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Editorial overview: Next generation therapeutics

Adrian Whitty and Peter J Tonge

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Adrian Whitty[1,2,3,4]

[1] Department of Chemistry, Boston University, Boston, MA, USA
[2] Department of Pharmacology and Experimental Therapeutics, Boston University, Boston, MA, USA
[3] Center for Molecular Discovery, Boston University, Boston, MA, USA
[4] Biomolecular Engineering Research Center, Boston University, Boston, MA, USA
e-mail: whitty@bu.edu

Adrian Whitty joined the Department of Chemistry at Boston University in 2008, from his previous position as Director of Physical Biochemistry at Biogen. He obtained a B.Sc. in Chemistry at King's College London, and a Ph.D. in Organic Chemistry at the University of Illinois at Chicago, followed by Postdoctoral work with William P Jencks at Brandeis University. His research focuses on inhibition of protein–protein interactions, and on activation and signaling mechanisms of growth factor receptors.

Peter J Tonge[1,2]

[1] Department of Chemistry, Stony Brook University, Stony Brook, NY, USA
[2] Department of Radiology, Institute for Chemical Biology & Drug Discovery, Stony Brook University, Stony Brook, NY, USA
e-mail: peter.tonge@stonybrook.edu

Peter Tonge is a Professor of Chemistry and of Radiology (by courtesy) at Stony Brook University. He obtained his B.Sc. and Ph.D. degrees from Birmingham University, UK, and subsequently held positions at the National Research Council of Canada and the Picower Medical Research Institute before moving to Stony Brook. His research program is focused on the role of drug–target kinetics in drug discovery, the development of positron emission tomography radiotracers to image infection, and the mechanism of photoreceptors and optogenetic devices.

Although the development of new drugs can in no case ever be considered easy, the investment of enormous intellectual and financial resources over many decades has brought us to a point where high quality drug candidates for certain classes of targets can be routinely generated. However, major unmet medical needs continue to exist across a wide range of diseases, driving the drug discovery enterprise to solve increasingly complex problems and to confront ever more difficult targets. This evolution requires, among other things, an increasingly sophisticated understanding of how drugs work, a willingness to go after non-traditional target classes, the use of an expanded range of drug compound types and modalities, and improved methods for tracking drug distribution *in vivo*. Particular challenges include how to assess target druggability, and how to tackle target classes previously considered undruggable. We additionally need to continually improve our understanding of drug mechanism of action, to enable the efficient discovery and development of drugs with better attributes, and to improve dosing and safety profiles. In putting together this issue on Next Generation Therapeutics, we have solicited articles that describe recent progress and future prospects covering many of the above needs.

Virtual screening — the computational assessment of a collection of compound structures to identify those most likely to bind at a particular site on a target — remains a mainstay of lead identification, especially for conventionally druggable protein targets such as the nucleotide binding sites of kinases. However, the application of computational docking to unusual or particularly challenging targets, such as protein–protein interaction interfaces and others discussed in this issue, has been less successful. Many different approaches to docking and pose selection are now available involving, for example, different scoring functions, or different ways of accounting for flexibility on the part of the receptor. Wingert and Camacho (https://doi.org/10.1016/j.cbpa.2018.06.006) discuss recent advances in both the software and strategies used for computer-aided drug design. They compare the predictive utility of various approaches across a range of target classes, concluding that the choice of which method is best is contextual, and depends on target type, and on what other information is available about the structure of the target and its known ligands. Often the choice of software and scoring function is less important than proper matching of strategy to target, and selection of which experimental target structure is most appropriate to use.

There is increased awareness that drug–target kinetics must be considered in the selection and optimization of drug candidates to improve the success rate of new drug discovery. However, our understanding of the molecular factors that control the lifetime of the drug–target complex is still in its infancy. The article by Lu *et al.* (https://doi.org/10.1016/j.cbpa.2018.06.002)

discusses the current state of knowledge about the mechanisms that govern drug–target residence time, illustrated by discussion of examples from several target classes, including kinases and G protein-coupled receptors (GPCRs). Their article highlights current approaches to unravelling the drug binding reaction coordinate, including structure–kinetics relationships and molecular dynamics simulations, with a view to developing the ability to tailor the residence time of a drug candidate to its particular application.

A class of drug targets that has received much attention in recent years, but which still remains highly challenging, is that of protein–protein interaction (PPI) interfaces. As a field, we are still in the early stages of developing reliable approaches to the discovery of potent, selective and bioavailable small molecule PPI inhibitors. Ran and Gestwicki (https://doi.org/10.1016/j.cbpa.2018.06.004) review the 66 small PPI inhibitors that have been reported during the past three years, with a view to learning which approaches are working and which are not. They discuss how PPI interface area correlates with inhibitor binding affinity, and with whether success was found using conventional small molecule compounds versus peptides. They extract lessons concerning how considerations such as the availability of an experimental X-ray structure of the target, or whether the target undergoes a conformational change, affect prospects of finding an inhibitor. Finally, the authors present an overview of what these recently published examples reveal concerning how to think about the 'druggability' of a PPI target, and discuss the outlook for inhibiting that subset of PPI targets that is truly intractable to conventional small molecule inhibitors.

Another class of targets that is considered to be highly challenging includes proteins involved in protein folding disorders, such as those associated with serious neurodegenerative diseases including Alzheimers's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis (ALS), and others. Scannevin (https://doi.org/10.1016/j.cbpa.2018.05.018) reviews current efforts toward developing therapies for protein misfolding disorders, focusing on drugs that have entered human clinical trials. He considers these therapies not in terms of which disease indication(s) they address, or the identity of their molecular target, but instead in terms of the different strategies they employ. He identifies four classes of approach: inhibiting production of the parent protein, inhibiting the aggregation of the misfolded protein, removing the toxic aggregated forms of the misfolded protein, and mitigating the toxicity of the misfolded proteins. Comparing the clinical candidates in this way allows useful comparisons to be made between drugs that address different diseases and target different proteins, but work in a similar manner.

Structure-based drug design involves the development of molecules that bind to defined pockets or sites on the target, resulting in a desired pharmacological outcome. However, in many cases suitable binding pockets cannot be readily identified in unliganded X-ray structures, hindering the development of antagonists and inhibitors using rational design approaches such as *in silico* docking. Cryptic sites are binding sites that are not found in the unbound protein but, as a result of conformational change, become apparent when a ligand is bound. Targeting cryptic sites is a topic of high recent interest as a strategy for inhibiting targets for which the main active site is poorly druggable. Vajda *et al.* (https://doi.org/10.1016/j.cbpa.2018.05.003) address the ambiguity that exists in the literature concerning what constitutes a cryptic site, and review recently published computational strategies for identifying cryptic sites. They review evidence showing that a substantial fraction of the putative cryptic sites identified by Molecular Dynamics (MD) simulations appear unlikely to be druggable, and discuss how the reliable detection of pharmacologically relevant cryptic sites can be improved by supplementing MD with other approaches such as computational hot spot mapping or machine learning.

Another approach to drug discovery against poorly druggable targets that has received substantial recent attention involves the use of compound types that violate conventional guidelines for 'druglikeness', as embodied for example in Lipinski's Rule-of-Five or Veber's Rules. These so-called 'beyond Rule-of-Five' (bR05) compounds, many of which have molecular weights well above 500 Da, can be better suited to bind to poorly druggable sites. However, at least since the concept of 'druglikeness' was developed in the 1990s, such compounds have been strongly disfavored, primarily due to the increased difficulty in achieving good oral bioavailability and other desirable pharmaceutical properties. Poongavanam, Doak and Kihlberg (https://doi.org/10.1016/j.cbpa.2018.05.010) review instances of approved oral drugs with molecular weight >500 Da, and discuss our rapidly growing understanding of how oral absorption and cell permeability can be achieved with such bRo5 compounds. They also provide an overview of current guidelines for the design and optimization of compounds that lie in bRo5 space.

Yet another emerging approach to drug discovery against challenging targets is the use of Targeted Covalent Inhibitors (TCI). TCIs are compounds that bind with moderate affinity to the target site, but in so doing place a reactive 'warhead' in a position that allows rapid covalent reaction with a specific amino acid side-chain on the protein. Formation of a covalent adduct with the target promotes high inhibitor occupancy of even a poorly druggable site, can provide a long drug–target residence time, and can confer enhanced selectivity over related proteins if the covalently-targeted residue is poorly conserved across the protein family. To-date, efforts to