. Certainly, many of these structures would have been out of reach using X-ray crystallography. Several reviews have recently focused on the potential role of cryo-EM in drug discovery and in particular structure-based drug design (see for instance [5,6]). Even though it has been predicted that "the revolution will not be crystallized" [7], crystallography is still alive and constantly reinventing itself [8] and will certainly remain at least for a couple of years the main technique for high-throughput structure determination in structure-based drug design. X-ray crystallography and cryo-EM as well as NMR should rather be considered complementary techniques [9] and drug discovery scientists should choose in each situation the one better suited to the question to address or, even better, use them in combination. The recent rebirth of chemical biology is the perfect opportunity for structural biologists / biophysicists to work hand in hand with medicinal chemists to exploit the wealth of new modalities and potential new therapeutic targets [1,10] to address challenging unmet medical needs, as illustrated by the development of PROTACs to target previously undruggable proteins.

[1] Renaud J.P. (2019) The evolving role of structural biology in drug discovery in *Structural Biology in Drug Discovery*, J.P. Renaud Ed., Chapter 1, Wiley, in press
[2] Erlanson D. et al. (2016) Twenty years on: the impact of fragments on drug discovery. **Nat. Rev. Drug Discov.** 15:605–619
[3] Renaud J.P. et al. (2016) Biophysics in drug discovery: impact, challenges and opportunities. **Nat. Rev. Drug Discov.** 15:679–698
[4] Cheng Y. (2018) Single-particle cryo-EM – How did it get here and where will it go **Science** 361:876–880
[5] Renaud J.P. et al. (2018) Cryo-EM in drug discovery: achievements, limitations and prospects **Nat. Rev. Drug Discov**. 17:471–492
[6] Ceska T. et al. (2019) Cryo-EM in drug discovery **Biochem. Soc. Trans**., in press
[7] Callaway E. (2015) The revolution will not be crystallized **Nature** 525:172–174
[8] Bricogne G. (2019) High-throughput macromolecular crystallography in drug discovery: Evolving in the midst of revolutions in *Structural Biology in Drug Discovery*, J.P. Renaud Ed., Chapter 10, Wiley, in press
[9] Vénien-Bryan C. et al. (2017) Cryo-electron microscopy and X-ray crystallography: complementary approaches to structural biology and drug discovery **Acta Cryst. F** 73:174–183
[10] Valeur E. and Jimonet P. (2018) New Modalities, Technologies, and Partnerships in Probe and Lead Generation: Enabling a Mode-of-Action Centric Paradigm **J. Med. Chem.** 61:9004−9029