Reverse Pharmacology: Fast Track Path of Drug Discovery

Mini Review

Volume 4 Issue 3 - 2016

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Received: May 20, 2016 | **Published:** May 24, 2016

Introduction

Reverse Pharmacology (RP) is a science of integrating documented experiential hits, into leads by transdisciplinary exploratory studies and further developing into drug candidates by experimental research. RP enhances the connection, communication and collaboration between modern sciences and technology with traditional medicine and modern biomedicine. Classical drug discovery process is an expensive and time consuming process, whereas RP is an economical, time sparring and has least bottlenecks. It also allows understanding the mechanisms of drug action at multiple levels and helps in optimizing the safety, efficacy and acceptability of the leads from the natural products. RP utilizes traditional knowledge of medicines to discover drugs and is also called as a path of pharmacology from the bedside to bench experiments.

Every day, potential new medicines are being researched and developed in various parts of the world. The identification of these potential new drugs is done through a vigorous process known as the drug discovery process. The drug discovery process can be divided into two opposing approaches, which are the classical pharmacology and the reverse pharmacology (Figure 1).

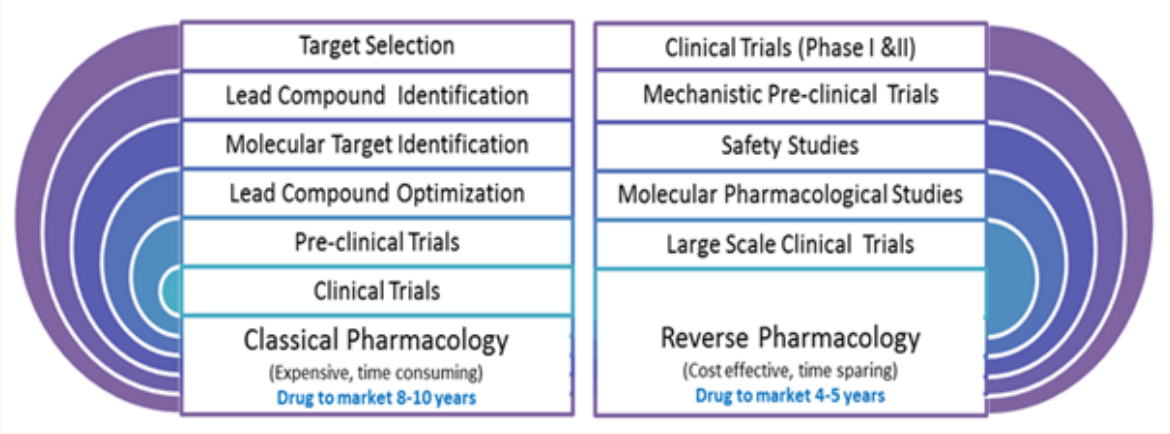

Figure 1: Differences in pathways of classical and reverse pharmacology.

For years, drugs (synthetic or naturally-derived) were discovered using the forward approach, thus it is also known as the classical approach. Forward pharmacology (phenotypic-based screening) involves first identifying the functional (phenotype) activity of a compound through cellular or animal models [1]. Once knowing the physiological affect of the certain compound, only then the compound's ligand and its derivatives are identified, purified and synthesized respectively and their binding capabilities with a target receptor are determined through biological assays/screenings. The most potent and selective ligand was identified as the new possible drug and further research is done with this ligand. The mechanism of action, selectivity for specific tissue receptor and dose-response of the ligand are then determined through pre-clinical studies, *in vitro*-ly and *in vivo*-ly [2,3]. The aim of forward pharmacology is to enhance the desired physiological effect of a compound [4]. Researchers would already have some knowledge on the desired physiological effect, duration of action, safety and the metabolism of the compound and thus, in order to enhance the efficiency of the compound, the potent ligand is determined. However, since the mechanism of action and dose-response of the compound or the ligand are not accurately determined, potential secondary effects are not understood and therefore could be dangerous for human consumption [5]. The discovery of a new potential drug candidate from a compound is time consuming (about 5 years) and costly. Besides that, there are many diseases that cannot be accurately replicated in animal

models or *in vitro*-ly (low throughput) [1]. Thus a less costly and more efficient (about 2 years) drug discovery approach was proposed, the reverse pharmacology [2,5].

Reverse pharmacology (target-based screening) began with the growth of molecular biology and caused a paradigm shift in drug discovery worldwide [4]. It starts with the identification of a molecular target (protein; enzyme, receptor, etc.) that is involved in the pathophysiology of a disorder or disease through genomic, proteomic and metabolomics studies [3,4,7]. Then potential ligands (compounds) are screened through binding assay where the highly selective ligand that binds with the molecular target is identified. This is a process known as 'ligand fishing' [2]. Then this potential ligand (compound) undergoes functional studies (animal models) to significantly show the desired physiological effect [2,6]. Once experimental results are consistently significant, clinical studies can began. Nevertheless, thorough understanding of the molecular target and its compatible ligand is of great importance in the midst of discovering a potential drug through reverse pharmacology as this will speed up the process, provide clear understanding of the mechanism of action, optimize safety as well as increase efficiency (highly selective and potent) of the drug [4].

Nowadays, the discovery of drugs through natural products heavily involves the utilization of reverse pharmacology [5,6]. Natural products are screened against receptors/targets of known physiological function in order to determine their functional activity. Natural products screening begins with re-examination of ancient/classic Ayurveda remedies that have been stated to cause the desired physiological effect but have not been proven or scientifically tested [7].

Thus, these herbs used in these remedies are screened against the target molecules that are known to play a role in the physiological effect, in order to understand their effect and improve their efficacy. Therefore, natural products undergoing reverse pharmacology start with humans and ends with humans, which validate their safety, improve their function and saves time and cost.

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Citation: Arulsamy A, Kumari Y, Shaikh MF (2016) Reverse Pharmacology: Fast Track Path of Drug Discovery. Pharm Pharmacol Int J 4(3): 00077. DOI: 10.15406/ppij.2016.04.00077