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EC PHARMACOLOGY AND TOXICOLOGY
Mini Review

An Opportunity in the Realm of Off-Target Effects

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Received: December 05, 2017; **Published:** January 02, 2018

Abstract

The increasing cost of drug discovery and drug resistance are the major issues limiting the clinical uses of drugs. Drug toxicity is another limiting factor for many drugs including chemotherapeutic molecule. Many major drugs have become prone to drug resistance in last decade. While drug affordability has become major topic of debate in recent years. Traditional drug discovery has limited success in counteracting aforementioned giants. Hence, this review has tried to focus on alternative approach that can help to overcome these problems and reduce the cost of drug discovery. Majority of drugs facing resistance act against single target in the target cell/organism. The careful selection of targets other than the main target may help in minimizing the undesired off-target effects while selectively choosing the off-target effects that can be beneficial in clinic. This review will discuss the applicability of this strategy along with major scope. We will also discuss the clinical issues that can be tackled using such a drug-discovery strategy along with the economic benefits of this approach.

Keywords: *Drug-Discovery; Drug-Resistance; Chemotherapy; Drug-Design; Toxicity*

Introduction

Unraveling the molecular mechanism of pathogenesis and targeting those mechanisms by various strategies is the ultimate aim of every pharmacologist. Every pharmacologist dreams to find a panacea that can help to eradicate the diseases and prolong the human life. However, in the quest for finding the wonder drug, the question always remains the same for pharmacologist i.e. what should be the target and what should be the targeting strategy?

It is evident from the decades of the pharmacological research that every disease is an effect of several unique molecular signaling pathways that work in collaboration to produce the pathological condition. Few of these signaling pathways are more important for the pathogenesis compared to others. The best way to target a disease is by targeting the most important molecular signaling pathway underlying the disease. However, many of the intracellular signaling pathways play multiple different roles in the multicellular organism depending on the cells/organ types and the developmental stage where the signaling molecules are expressed. For example, the cell-surface glycoprotein CD56 plays an essential role in the development of normal kidney as well as Wilms tumor [1]. In other example, the peroxiredoxin is a group of proteins that play an oncogenic role in variety of cancer whereas the same proteins play a protective role against the cardiovascular and neurological disorders [2]. There is plethora of similar examples where a particular signaling pathway plays essential roles in multiple pathological as well as physiological conditions. Also, the related members of same family of signaling proteins tend to have similar structures leading to the chances of non-specific interaction. However, minor differences in structure can sometime have substantive effect on the cell signal transduction and/or the targeting strategy. For example, lung cancer patients with a mutated (L858R) form of EGFR (epidermal growth factor receptor) has better response to the Icotinib (i.e. EGFR-tyrosine kinase inhibitor) treatment compared to patients with wildtype EGFR [3]. Considering the complexity of cell signaling cross talk and the effect of minor

molecular variations on the drug-target interactions, the pharmacologists spend a substantial amount of time ensuring the selectivity and specificity of the targeting strategy.

There are millions of molecules synthesized for testing their therapeutic potential. However, only few thousands of those molecules are safe/non-toxic enough for the exploration of their therapeutic uses. Every change in structure of the molecules directly or indirectly affects the pharmacokinetics of the molecule. The pharmacokinetics has led to the failure of thousands of molecule in human testing. Just increasing the number of molecules in a drug discovery pipeline does not lead to increased success in the clinics [4].

Off-target effect is any effect produced by a drug molecule due to its interaction with any physiological pathway other than the one which is desired target of drug action in particular therapeutic regimen. Thousands of molecules are scrapped during pre-clinical studies due to their off-target effects. Researchers always try to maximize the specificity of drug molecule for some specific target that often times leads to compromise with the efficacy of drugs. However, when it comes to curing a disease, carefully controlled off target effects may not be all that bad. There have been several instances when a drug or molecule under research is considered for their clinical utility against second indication other than the one for which it was primarily developed. The table 1 has enlisted few examples of such drugs. However, the list is not exhaustive and there could be several other drugs that fit this example. Sometimes it can be a common/related mechanisms involved in two different diseases. Cyclooxygenase-2 (COX-2) inhibitors are best example in this group as they were initially discovered for use in inflammatory conditions and pain leading to clinical uses further leading to their utility in variety of cancer and testing in neurological disorders like Parkinson's disease [5,6]. However, clinical utility through independent mechanisms and a second target is found to be useful too as in the case of R-enantiomers of few non-steroidal anti-inflammatory drugs (NSAIDs) [7]. Hence, in aforementioned cases, off-target effects brought more revenue for pharmaceutical firms and provided a future direction of research to drug-discovery researchers. This review will cover few more examples where second use of drugs were clinically meaningful. Furthermore, this review will discuss how the off-target effects can help in making discoveries of second use of existing clinically approved molecules.

S. No.	Name of Drug	First approved use	Other Explored Indications
1	Metformin	Diabetes	(i) Obesity (ii) Polycystic ovary syndrome (iii) Atherosclerosis (iv) Cardio-protective (v) Limited cases of female infertility (vi) Cancer (vii) Aging
2	Aspirin	Fever	(i) Pain (ii) Inflammatory conditions (iii) Prevention of stroke (iv) Prevention of heart attack (v) Cancer (vi) Neurodegenerative diseases e.g. Alzheimer's Disease, Parkinson's disease etc.
3	Clonazepam	Epilepsy	(i) Restless Leg Syndrome (ii) Rapid Eye Movement Sleep Behavior Disorder (iii) Dyskinesia (iv) Tardive Dystonia (v) Orthostatic Tremor (vi) Orofacial pain (vii) Burning mouth syndrome
4	Celecoxib	Arthritis	(i) Cancer prevention (ii) Depressive disorder (iii) Neurodegenerative diseases e.g. Alzheimer's Disease, and Parkinson's disease
5	Botulinum Toxin	Strabismus	Cosmetic uses, Migraine, Muscle spasticity in different regions of body
6	Tranexamic Acid	Hemorrhage from wounds in soldiers	Excessive postpartum hemorrhage
7	Minocycline	Infectious diseases (Broad Spectrum Antibiotic)	Depression
8	IVIG	Autoimmune idiopathic Thrombocytopenic purpura	Used as immunomodulatory in variety of autoimmune disease, idiopathic disease, and infectious diseases
9	Actinomycin D	Infectious diseases (Antibiotic)	Cancer

Table 1: *List of drugs with first approved use and other clinical applications.*

Examples of drugs approved for second pathology

Metformin

Metformin is listed as an essential medicine in World Health Organization (WHO) model list of essential medicines 2015. It is also the most commonly prescribed anti-diabetic drug for the treatment of type-2 diabetes [8]. It was first tested in human diabetic patients by a French physician scientist, Jean Sterne in 1950s. Metformin also has corrective effect in prediabetes as the patients with prediabetes who received metformin have lower chances of developing the diabetes [9,10]. However, it could not be confirmed whether the corrective effect of metformin in prediabetes is a true preventive effect or just a treatment effect [11].

Apart from its use in prediabetes and diabetes, a recent clinical trial led to the conclusion that the metformin can have a protective effect against coronary atherosclerosis in men, but not women [12]. The metformin is approved for its use in polycystic ovarian syndrome among the women with higher body mass index [13]. The metformin is also recommended for treatment of female infertility [14]. However, the experts dissent about the exact mechanism behind the ovulation inducing mechanism of metformin. Few experts consider insulin-sensitizing activity while others consider reduction in the circulating androgens as an underlying mechanism behind the utility of metformin in female infertility treatments [15].

In addition to approved clinical uses of metformin, there is recent evidences indicating that the metformin can be useful therapeutic tool in few other pathological conditions. For example, Ma A., *et al*. (2017) reported that the metformin-induced AMPK activation results in a protective action against atherosclerosis [16]. Also, there is some conclusive evidence indicating that the metformin can reduce the potential weight gain in variety of subjects including (but not limited to) type 1 diabetes patients, and patient undergoing antipsychotic therapy (i.e. antipsychotic drug-induced weight gain) [17,18]. In future, we may foresee the clinical utility of metformin in the treatment of cancer, diabetic organopathies, and aging [19-21].

Aspirin

Aspirin (Chemical name: Acetylsalicylic acid) is listed as an essential medicine in World Health Organization (WHO) model list of essential medicines 2015. It was launched by Bayer (a healthcare company) in 1899 and has survived the market fluctuations and competitor medicines for more than a century. Nonetheless, the clinical uses of aspirin have increased to a level where majority of layman know the name of this medicine and it has become the most commonly used medication worldwide [22]. Within 3 years of its market launch, the researchers started to look for its alternative uses in other pathological conditions [23].

Aspirin was first discovered as an antipyretic alternative of salicylic acid but soon gained popularity as analgesic and anti-inflammatory drug [24,25] partly due to the similar uses of its natural counterpart (i.e. Willow bark extract and salicylic acid) in past centuries. Aspirin also has anti-platelet activity that increases the risk of internal bleeding in patients [26]. The anti-platelet activity of aspirin is now utilized by clinicians as a stroke prevention strategy in the patients who has higher risk of stroke and heart diseases [27,28]. It is a perfect example of an off-target effect leading to the second use of drug.

Apart from accepted clinical uses, current ongoing research worldwide has indicated its potential uses in conditions where inflammatory markers can play a role in the pathogenesis. For example, aspirin is reported to produce beneficial effects on population by reducing the cancer incidents and increasing the cancer survival [29]. In another example, aspirin is demonstrated to have a preventive effect on the development of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [30]. Aspirin is also being further explored for its uses in variety of other inflammatory conditions not covered in this section.

Clonazepam

Clonazepam is a benzodiazepine that was originally developed in 1960s and first marketed in 1970s as a antiepileptic agent [31]. Due to its central inhibitory potential, the clonazepam was studied for its effectiveness to treat the trigeminal neuralgia [32]. It is still considered an effective treatment for orofacial pain, burning mouth syndrome and other neurological pain [33-35]. Within 5 years of its market launch, it was also found to be effective for the treatment of drug-induced dyskinesia leading to continued uses in treatment of tardive dyskinesia [36,37]. The list is not exhaustive as its potential is continued to be explored in various neurological conditions.

Discussion and Conclusion

Considering the immense opportunity in the realm of the off-target effects, it can be applied to multiple fields of drug discovery. For example, off-target effects can be explored (1) to reduce the chances of drug resistance; or (2) to identify an alternative use of already clinical approved molecules; or (3) to use a toxic molecule as a treatment in a high-risk disease where the benefit of using otherwise toxic molecule, still outweighs the risk associated with the use of that molecule.

Drug resistance is a giant that limits the clinical uses of many highly potent drugs of last generation. Chemotherapeutic drugs and antibiotics are best examples of drug classes that have faced highest development of drug resistance. Treatment with single chemotherapeutic molecule generally results in survival of few cells resistant to that molecule. These resistant cells survive the chemotherapy and come back with a greater vengeance that is normally more dangerous to patients compared to the original disease. So is true for few infectious diseases. The repeated exposure to anti-infectious agents leads to selection of drug resistant phenotype in microorganisms. These strains of microorganisms prove to be much more deadly than non-resistant strains. Majority of drugs are designed to target a macromolecule or macromolecular complex in target cells. These target cells can be microorganisms in case of infectious diseases or a tumor cell in case of wide varieties of cancer.

Considering the risk associated with chemotherapy resistant tumor cells and increasing incidences of antibiotic resistant microbial species, the combination therapy becomes the best shot in the hands of physician. The basic idea behind drug combinations is to target the risk causing cells by multiple weapons so that even if one cell is resistant to one weapon, that may still be susceptible to other. If targeting

multiple sites is so effective to minimize the chances of multi-drug resistance, why not to target two or more target sites using a single molecule? The utility of targeting multiple targets with single molecule is already being tested in cancer as well as infectious conditions [38,39]. However, wider use of this strategy may help to expedite the healing in several pathological conditions. Using single molecule to target two or more target sites have several advantages that are enlisted in next paragraph.

Firstly, if we carefully design/select molecules that has two or more desirable target sites in tumor cells or infectious agents, it will reduce the chances of drug resistance as probability of having mutations together in two or more target sites leading to drug resistance is much lower than the probability of mutation in single target leading to drug resistance. Secondly, the chances of success in drug-discovery process may increase as researchers will not have to look for highly specific molecules. Rather the molecules having selective inhibition or activation potential towards two target molecules may be streamlined for testing. Thirdly, it will help the researchers involved in *in-silico* drug-discovery to reduce the number of false positives selected for *in-vitro* testing. For example, chances of a molecule to be false positive to two different targets are way lower than chances of same molecule being false positive for one of those targets. In this way, even if molecule comes out to be a false positive against one target, there will always be some probability of molecule being actively able to modulate the activity of other desirable target leading to its *in-vitro* success that may further lead to development of a novel therapeutic strategy. Equipped with highly reliable modern *in-silico* drug-discovery tools, researchers can utilize this strategy to enhance the efficiency of research outcome [40]. Fourthly, carefully controlling two or more targets that add to efficacy may help to minimize off target effects due to interaction with other macromolecules in the cell. Considering sacrifice of laboratory animals in drug discovery, this approach may help to reduce the number of animal (pre-clinical) experiments that are performed for successful development of clinically important molecules. Financially, this strategy may help to bring better revenue for pharmaceutical industry and better utilization of resources by researchers (Figure 1). For example, this strategy can help to develop a clinically useful drug out of thousands of molecules that are scrapped by research community due to lack of specificity. It will be like bringing revenue out of something that has already been considered a useless data dump.

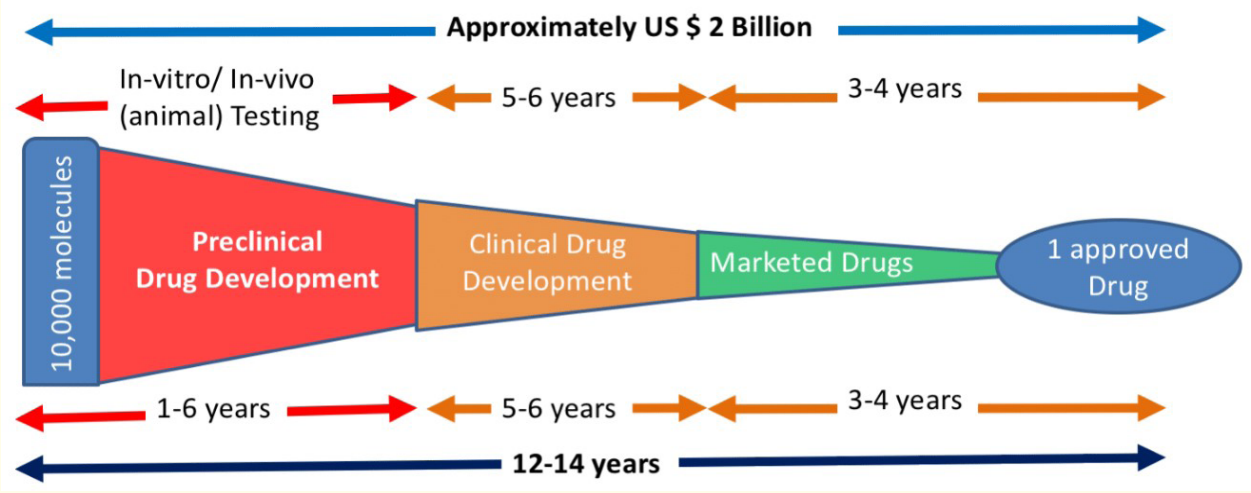

Figure 1: *A depiction of drug discovery process with estimated requirements of time and other resources.*

These strategies of dual targets need not to be limited to treatment of cancer or infectious diseases. This strategy need not to be limited to two different targets in a single pathological condition either. Rather, this strategy can be used to identify two different targets

in co-morbid conditions. In case of chemotherapy, it can also be used to reduce the resistance of a co-administered drug. For example, a chemotherapeutic molecule with moderate efficacy can still be useful if it can simultaneously block an efflux transporter responsible for drug resistance to another chemotherapeutic molecule. Alternatively, a moderately active cell proliferation inhibitor with low toxicity that can reduce the chances of metastasis or act as a chemosensitizer for other chemotherapeutic molecule will do wonder too. This strategy will result in reduction of required dosage of both chemotherapeutic molecules to an extent where toxicity can be substantially reduced.

In summary, targeting two or more sites using single molecule can be a very useful tool to minimize the probability of drug resistance. Single molecules targeting comorbid situations can also be a useful tool in the arsenal of physicians. Off-target effects will not be all that harmful if it is carefully picked during drug-discovery process. After decades of drug-discovery research that gave us many excellent drugs, we are watching many of them fail due to multi-drug resistant pathological conditions. We need a better strategy to avoid the failure of next generation of drugs. Molecules carefully designed against two or more targets will probably be the best bet for a secure future of next generation drug molecules.

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