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Target fishing: a key to unlock the One-To-Many puzzle in drug discovery

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Editorial

The past two decades have marked significant advancements in the field of drug design and development. With the emergence of more sophisticated experimental techniques, advanced computational methods and complementary technologies the current drug development cycle is optimized for drug fishing [1-4] Meaning that, all current efforts are maximized toward the search (and/or design) for more potent small-molecules for the selective modulation of known disease targets. Nevertheless, it is becoming increasingly evident that a drug often tends to interact with more than one protein target or a signaling pathway [5-7], a phenomenon that is usually referred to as 'polypharmacology' [5,6]. Such unintended off-target and multiple-target interactions could cause unsafe side-effects [8], raising serious concerns in drug research [9]. There have been several instances in the past where drugs were withdrawn due to harmful side-effects; for instance, in 2010, the pain medication propoxyphene was withdrawn from the market due to its' adverse effects to the heart (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234350.htm). The Drug Bank database alone lists 201 such withdrawn drugs (http://www.drugbank.ca/stats) and the mode of actions and therapeutic targets of a number of them remain elusive. The entire development cycle of a single drug, from research labs to market, is too much a lengthy, painful and expensive process to be squandered due to side effects from off-target interactions. On the brighter side, some drugs could bind to different targets and elicit positive responses in all; for example, Selvita was recently submitted as an investigational new drug to FDA for SEL24, a dual inhibitor of two promising targets of acute myeloid leukemia, PIM and FLT3 kinases (http://www.selvita.com/news-events/news-releases/selvita-initiates-ind-enabling-studies-for-its-first-in-class-pim-flt3-inhibitor). Thus, the drug design field is seeing a rapid paradigm shift from a 'one-drug-one-target' design to a multidimensional 'one-drug-many-targets' model, where the focus is mainly on the identification of all the possible protein targets of an active small molecule (or target fishing) [10]. Target fishing could also be useful in repurposing an existing or a failed drug for new applications [11,12], thereby offering economic benefits to drug research [5]. For instance, very recently scientists from the University of Dundee have shown that the anti-tubercular drug delamanid has the potential to be repositioned as an oral drug for Visceral leishmaniases, one of the major diseases seen in developing countries [13].

Given their significant impacts on drug design and development, several strategies have been developed for target identification; these approaches generally fall into three categories such as proteomics-based, genomics-based and bioinformatics-based [7,14]. Several excellent reviews discuss various target fishing methods in detail [5,7,15-18]. Such methods have led to the de-convolution of several functional targets of small-molecules [7,10,14,15,17]. Nevertheless, it is obvious that the experimental identification and validation of targets for a given small molecule, say through affinity chromatography, are significantly limited by the need for horrendous costs, labor and time. In addition, the experimental techniques are also prone to other technical complexities arising from, to name a few, solubility concerns, hydrophobicity of proteins and incorrect folding of enzymes in experiments. As a result, computational target fishing methods have become cost-effective alternatives, sometimes complementary, to experimental techniques. Different computational methods, such as chemical similarity search methods, data mining or machine learning methods, bioactivity spectra analyses methods and molecular docking methods, have been employed for in silico target fishing [19]. Chemical similarity search is the most popular ligand-only virtual screening approach that functions on the assumption that small-molecules with similar structural features bind against similar targets. This method employs a set of 2D and/or 3D descriptors to compare the query small-molecule against all the compounds with known targets in a selected database (ChEMBL or PubChem, for instance) so as to predict plausible protein targets of the compound of interest [20, 21]. Nevertheless, this approach often suffers from false positive and false negative predictions, particularly when inactive and active compounds display structural similarities [5]. In data-mining or machine learning methods, the properties of known active compounds against a target are analyzed carefully and statistical models are generated, which after rigorous training are employed to predict the probable targets that associate with the query compound, for examples refer to the following studies [8,22,23]. The main limitation of this method is that every target may bind structurally diverse classes of compounds and hence one model may not cover all the features, consequently affecting the performance in target fishing [5,16,20]. Bioactivity spectra analyses methods work on the principle that compounds binding to same target should display similar bioactivity spectra (i.e., the readouts from microarrays, cell lines and in vitro screening) [5,19,24,25]. The bioactive spectra collected from different targets and assays are later employed in the computational method to predict targets for the drugs. The important caveat of this method is the need to perform expensive experiments to collect bioactivity spectra for different targets [20]. Alternately, molecular docking methods for target fishing employs a 'reverse' virtual screening approach, in which a compound of interest is docked into a wide array of protein structures in public databases, such as protein data bank (PDB), and the target in the best scoring complex is predicted to be a probable partner of the query compound [26,27]. Several online servers, such as TarFisDock [22], INVDOCK [28] and idTarget [29], have been developed for this purpose. However, the accuracies of these docking-based methods are dependent on the efficacies of the scoring functions employed and the availability of high-performance supercomputers. It is important to note that PDB (www.pdb.org) currently contains only 31,794

experimentally determined protein structures of humans, while the total numbers of human protein sequences in the Uniprot database (www.uniprot.org) is 133,514. Such a huge gap between the available structures and sequences indicates that significant numbers of possible targets of a query small-molecule could be missed during target fishing predictions made by molecular docking methods. In addition, it is now well established that small-molecule drugs also tend to bind in much complicated protein surfaces, such as flat and wide shallow regions at protein-protein interfaces [30,31] and transient cryptic binding pockets [32] (i.e., cavities that are normally hidden and open only in the presence of ligands) in enzymes. None of the above computational methods are able to efficiently predict targets of small molecules, where such complex interactions are involved. Thus, there is a significant room for improvements in computational methods so as to achieve more effective and promising in silico target fishing for small-molecule drugs.

Target identification for small-molecule drugs remains a critical, but very difficult, phase in modern drug design and development. Robust target fishing extends multitude benefits to drug research, such as avoiding unwanted side effects from poly pharmacology of small-molecules at clinical stages, to reveal the mode-of-actions of a compound and also to repurpose old drugs for new targets. The rule of 'one-size-does-not-fit-all' still holds good in target fishing approaches as well. Therefore, it is important to carefully assemble the available methods and resources such that all levels of biological information, from sequences to structures to pharmacophores, are maximally utilized for fishing out the targets for the design of safer next-generation drugs.

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