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A Review On Poly Pharmacology; One Drug Multiple Targets

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Abstract

This review discusses the concept of polypharmacology in drug discovery and development. The relationship between polypharmacology and polypharmacy, drug repurposing, combination of drugs and in vivo testing are discussed. Modern applications of polypharmacology and polypharmacy in epigenetic and antiviral drug development are described as examples. A survey of modern methodologies to design and develop multiple-target ligands is presented with a special focus on computational-based methods. These approaches include, but are not limited to, target fishing, proteochemometric modeling, data mining of side effects of drugs, and computeraided drug repurposing.

Key words: biological space, chemogenomics, chemical space, drug repurposing, polypharmacology, polypharmacy

Introduction

Polypharmacology is defined as the design or use of pharmaceutical agents acting on multiple target.Polypharmacology is the concept that a molecule is designed to bind to two or more targets simultaneously such that the combined effect has a greater therapeutic outcome than binding to just one target. Unlike the conventional drug discovery paradigm of “one drug-one target”, polypharmacology is based on the idea of “one drug-multiple targets”, where a single drug is designed to act on multiple targets of a single

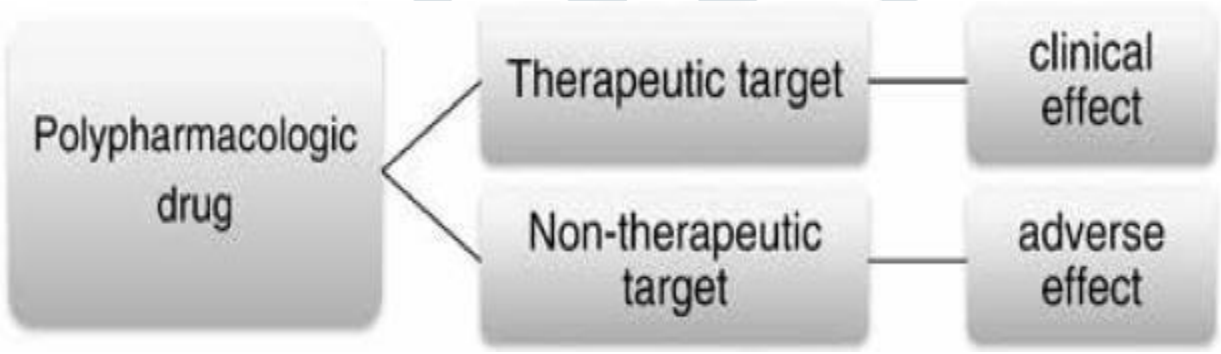
disease pathway or multiple targets involved in multiple diseases. Polypharmacology also refers to the ability of a molecule to inhibit targets that produces an effect which is opposite to that of the primary therapeutic target of the molecule, ultimately resulting in a more pronounced therapeutic effect.

Conventional research has typically aimed at designing highly specific molecules which exhibit little to no off-target interactions in an effort to minimize the molecule's adverse effects. This approach has found widespread success, especially with diseases which are simple and have a well-established mechanism. However, with diseases which are more complex and multi-factorial (e.g., cancer, central nervous system (CNS) disorders and infection) a single target approach is not as effective. For such diseases, a polypharmacologic drug can be much more useful since it targets multiple proteins and pathways involved in disease onset and development. Advances in medical research have unveiled the etiology of many diseases, as well as identified multiple etiological factors for many diseases, such as schizophrenia, asthma and heart disease. These factors all highlight the great need for polypharmacologic drugs, and recently there has been a steep rise in their development.

Multi-target vs. target-specific drugs

As discussed before, the increasing awareness of the large complexity of systems biology is shifting the paradigm in drug discovery from a single-target to a multi-target approach. Despite the fact that the latter approach is significantly more complicated than the one-drug – one-target strategy (largely influenced by a reductionist perspective of systems biology) it may lead to drugs that are more effective in the clinic. However, it has to be considered that multi-target drug design, and polypharmacology in general, highly depend on the dose to deliver an overall clinical benefit. For instance, a drug may have a positive effect at therapeutic doses because of the interaction with multiple targets. However, the interaction of the same compound with anti-targets at higher doses will lead to undesirable side effects. Thus, similar to the appropriate or inappropriate polypharmacy discussed by Aronson, polypharmacology can also lead to desirable or undesirable (e.g., unwanted promiscuity) multitarget drug interactions that will depend not only on the nature of the structures of the drugs and targets but also on the compound concentrations. The 'dual-face' of multi-target drugs is schematically illustrated in Figure 1.

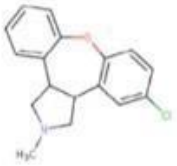
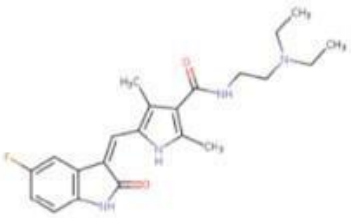
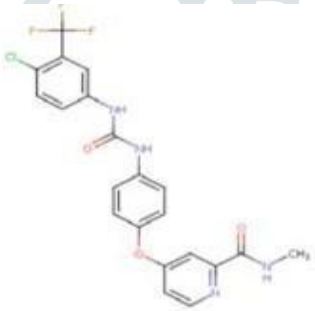
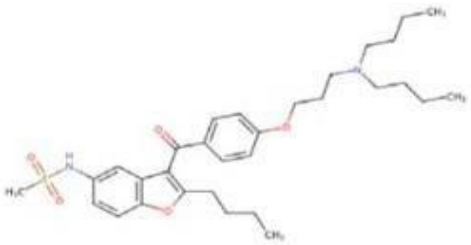
Figure 1. The 'dual-face of multi-target compounds and relationship with 'master key drugs



Master key compounds

A 'master key compound' (luckily 'master key drug') is a molecule that binds to a given number of targets that produce a desirable clinical effect without hitting (or with a minimum effect) offtargets that are related to undesirable, secondary effects [10]. In a simple analogy with a master key, a 'master key molecule' should have the ability to operate on a group/set of selected targets (doors) but not on any 'doors', in particular those anti-targets that lead to undesirable side effects. Table 1 illustrates examples of master key drugs that are used in the market. The table summarizes the name, chemical structure, clinical use and the associated molecular target receptors

Table 1 Examples of master key drugs approved for clinical use. The name and targets are indicated

Name	Structure	Clinical use	Associated receptors
Asenapine Schering- Plough (2009)		Antipsychotic	$D_1 - D_4$ dopaminergic, 5-HT1A, 5-HT1B, 5-HT2A-C, 5-HT5A, 5-HT6, 5-HT7 serotoninergic, $\alpha 1$, $\alpha 2$A-C adrenergic, and H_1, H_2 histaminic
Sunitinib Pfizer (2006)		Anti-cancer	VEGFR, PDFGR, c-Kit, Flt-3, RET, colony stimulating factor 1 receptor (CSF-1R)
Sorafenib Bayer (2005)		Anti-cancer	B-Raf, VEGFR, PDGFR, c-Kit, Fms-like tyrosine kinase 3 (Flt-3), RET
Dronedarone Sanofi-Aventis (2009)		Anti-arrhythmic	Sodium, calcium and potassium channels, α_1, β_1 adrenergic

Safetypels

Many of the adverse drug reactions (ADRs) are caused by unintentional interaction of a drug with a non-therapeutic target to which is given the name “antitarget”. The most frequently found antitargets are already well studied and characterized. Examples of these receptors are shown in Table 2.

Table 2 Major antitarget receptors

Antitarget receptor	Hit rate	Adverse Drug Reaction
hERG channel	-	Arrhythmia
Serotonin 5-HT_{2B}	14	Valvulopathy, pulmonary hypertension
Serotonin 5-HT_{2A}	11	Cognition impairment, hallucination
α_{1A} adrenergic	10	Arrhythmia, orthostatic hypotension
dopamine D_2	9	Confusion, emesis, orthostatic hypotension
histamine H_1	6	Weight gain, sedation, somnolence
α_{2A} adrenergic	6	Hypotension, sedation
dopamine D_1	5	Dyskinesia, tremor
M_{1-5} muscarinic	5	Multiple cardiovascular and metabolic adverse effects, cognition impairment
μ-opioid	3	Sedation, respiratory depression, abuse potential

Antitargets – the mines to avoid :

In order to be polypharmacologic, a molecule needs to possess all the structural features required for it to act on multiple targets. The ability of a molecule to bind to multiple proteins within a disease pathway is called "promiscuity". It is the intrinsic property which makes a molecule polypharmacologic. Despite promiscuity being closely associated with polypharmacology, the term often has a negative connotation to it, implying it binds to off-targets resulting in adverse effects.

Polypharmacology and related concepts In drug discovery

The interaction of a compound with multiple targets is at the Core of several major concepts in current drug discovery [10]. Herein we further elaborate on these relationships.

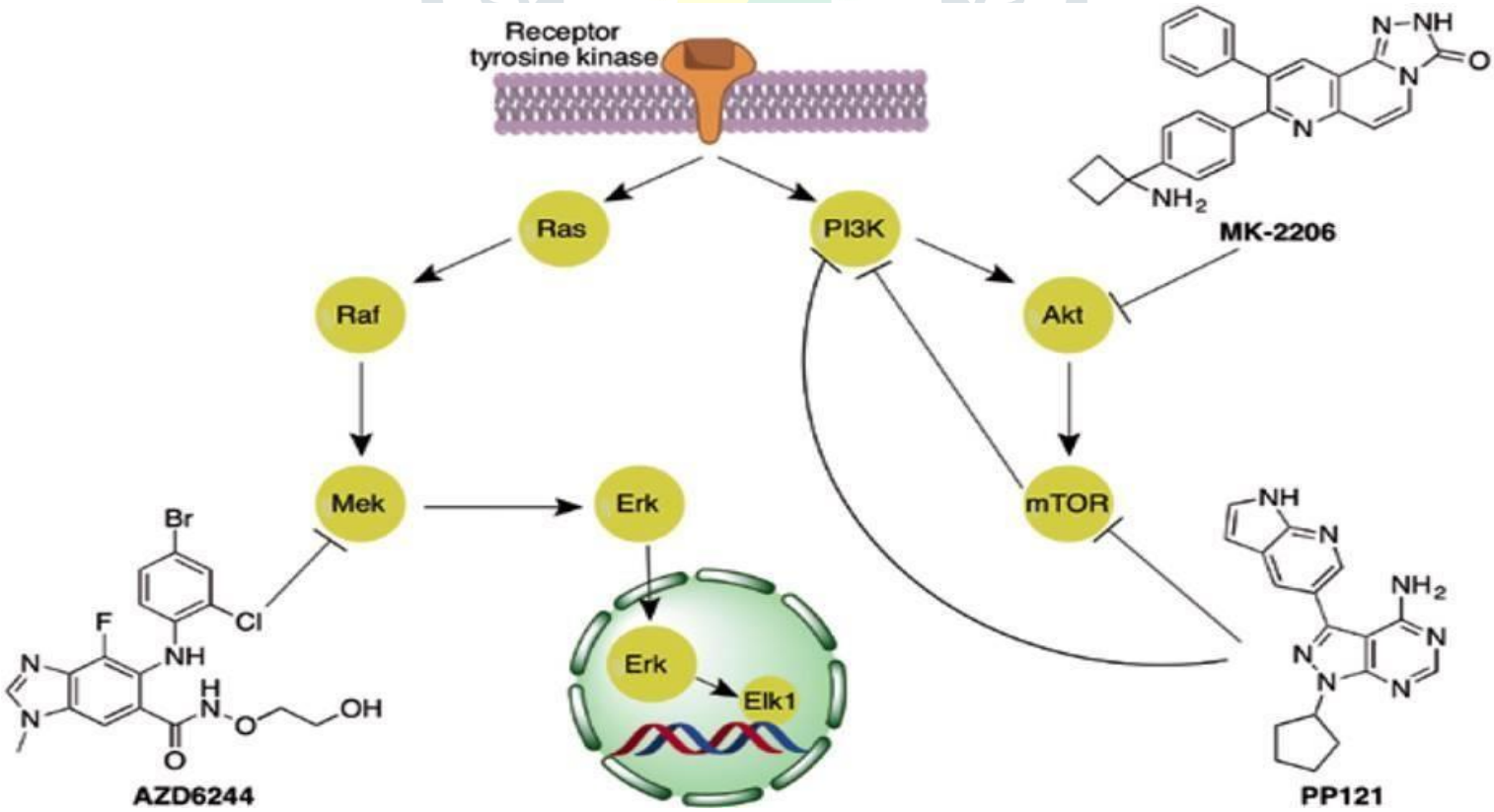


Figure 2 Examples of the use of polypharmacology against kinases. Compounds AZD6244 and

MK-2206 have been used in combination to inhibit the MAPK and PI3K pathways to obtain an enhanced phenotypic effect. Compound PP121 inhibits both PI3K and mTOR simultaneously. This dual inhibition has been proposed to be more potent than inhibiting either target individually. The rationale behind this idea is that mTOR activates a negative feedback loop that inhibits PI3K. The inhibition of mTOR alone results in the blockage of the negative feedback loop and in a hyperactivation of PI3K.

DRUG REPURPOSING

An important implication of polypharmacology is drug repur-Posing, which seeks to discover new clinical application of existing Drugs used in the treatment of a given pathology. The al-Ready approved drugs are more probably to be repurposed for other Neglected and rare diseases, thus extending the chemical libraries Other than known drug. The major advantage of drug repurpos-Ing approach is that the pharmacology and toxicity profiles of drugs Are already well known in the preclinical and Phase I studies. Thus, These drugs could be rapidly translated into Phase II and III clinical Studies and the associated cost could be significantly reduced. Furthermore, the medical companies are attracted by drug repurpos-Ing with respect to efficacy (e.g. for the novel indication), and Sometimes for safety as well (e.g. when doses higher than the ap-Proved ones are needed). Therefore, the interest in drug repurPosing seeks to balance both profit and the service drive, which Could save time and economical cost in the drug discovery process. Currently, drugs for repurposing today would involve in a new use Obtained in and beyond clinical trials. For example, two nonsteroi-Dal anti-inflammatory drugs (NSAIDs), the ®-enantiomers of Naproxen and ketorolac have exerted specificity for inhibit-Ing Rho family GTPases, in particular Rac and Cdc42. These two Drugs are potential candidates as adjuvant therapy to prevent ovar-Ian tumor growth and dissemination during postsurgical recovery. Wang et al. analyzed 61 approved drugs targeting on 16 can-Cer genes from the Therapeutic Target Database (TTD), inferring 11 approved drugs that are not relevant to cancer may be reposi-Tioned as anticancer drugs by combining the medical genetic infor-Mation of the targets. These drugs was listed in Table 1. Among them, dienestrol and estradiol , two estrogen receptor Alpha (ESR1) agonists, have been clinically used to treat atrophic Vaginitis and serve as hormone replacement, respectively. Indeed, The breast cancer-inducing property of dienestrol and estradiol were
Recorded in Drugs.com and the anti-Breast cancer activity of danazand raloxifene have been Validated by experiments In addition, several Molecules related to drug repurposing are available in Table 2 by US National Institutes of Health (NIH) on April 21 2011 with Pharmaceutical industry leadership. These drugs have been proven Safe in clinical trials [55-58]. For example, raltegravir is HIV-1 Integrase inhibitor approved by the FDA in 2006, Rob Hromas, MD (UNMCC) and clinical scientists at UNM identified it as a potential Drug for adjuvant therapy in cancer Phenothiazines used to Bind to versatile targets and exhibit several desirable therapeutic Effect. Phenothiazine derivatives have been used as antimalarials (late 19^{th} century), antihelminthics (mid-20^{th} century), antihista-Minics (1940s), sedatives, and antipsychotics (1950s). Nowadays, Scientists suggest that Phenothiazines and their derivatives are po-Tential drugs for the treatment of Parkinson's and Alzheimer's dis-Eases, and as antibacterial and antifungal compounds . How-Ever, these drugs targeted novel proteins are currently under inves-Tigation to determine the mechanism of action. Besides, how to Discern the various functions of already approved drugs and target Profiles is an unsolved problem. Recent developments have opened the door to using drug re-Purposing approaches that rely on both empirical data and computa-Tional models. The inverse genomic signature approach is based on The premise that an effective drug targets on a gene expression pro-File that is inversely correlated to the host signature associated with The disease. The approach integrates the complexity of the genome-Wide response of the host to both the disease and the treatment, it is Rooted in scalar theory. Importantly, there has already been Successful application for several disease indications. On the Basis of the approach, a public database Connectivity Map that covers over 6000 transcriptome profiles established downstream of treatment of Human cell lines with over 1300 compounds. Then, Lamb et al. Modified the computational approach, and they used it to compare a Profile of 164 known drug compounds in cMap to an inflammatory Bowel disease (IBD) specific gene expression signature derived From 176 datasets available in Gene Expression Omnibus (GEO).

Combination of Drugs

Combinations of drugs are clinically relevant for treating a variety of chronic medical conditions, such as infectious, metabolic, malignant, or neurological diseases. A clear example is the highly active antiretroviral therapy (HAART) used for the treatment of patients infected with the human immunodeficiency virus (HIV). Combinations of drugs could be used to prevent or attack resistance to single agents and to improve the clinical effect of the treatment. However, this approach often end with polypharmacy (the intake of five or more drugs), a well-described clinical =]condition that can lead to increased risks and adverse effects from medications, especially in the elderly or patients with multiple chronic diseases. In the scientific literature, it is generally conceived that the development of polypharmacological agents is the next logical step once it is known that a single chemical compound may affect multiple biological targets (e.g., adverse or off-target effects) and that combinations of drugs that act on different targets might have additive or synergic effects against a disease. Polypharmacology is believed to be a promising feature of drugs that could replace combined drug therapies and thus avoid polypharmacy.Nonetheless, there is K,Ianother point of view in which drug combinations are included within polypharmacology approaches following the multitarget paradigm while still recognizing the advantages of multitarget single agents. A third approach was developed recently by Gujral et al. after this group identified kinases involved in cellular migration that are specific for cell type.To accomplish this, they tested polypharmacological kinase inhibitors. Their proposal is to exploit polypharmacology of chemical probes to aid in the rational design of more potent and specific drug combinations. This last approach is supported by the finding that combination therapies acting synergistically are also more specific in their pharmacological actions when administrated in combination than as single agent's. Hence, combination of drugs and polypharmacology does not necessarily imply more severe adverse effects when there is a synergic effect, provided that selectivity is increased in these cases.Finally, the combination of drugs may be used for preventing adverse effects or severe risks of certain drugs used in monotherapy. For example, Zhao et al.discovered that coadministration of exenatide substantially reduces the myocar-dial infarction risk found in diabetic patients treated with rosiglitazone alone.Both exenatide and rosiglitazone are indicated for the treatment of diabetes Mel-litus type 2 and they act on different targ.

In Vivo Testing :

Several drugs have been identified following an in vivo screening or natural product mixtures or mixtures of individual compounds. In vivo testing is a drug discovery approach that distances itself from the "classical" one-target screening. It has been recognized that in vivo screening offers the advantage of an early. Demonstration that compounds may show activity in diseaserelevant models. Before proceeding with further development. Moreover, despite the limitations. 8

Polypharmacology (and Polypharmacy):

Case Studies:

In this section, we discuss briefly selected applications of polypharmacology and polypharmacy for the treatment of diseases associated with epigenetic alterations and antiviral infections caused by HIV, respectively. Both types of diseases are different in nature, but both are very complex and represent major challenges to design effective therapeutic treatment

Polypharmacology in Epigenetics

For diseases with a complex metabolic substrate, such as diabetes, cancer, and autoimmune and neurodegenerative disorders, it becomes increasingly evident that aiming to a single pharmacological target would not be an appropriate strategy. It has been shown to a variable extent for each of the aforementioned diseases that epgenetics (inheritable traits that are not encoded within the genome, e.g., DNA methylation and histone modifications) plays an important role in the establishment and maintenance of the disease. Epigeneticb mechanisms are extremely complex, and not yet totally understood, which makes quite difficult to design therapies directed against them. However, epigenetic drugs are appearing in the clinical scenario,

mostly for the treatment of malignant or premalignant states, with favorable results. More-over, there is a current trend for shifting toward epi-polypharmacology drugs against either more than one epigenetic target or combined epigenetic and other targets. Notably, many different epigenetic biological targets share a reduced number of cofactors (e.g., Zn+2, NAD+, SAM), and thus it is feasible to guide the design of cofactor inhibitors with polypharmacologic properties. Another approach is the design of hybrid molecules. This strategy has led to the development of pan-demethylase inhibitors by synthesis of hybrid molecules containing inhibitors of histone demethylases LSD1 and JmjC, thus generating compounds that increase H3K4 and H3K9 methylation levels and produce apoptosis selectively to cancer cell lines, with little effect on noncancer cells. In other cases, compounds that are likely to inhibit concise epigenetic targets show polypharmacology against other epigenetic targets. This was the case of the AMI-5 analogs synthesized by Mai et al. AMI-5 was described previously as a small molecule inhibitor of protein arginine and histone lysine

A)Cancer

Cancer is a complex, polygenic disease that activates multiple redundant signaling pathways, enabling tumors to evade single-target inhibitors. While combination chemotherapy is common, an alternative is to develop single agents that act on several oncogenic targets. Many modern anticancer drugs, such as sorafenib and sunitinib, are multi-kinase inhibitors that suppress tumor growth and delay resistance by blocking multiple pathways. Polypharmacology is especially advantageous in cancers driven by intricate networks (e.g., PI3K/Akt/mTOR), as multi-target agents can induce synthetic lethality and prevent compensatory mechanisms, resulting in more durable responses.

Notably, many FDA-approved cancer drugs display polypharmacology, reflecting a shift in oncology drug design toward targeting cancer's network biology.

B)Neurodegenerative Disorders

Neurodegenerative diseases like Alzheimer's (AD) and Parkinson's (PD) involve complex pathological processes, including β-amyloid accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and neurotransmitter deficits. Single-target therapies have largely failed in AD, prompting a shift toward multi-target strategies such as combination therapies and multi-target-directed ligands (MTDLs), which integrate activities like cholinesterase inhibition and antioxidant or anti-amyloid effects within one molecule. For example, the MTDL "memoquin" was designed to inhibit acetylcholinesterase and combat β-amyloid aggregation and oxidative damage, showing promise in preclinical studies.
Polypharmacology enables simultaneous modulation of multiple disease mechanisms and can also reduce medication burden and drug–drug interactions in elderly patients with multiple comorbidities. As a result, polypharmacology is increasingly viewed as essential for developing disease-modifying therapies for AD and related disorders, where single-target drugs have mostly offered only symptomatic relief.

C)Infectious Diseases

Antimicrobial resistance highlights the limitations of single-target therapies, as pathogens quickly develop resistance mutations under selective pressure. Polypharmacology addresses this by enabling the design of antibiotic hybrids—single molecules that attack multiple bacterial targets, such as combining a quinolone with a membrane disruptor, thus achieving synergistic effects and reducing resistance risk since bacteria would need simultaneous mutations in different pathways to survive. Similarly, multi-target antivirals can inhibit both viral and host factors needed for replication. While combination therapies are standard (e.g., HAART for HIV or multidrug TB regimens), single multi-target agents can simplify treatment and ensure coordinated delivery. Multi-action antimicrobials may also disrupt pathogenic processes like biofilm formation or virulence, although optimizing their pharmacodynamic and pharmacokinetic profiles remains challenging. Overall, polypharmacology is emerging as an essential strategy to combat complex infections in the post-antibiotic era, where single-target drugs increasingly fail.

Chemogenomics: Integrating chemical and target spaces

Ideally, polypharmacology can be fully explored if there was readily available information linking the relation between the entire chemical and target spaces. In the pursuit of this goal, chemogenomics has emerged as a research field that aims to identify all possible ligands for all possible targets. Chemogenomics and related concepts, reviewed here, are schematically illustrated in Figure 3

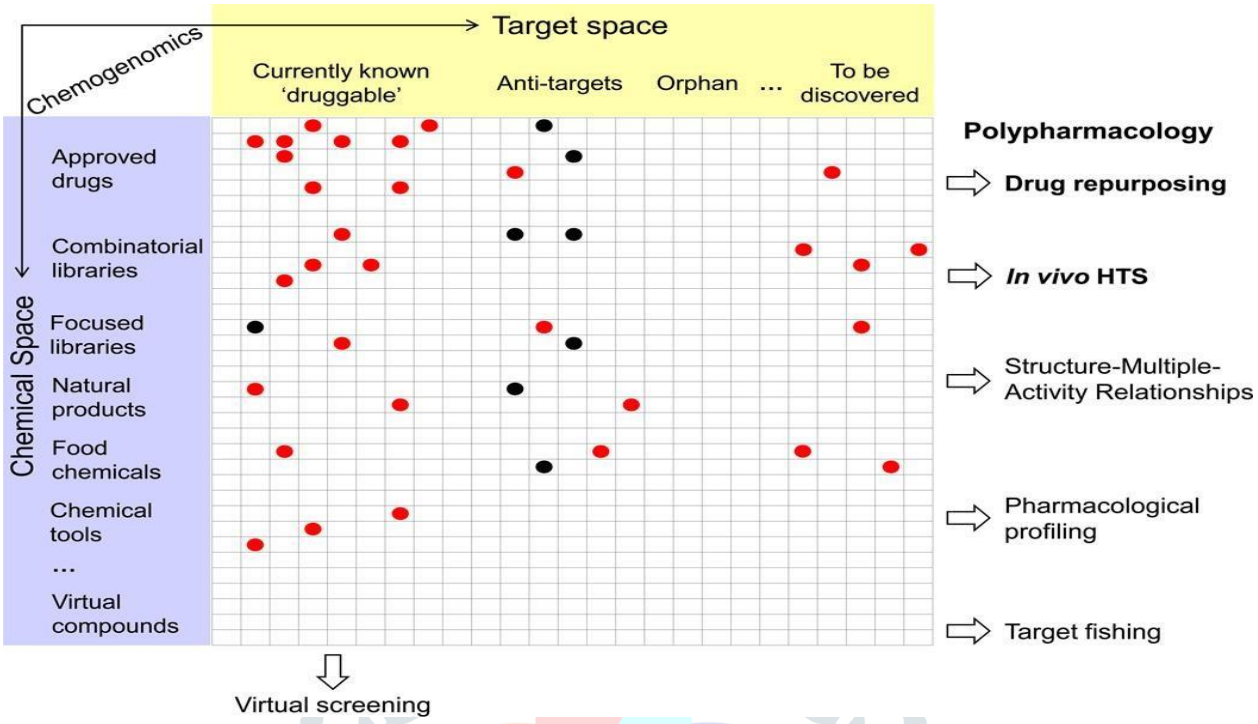


Figure 3. [LM2]Schematic representation of the relations between the concepts reviewed in this article. The table represents the association between all possible molecules in chemical space
(rows) (organized in different types of chemical library), and targets in the 'target space' (columns) (collected in different types of target). The red circles indicate that there exists a compound–target interaction, whereas the black circles denote that there is no interaction. Empty cells indicate that the intersecting compound–target interaction is not known. Abbreviation: HTS, high throughput screening.

Table 3.Representative chemogenomics data sets to explore polypharmacology.

Data set	Summary contents	Ref.
ChEMBL	Contains more than 13 million activity data points corresponding to 1,463,270 compounds against 10,774 targets.	[51, 52]
PubChem BioAssay	Contains more tan 130 million activity outcomes covering more than 5,000 protein targets.	[53]
Binding Database	Contains more than 1 million binding data for 7,302 protein targets and 495,498 small molecules.	[54]
MOAD	Collection of 25,771 high resolution crystal structures, 9141 of them with activity data.	[55, 56]
PDBbind	Binding data for 14,260 biomolecular complexes contained in the PDB. Noteworthy, 11,987 correspond to protein-ligand interactions.	[57]
EpiDBase	Focused to epigenetic targets. It contains 11,422 activity data corresponding to 5784 ligands against 220 epigenetic targets.	[58]
CMAP	More than 7,000 gene expression profiles of 1,309 compounds in different cell lines	[59]
LINCS L1000	Gene expression signatures of 22 412 unique perturbations (compounds and knockdowns)applied to 56 different cellular contexts including human primary cell lines and cancer cell lines	[60]

Proteochemometric Modeling

chemogenomics to identify protein-ligand interaction in all chemical spaces. Chemogenomics is also known as proteochemometrics.

This technique is basically a generalization of QSAR methods (Azencott et al., 2007). QSAR predicts interaction for a given protein, while chemogenomic models are capable of concurrently predicted interactions for several proteins (Jacob & Vert, 2008), with the fundamental idea that the prognosis of DTIs can be beneficial from knowing interactions between different targets and extra molecules present. Chemogenomics facilitates predictions of unexpected drugs' “off-targets,” and pilots the experiments to examine interactions predicted showing higher probability scores (Playe & Stoven, 2020). For example, the interaction between a GPCR and positive allosteric modulators for metabotropic glutamate receptor 5 (mGluR5), were searched using QSAR and neutral network sequencing. mGluR5 is involved in Parkinson’s disease and Schizophrenia (Mueller et al., 2010).
Chemogenomics starts with deep learning formulating a chemogenomic neural network (CNN), and taking input through molecular graphs and protein sequence encoders. These graphs and encoders are used for learning combinations of molecules and protein representation. The deep learning CNN model is preferable for large datasets. These are comparable with skilled/expert descriptors, whereas on small-scale datasets shallow methods perform finer prediction on small-scale datasets. Multiview and transfer learning data augmentation techniques are used to upgrade the execution of the CNN and also its prediction (Playe & Stoven, 2020).
Workflow in chemogenomics can be broadly divided into four parts: first, a molecular coder comes into use that comprehends abstract labels for molecules based on their structures .

Target fishing and ligand profiling

Despite the rich chemical databases available to date annotated with biological activity, current experimental data are not sufficient to fill in all possible relations between chemical and target spaces.Given that a considerably large and perhaps prohibitive investment of time and resources would be required to generate experimental data to cover all possible chemical–target associations, computational approaches are actively being pursued to identify either new ligands for known targets (computational or virtual screening) or putative targets for known ligands (target fishing). Computational approaches, such as docking, similarity searching and pharmacophore modeling, are a few examples of well-established virtual screening techniques that can be used to select compounds for further experimental investigation. Of course, despite several successful applications of virtual screening methods, these approaches are not free from pitfalls, and the improvement of computational screening methods is actively being pursued.Target fishing leads to the generation of the global pharmacological profile or ligand profiling. In addition, computational approaches are being developed to visualize and mine the SAR of chemogenomic data sets. Similar to virtual screening, the prediction of the polypharmacological profile of bioactive compounds can be performed based on the chemical structure of the bioactive compounds themselves (ligand-based methods) or on the structure of the targets (structure-based methods). Specific methodologies and successful applications of both approaches have been the subject of extensive reviews. More recently, computational and experimental approaches are emerging that investigate systematically potential additional targets of chemical probes used in chemical biology.

Data Mining of Side Effects and Interactions for Drug Repurposing

Drug repurposing through data mining has two principal premises: (i) there is vast information (e.g., clinical, phenotypical, and experimental) regarding the drugs that are intended to be repurposed, and (ii) the obtained information is sufficient to fit a statistical model to predict whether a compound would be active against another target or disease. Text similarity is a particularly developed tool in these settings. Through text similarity searching, the scientific literature can be mined, in order to link, often indirectly, drugs and diseases by association of terms. A clear example is data mining of adverse effects; this approach assumes that drugs with similar adverse (also called off-target) effects may be active against similar diseases. Within this pipeline, Campillos et al. developed a model for drug repurposing with efficiency rates higher than 50%. Notably,

comprehensive online databases have been developed to address the problem of disperse information about drugs; these resources are a result of scientific literature mining and contain complete references about different compounds.

Systems Pharmacology

Systems pharmacology has arisen as an emerging trend strongly connected to polypharmacology. The main similarity between these two lies in their fundamentals: both try to overcome the simplicity of the old-fashioned "one drug,one target" paradigm.Polypharmacology has often the connotation of "one drug,more than one target," implying both the possibility of drug repurposing and the feasibility of multitarget treatments with a sole drug, as we have explored throughout this chapter. However, systems pharmacology is a wider concept than polypharmacology, described by the phrase "one treatment, one network. "Therefore, the focus of systems pharmacology implies the rational design of therapies accounting for the overall cellular and physiological complexity, aiming for bio-logical networks rather than isolated targets. The two main strategies emerging from systems pharmacology are.

(i)those based on simulations in interaction networks validated in the scientific literature and

(ii) approaches exploiting high-throughput data such as expression or genetic microarrays.Both approaches aim to find a differential function of pathways in pathologic processes compared to healthy states and drugs that can reverse the pathogenic features. Therefore, the objective is to develop treatments that avoid the studied pathological phenotypes.

Summary Conclusions

To better understand and potentially predict polypharmacology, it is necessary to explore the intersection between the chemical and biological spaces. One approach to explore such intersection is through the emerging research field of chemogenomics. To date, there are chemogenomics data sets available to conduct drug repurposing, several in the public domain. A major challenge While working with these chemogenomic resources is that the data may be Incomplete. Also, the need to conduct curation of the chemical and biological. Information has been recently emphasized. A broad range of novel computational strategies are being developed and implemented to mine, understand, And predict polypharmacology. For instance, PCM modeling and multitarget. Activity landscapes enable the simultaneous analysis of chemical and biological. Relationships. Using structure- or ligand-based approaches, target fishing aims.To identify potential targets for a given ligand. Data mining of side effects and Systems pharmacology are further examples of novel approaches employed in Polypharmacology, which is a promising avenue in emerging and complex drug Discovery strategy such as the development of epidrugs.

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