Editorial

New Targets for Structure-Based Drug Discovery

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This issue of Current Topics in Medicinal Chemistry will focus on targets for which active research is ongoing using the application of structure-based drug design (SBDD). The specific topics are outlined below and are judged to be areas of particular interest in the practice of SBDD today. The biological targets have been selected of high interest for the development of new agents to treat human diseases.

SBDD is of course a long established paradigm in drug discovery and has grown steadily in its application over the last 25 years. Of increasing interest in the last 10-15 years has been the use of fragment based screening and fragment X-ray complexes. As our ability to solve X-ray complexes of bound ligands has improved over time it is now increasingly the case that medicinal chemists will have access to these data during an active drug discovery campaign. Previously the X-ray data would often arrive too late and was used to post-hoc rationalise how a molecule was binding and give confidence in the mode of action of the eventual drug candidate. Today new targets with exciting potential to treat disease are the focus of structural biology efforts and we see seven examples in this issue. Two of the articles focus on G Protein-Coupled Receptors (GPCRs) for which X-ray crystal structure information has only been available relatively recently and for which SBDD is now possible for the first time.

The first article is by Michelle Arkin and colleagues from the Small Molecule Discovery Center and Department of Pharmaceutical Chemistry, University of California, United States and focuses *on Targeting Non-Catalytic Cysteine Residues Through Structure-Guided Drug Discovery*. Despite worries of potential toxicity for agents designed to form covalent bonds with their biological target, this approach is finding increasing application and yielding clinical agents and drugs on the market. This timely review introduces the field and highlights how the rational design of compounds can increase the chance of success, particularly by increasing specificity for the target.

The second paper is by Edward Tate and a team from the Department of Chemistry, the Department of Life Sciences, and the Department of Surgery & Cancer, Imperial College London, UK on *Direct Targeting of the Ras GTPase Superfamily Through Structure-Based Design*. The Ras superfamily of small monomeric GTPases includes some prominent cancer targets but so far no selective therapeutic agent has yet been successfully developed. Tate discusses the recent progress in targeting the Ras GTPases using SBDD.

Next, Jun Yong Choi and William Roush from the Department of Chemistry, Scripps, Florida, United States review the *SBDD of CYP51 Inhibitors*. CYP51 is a proven therapeutic target for anti-fungal drugs and SBDD of therapeutic agents targeting CYP51 has recently been attempted. The structural features of CYP51 and its complexes formed with previously known drugs and newly designed inhibitors are highlighted and the potential for the development of drugs targeting this protein using SBDD discussed.

Hugo Gutiérrez-de-Terán and colleagues from the Department of Cell and Molecular Biology, Uppsala University, Sweden and the Center for Research in Biological Chemistry and Molecular Materials (CIQUS) and Department of Organic Chemistry, University of Santiago de Compostela, Spain, describe progress with the *Structure-Based Rational Design of Adenosine Receptor Ligands.* The family of adenosine receptors (ARs) has been a focus of many medicinal chemistry programs aimed to find new potent and selective drugs for many years. Each receptor subtype has been proposed as a relevant drug target in the treatment of, e.g., cardiovascular or inflammatory diseases, asthma or Parkinson's disease. Recent advances in GPCR crystallography have given a number of agonists and antagonist co-complexes with the adenosine A_{2A} receptor allowing SBDD to be applied for the first time.

Sandra Cowan-Jacob and co-workers from the Novartis Institutes for Biomedical Research, Basel, Switzerland discuss *Expanding the Opportunities for Modulating Kinase Targets with Allosteric Approaches.* Despite the huge amount of literature on the inhibition of kinases with small molecules targeting the ATP site the idea of targeting other sites on kinases is relatively under-explored. In this review an overview of structurally characterized allosteric kinase inhibitors is given along with the potential benefits of these agents.

John Christopher and colleagues from Heptares Therapeutics, BioPark, Hertfordshire, UK discuss the *Potential for the Rational Design of Allosteric Modulators of Class C GPCRs.* Class C GPCRs encompass a range of promising therapeutic targets and recent advances in structural biology have revealed the X-ray crystallographic structures of allosteric ligands bound to two Class C metabotropic glutamate (mGlu) receptors, mGlu1 and mGlu5. The review examines how this information helps rationalise the challenges of mGlu receptor allosteric modulator drug discovery and how SBDD can now be leveraged for these targets.

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Finally, Martin McPhillie and co-workers from the School of Chemistry, University of Leeds, UK outline *New Opportunities in the Structure-based Design of Anti-Protozoan Agents.* Anti-protozoan agents have generally been identified by phenotypic screening. However, opportunities also exist for target-based approaches to find new lead compounds. Recent structure-based design efforts to inhibit four relevant targets are reviewed, reviewing their crystal structures and the ability to accommodate potent and selective compounds.

We would like to express our thanks to all authors of the articles in this issue and to those experts that improved the quality of the final articles during the peer review process. It is their efforts that made this issue possible.

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