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Future Frontiers in Small Molecule Inhibitors of Protein-Protein Interactions

Editorial

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Protein-protein interactions (PPIs) are ubiquitous in essential biological processes such as cell proliferation and differentiation, host-pathogen interactions, and signal transduction pathways [1]. Pioneering advances in the field of interactomics have uncovered new net-works of protein interactions within cells, with esti-mates for the size of the interactome ranging up to 650,000 PPIs [2]. However, targeting PPIs has histori-cally been considered to be a particularly challenging task due to their typically large size (>1,500 Å) and amorphous nature that lack well-defined crevices for recognition by small molecules. Not surprisingly, the pharmaceutical landscape over the last century has been dominated by programs for small molecule in-hibitors of enzymes (particularly kinases), G-protein-coupled receptors, protein transporters and ion chan-nels that account for the majority of known drugs.

Over the past two decades, however, revolutionary studies have established the notion of so-called "hot-spots" within protein-protein interfaces, which are small subsets of residues that are responsible for most of the binding affinity of the protein to natural part-ners or synthetic small molecules [3]. Furthermore, scientists have gained greater appreciation into the plas-ticity of protein surfaces, such as the realization that protein-protein interfaces are dynamic and allow the formation of transient binding pockets that may not be observable in the static structure of the apo-protein or protein-protein complex. Protein-protein interfaces are exceedingly diverse, and, unfortunately, have not evolved for optimal interactions with small molecules. A computational study has suggested that the drug-gable sites within PPI interfaces typically comprise a cluster of binding hotspots characterized by concave topology combined with a pattern of hydrophobic and polar functionality [4]. Thus, the development of PPI inhibitors has largely focused upon relatively large, rig-id and hydrophobic molecules that could interact more effectively with the binding pocket of the protein-protein interface [5]. Indeed, the frugal success rate of early PPI inhibitor discovery programs may have stemmed from the bias for "drug-like" molecules in high-throughput screening libraries. Most PPI inhibi-tors reported to date do not adhere to Lipinski's rule of five. A recent statistical analysis of 39 PPI inhibi-tors suggested a "rule of four" framework for small molecule PPI inhibitors where molecular weight > 400, ALogP > 4, number of rings > 4 and number of hydrogen bond acceptors > 4 [6]. Although pep-tide or antibody biologics show strong efficacy against PPIs in isolated systems, issues with oral bioavailability, cell permeability and metabolic stability tend to limit their further development as potential PPI-modulating drugs.

An overarching goal in PPI inhibitor discovery has therefore been to expand the arsenal of available chemical scaffolds, such as through biology-orientated or diversity-orientated approaches, to generate mol-ecules capable of accessing larger regions of chemical space available within the binding interfaces of PPIs. Two small molecule PPI inhibitors, navitoclax and oba-toclax, function by antagonizing the Bcl-2 family of proteins and are currently in Phase II clinical trials as anti-cancer agents. Our view is that two special classes of compounds, natural products and metal complexes, may represent the next frontier in the development of PPI inhibitors for the treatment of human diseases. Natural products represent a privileged source of bioactive substructures that have been evolutionarily selected for optimal interactions with biomolecules. Furthermore, natural products offer a cornucopia of structural motifs, many of which would fail simple drug-likeness screens, for sampling the diverse archi-tectures of protein-protein interfaces. As an example, paclitaxel (Taxol), a diterpenoid isolated from the bark of the Pacific yew tree and its semisynthetic deriva-tive docetaxel (Taxotere) have been found to bind to and stabilize the β-subunit of the tubulin heterodimer, thereby interfering with the normal breakdown of mi-crotubules during cell division. Our group has recently utilised high-throughput virtual screening to identify natural product-like inhibitors of the TNF-α homo-trimer interaction[7].

Cytotoxic metal complexes, best exemplified by cispl-atin and its analogues, typically target DNA or other biomolecules through covalent, non-specific interac-tions to exert their anti-neoplastic effects. Due to the adverse side effects associated with such "shotgun" metal complexes, however, there has been a recent up-surge in interest in the development of kinetically-inert metal complexes as molecularly-targeted agents against enzymes or PPIs[8,9]. Transition metals possess vari-able oxidation states and molecular geometries (e.g. octahedral, square-planar) that enable

the design of in-tricate coordination sphere architectures. The ability to arrange organic ligands in a precise three-dimensional arrangement around the metal center can be harnessed to generate unique scaffolds for recognizing the bind-ing sites of PPIs. However, few metal-based PPI mod-ulators have yet been discovered in the literature.

Despite promising initial studies, the realm of small molecule modulators of PPIs can be still considered as an immature discipline. Besides exploring new classes of molecules, future studies could be directed towards the further elucidation of protein-protein interfaces and the mechanisms of inhibition exhibited by small molecules. For example, α-helix, β-strand and mixed α/β PPI domains have all been successfully targeted by small molecules, and it might be envisioned that par-ticular 3D topological scaffolds would necessitate dis-tinct structural requirements in the ligands. In terms of mechanism, molecules may be designed to inhibit PPIs via orthosteric or allosteric inhibition, where ligands bind at or away from the protein-protein interface, respectively. Improved structural biological under-standing and computational algorithms could also en-hance the utility of molecular docking techniques for high-throughput virtual screening or structure-based rational design of PPI modulators [10]. Challenges notwithstanding, we believe that this exciting field will continue to thrive and mature in the years to come.

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