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The Multi-Target Drug Design Era is Here, Consider it

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Abbreviations: HIV: Human Immunodeficiency Virus; nM: nanomolar; GPCRs: G-Protein Coupled Receptors; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; μM: micromolar; PCa: Prostate Cancer agents; CNS: Central Nervous System; ALS: Amyotrophic Lateral Sclerosis; CYP450: Cytochrome P450; DDIs: Drug-Drug Interactions

The desire to develop more effective treatment agents for complex disease states (Alzheimer's, Parkinson's, diabetes, cancer, etc.) seems to be pushing drug design towards the multi-target approach. This shift in drug design is partly driven by the success of combination (multi-drug cocktail, multicomponent) chemotherapy utilized in cancer and HIV. Just how much drug design, in general, has shifted from the traditional *mono-target* to a pluralistic *multi-target* paradigm is still an open question.

Chemotherapeutics history informs us that Paul Ehrlich, with his "*magic bullet*" concept, inspired the era of designing *target selective* drug molecules [1]. Since then, most drug research programs have emphasized designing molecules with activities at single receptors, that is, one drug targeting one receptor. Indeed, this approach has yielded drugs with remarkably high affinities (nanomolar or nM), however, achieving receptor selectivity continues to be a daunting task and has sometimes been likened to finding a needle in stacks of hay. Case in point, designing selective ligands for high homology G-protein coupled receptors (GPCRS). On the other hand, several arguments have emerged in support of the multi-target model. It has been established that the therapeutic utility of NSAIDs and tyrosine kinase inhibitors (Imatinib, Sunitinib, etc.), for example, resides in their multi-target spectra of activities [2,3]. On face value, multi-target drug discovery seems easier to attain but the challenge lies in obtaining molecules with appropriate affinities at select multiple receptors. To that end, others have argued that low affinity (micromolar or μM) or transient activities suffice for these agents due to their multi-pronged attack on disease biology [4]. To be clear, although I am arguing for a serious consideration of multi-targetdesign, I am not advocating for the abandonment of the *mono-target* model. My intention is to promote the "*multi-target*" design concept through the OMICS Drug Designing Journal Open Access readership, and expose burgeoning drug discovery researchers to the idea. The hope is that more researchers can begin to incorporate this design paradigm in their future drug discovery efforts. Another way of looking at this topic is that instead of *magic bullets*, the multi-target approach can be likened to bullets with *cluster activity*. To this extent, I opine that equal or more energy and resources need to be spent towards the discovery/development of pharmacotherapeutic agents which are multi-target selective by nature or by design.

Ever since I read Espinoza-Fonseca's article describing *promiscuous drugs* (single drug molecules capable of selectively interacting with multiple receptors involved in the pathology of a given disease), my interest in multi-target agents has grown and continues to be nurtured by more sources than I can list herein [5]. Zimmermann et al. [6] point to the use of multi-component drugs in cancer, type 2 diabetes and infectious diseases, as evidence for the need and utility of multi-target drug design. Other researchers have applied this concept and designed ta-

crine-based dimeric ligands as potential anti-Alzheimer's agents targeting cholinesterases and β-amyloid aggregation or utilized the fragment-based approach in their drug discovery efforts for single anti-Prostate cancer agents (anti-PCa) with activities against several key prostate cancer cell lines [7,8]. Wong et al. [9] actually provides a list of recent treatment agents for schizophrenia and mood whose mechanisms of action involve interactions with several CNS receptors. Hopkins [10] has even touted the idea of targeting network biology structure (pathways and interactions) as a way to design effective multi-target agents, while Csermerly et al. [11] observed that drugs with multiple targets may have a better opportunity to influence the complex equilibria of cellular networks than the single target drugs. Essentially, proponents of multi-target drug design have argued that a number of multi-factorial diseases including neurodegenerative conditions (Alzheimer's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis (ALS)), Psychiatric Disorders, Cancer, Diabetes, and HIV can significantly benefit from multi-target selective agents. However, for this approach to be successful more comprehensive tools (e.g., computer models, validated biological targets, *in vitro/in vivo* assays) for evaluating such agents need to be developed. Not to belabor the point, but below are a few of the additional notable points regarding the utility of *single molecule multi-target* drugs:

1) Often, single target agents do not intervene sufficiently in the complex biochemical processes, including back-up or feedback mechanisms, involved in disease pathology

2) Single multi-target or multi-functional molecules could effectively replace combination drug therapy which leads to heightened side effect profiles

3) Pharmacokinetic and metabolism related toxicity issues, arising from multiple drug intake, are minimized when single multi-target agents are employed

4) Compliance is enhanced because patients only have to remember to take a single drug to treat a particular disease

5) Single multi-target drugs can be tailored to affect the key disease targets or pathways in order to minimize drug resistance

6) Chemical or drug metabolism (CYP450 enzyme induction/inhibition) related drug-drug interactions (DDIs) are avoided with single multi-target drugs

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In conclusion, a definite shift in drug design paradigms has not occurred yet; rather a mix of both approaches to drug design is going on with a higher proportion still emphasizing the former of the two design methods. I am convinced, however, that as the need for disease modifying agents grows, and as knowledge base expands regarding network biology and key contributory factors in diseases with complex pathologies, the multi-target design model will prove to be the more effective approach. Already, the success of antipsychotics with selective cross receptor activities, mood stabilizers, and some anti-cancer agents is being attributed to the multi-target activities of these drugs. I endeavor to suggest that researchers who have accumulated libraries of compounds which do not meet the traditional mono-target activity paradigm should re-visit the activity profiles of their compounds. Re-evaluation of these libraries might afford new potential drugs with utility in multi-factorial diseases.

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