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COMMENTARY

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Medicinal polypharmacology: Exploration and exploitation of the polypharmacolome in modern drug development

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Abstract

At the core of complex and multifactorial human diseases, such as cancer, metabolic syndrome, or neurodegeneration, are multiple players that cross-talk in robust biological networks which are intrinsically resilient to alterations. These multifactorial diseases are characterized by sophisticated feedback mechanisms which manifest cellular imbalance and resistance to drug therapy. By adhering to the specificity paradigm ("one target-one drug concept"), research focused for many years on drugs with very narrow mechanisms of action. This narrow focus promoted therapy ineffectiveness and resistance. However, modern drug discovery has evolved over the last years, increasingly emphasizing integral strategies for the development of clinically effective drugs. These integral strategies include the controlled engagement of multiple targets to overcome therapy resistance. Apart from the additive or even synergistic effects in therapy, multitarget drugs harbor molecular-structural attributes to explore orphan targets of which intrinsic substrates/physiological role(s) and/or modulators are unknown for future therapy purposes. We designated this multidisciplinary and translational research field between medicinal chemistry, chemical biology, and molecular pharmacology as 'medicinal polypharmacology'. Medicinal polypharmacology emerged as alternative approach to common single-targeted pharmacology stretching from basic drug and target identification processes to clinical evaluation of multitarget drugs, and the exploration and exploitation of the 'polypharmacolome' is at the forefront of modern drug development research.

KEYWORDS
chemogenomic space, drug repurposing, network pharmacology

Drug discovery has seen tremendous advancements over the last decades increasingly emphasizing integral strategies for developing clinically effective drugs considering entire (and multiple) pathways rather than individual targets (Morphy & Rankovic, 2007; Proschak et al., 2019; Zimmermann et al., 2007). The "one target-one drug concept" ruled for decades (Anighoro et al., 2014; Jalencas & Mestres, 2013b) due to (i) the lack of knowledge in human physiology; (ii) the strong need to fully understand the function of

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individual players in human disease; and (iii) the assumption that high affinity and selectivity of drugs toward individual players will cure disease (Anighoro et al., 2014; Morphy et al., 2004). The investigation of individual drug targets still covers the majority of today's medicinal chemistry efforts (Anighoro et al., 2014; Jalencas & Mestres, 2013b; Morphy & Rankovic, 2007). However, drug research shifts the focus on more complex coherences including the consideration of several players and entire pathways in human physiology and pathology (Anighoro et al., 2014; Jamir et al., 2023; Morphy & Rankovic, 2007; Olson et al., 2023; Proschak et al., 2019). The clinical picture of many diseases is a result of cross-talk and feedback of multiple players which form networks that are inherently resistant to changes and feed into cellular and/or organismal imbalance and dysregulation (Anighoro et al., 2014; Azmi & Mohammad, 2014; Hopkins, 2008; McKie, 2016; Morphy & Rankovic, 2007; Zimmermann et al., 2007), finally promoting resistance to or ineffectiveness of (single-targeted) drug therapy (Anighoro et al., 2014; Proschak et al., 2019).

Modern systems biology and network pharmacology analyses steadily reveal important puzzle pieces of a "big picture" of complex diseases (Jamir et al., 2023; Olson et al., 2023) which allows for the conclusion that biological effects of small-molecule therapeutics in the human body result from multiple individual interactions with multiple targets (Anighoro et al., 2014; Jalencas & Mestres, 2013a; Paolini et al., 2006; Schmidt et al., 2014; Vulpetti et al., 2012). Today, modern drugs should intentionally engage multiple targets to overcome disease and/or therapy resistance (Hopkins, 2008; Jamir et al., 2023; McKie, 2016; Mogwera et al., 2023; Proschak et al., 2019; Zimmermann et al., 2007) to provide additive or even synergistic effects (Anighoro et al., 2014; Azmi & Mohammad, 2014; Proschak et al., 2019). This becomes evident considering the multifactority of many prevalent human diseases that can barely be addressed by single-targeted approaches.

Medicinal polypharmacology also stretches far into the very basis of drug design, discovery, and development itself (Anighoro et al., 2014; Proschak et al., 2019). Multitarget agents allow not only for addressing multiple druggable targets of the addressable "diseasome" (Wang & Yang, 2022); they also reach into a network of (yet) undruggable targets by either of two ways: (i) impact on a druggable target which subsequently reaches into a network of undruggable targets by a known or unknown pathway; or (ii) direct interaction with the to this point undruggable target itself (Korcsmaros et al., 2007). Multitarget agents are suitable ligands to de-orphanize undruggable targets:

1. The spatial structure of proteins is more conserved than protein sequences; thus protein structures resemble each other despite sequential differences (Grishin, 2001; Jalencas & Mestres, 2013a; Koch, 2011). Even phylogenetically distant protein (classes) have common and reoccurring structural motifs ("superfolds") (Grishin, 2001; Koch, 2011; Orengo et al., 1994; Russell et al., 1998). Superfolds can form chemoisosteric "supersites" (Anighoro et al., 2014; Jalencas & Mestres, 2013b; Jalencas & Mestres, 2013a; Russell et al., 1998) ("multitarget binding sites") (Namasivayam, Silbermann, Pahnke, et al., 2021) that attract common sets of ligands (Russell et al., 1998). Multitarget agents form a large interconnected network (Jalencas & Mestres, 2013b) of phylogenetically distant proteins and protein families, making them model molecules for the exploration and exploitation of undruggable targets of which no structural information is known other than the presence of superfolds and supersites. Multitarget drugs ("privileged ligands") (Jalencas & Mestres, 2013b; Kim et al., 2014) bear an invaluable potential as anchor points at the forefront of today's target identification and validation processes at the very beginning of the drug development pipeline.
2. Reoccurring molecular-structural motifs and physicochemistry profiles of multitarget agents are also limited (Anighoro et al., 2014; Hu & Bajorath, 2010; Jalencas & Mestres, 2013b; Namasivayam, Stefan, Gorecki, et al., 2022; Paolini et al., 2006). The definition of multitargeticity ("*when is a multitarget agent a multitarget agent?*") and its association to molecular-structural and physicochemical characteristics ("*what makes a multitarget agent a multitarget agent?*") promotes the elucidation of "multitarget fragments" and "multitarget fingerprints" (altogether "superpatterns") which allow for virtual screening of (almost infinite) chemical space. Recently, such a workflow successfully discovered novel multitarget drugs targeting ATP-binding cassette (ABC) transporters (Namasivayam, Stefan, Gorecki, et al., 2022, Namasivayam, Stefan, Silbermann, et al., 2022; Namasivayam, Silbermann, Pahnke, et al., 2021; Namasivayam, Silbermann, Wiese, et al., 2021). The creation of high-quality and high-diversity compound libraries of privileged ligands (Jalencas & Mestres, 2013b; Zimmermann et al., 2007) by virtual screening and diversity-oriented synthesis (Kim et al., 2014) could represent the starting point of future target identification and validation processes.

This opportunity space between structural limitation of target proteins and molecular-structural limitation of multitarget agents is referred to by us as "polypharmacolome." The knowledge about the polypharmacolome bears high potential for both single- and multi-targeted approaches. Annotation of multitarget fragments with multiple biological effects can be used for intentionally designing, synthesizing, and optimizing selective agents (Stefan et al., 2022, Stefan et al., 2023), contributing to the still immense need to understand individual protein function(s) in disease. These annotations may also be used to shape the safety profile of (multi- and single-targeted) drugs, for example, by circumventing off-targets in drug metabolism (e.g., cytochrome P450 [CYP] enzymes) or disposition (e.g., ABC transporters or solute carriers [SLCs]) (Bowes et al., 2012; Stefan et al., 2022).

Several key advancements promoted medicinal polypharmacology: (i) chemical space grew magnificently, offering today billions of novel make-on-demand compounds in more or less uncharted synthesis and bioactivity space; (ii) structural biology approaches thrived over the last two decades improving protein resolution

techniques (Brunst et al., 2021; Jalencas & Mestres, 2013a; Morphy & Rankovic, 2007; Proschak et al., 2019; Ravikumar & Aittokallio, 2018); and (iii) genome-wide association studies, multi-omics, and "big data" extended the relevant target space by actively uncovering new pharmacological drug targets and/or coherences. Systems biology and network pharmacology analyses applying computational approaches, particularly machine learning, neural networks, and artificial intelligence (Proschak et al., 2019; Ravikumar & Aittokallio, 2018) allow nowadays for more sophisticated analyses and the development of novel concepts.

Medicinal polypharmacology with all its facets is, however, still at an early stage. As a small and young field, major obstacles are addressed by a small number of researchers only:

1. It requires a large-scale biological assessment platform and interdisciplinary work environment to cover a vast panel of various targets, even if one particular protein (super)family is considered only (Jalencas & Mestres, 2013b; Stark, 2004; Stefan & Rafehi, 2024). A systematic screening of the entire human proteome is impossible (Anighoro et al., 2014; Jalencas & Mestres, 2013b). Minimum screening requirements (Bajorath, 2021) and safety screening panels (Bowes et al., 2012; Kim et al., 2014; Peters, 2013; Ravikumar & Aittokallio, 2018) to accurately profile ligands/small-molecule drugs may support resource and logistic management.
2. High throughput screenings (HTS) using physical compound libraries bear the chance to serendipitously find hit candidates. However, the biological relevancy, drug likeness, and molecular-structural diversity of used physical compound libraries are insufficient particularly considering several biological targets (Breinbauer et al., 2002; Kim et al., 2014), as mostly focusing one particular ligand class and/or target (family) only.
3. Historically, many multitarget drugs were discovered serendipitously by HTS and subsequently stored on public databases (Zhan & Liu, 2009). However, HTS is prone to unspecific effects due to assay artifacts. No standardization/harmonization of procedures exists amongst journals and other research platforms how to properly assess compound unspecificity, and if it did, it would not account for already published data. Thus, clever approaches are necessary to harness historical HTS data despite their potential lack of accuracy and/or reliability (Nissink & Blackburn, 2014).
4. Millions of small-molecules are known and stored on public databases, such as PubChem. However, the number of compounds annotated with multiple biological information, particularly with biological activity against the targets of interest, is very limited. Most databases store chemical and biological information on a "one target-one compound" basis only, necessitating (i) complementary and redundant biological assessments of new compounds; and (ii) curation of data sets of already published compounds (Mousavian & Masoudi-Nejad, 2014; Stefan et al., 2022; Wu et al., 2022). This is particularly true considering (i) literature pollution with bad actors (Stork & Kirchmair, 2018); (ii) the overall limitation in data comparability and accuracy (Kalliokoski et al., 2013; Kramer et al., 2012; Stefan, 2019), leading to incomplete and/or noisy data ("data barrier") (Schneider, 2014); and (iii) inaccurately and/or incompletely described assay procedures, limiting reproducibility (Goldmann et al., 2014).
5. Follow-up experiments with multitarget agents will inevitably lead to (i) the identification of bad actors; and (ii) compounds with a much larger extent of polypharmacology than anticipated, including off-target, antitarget, and adverse effects. Rigorous complementary assessment of hit molecules with an additional array of tests is necessary to exclude false-positive hits, which requires additional resources.
6. From a structural perspective, the vast majority of proteins, even from similar protein (super)families, have not yet been resolved at all or at insufficient resolutions only. Artificial intelligence-based deep learning methodologies like AlphaFold (Senior et al., 2020) indeed support computational approaches in structural biology. However, particularly large and complex proteins with heterogenous surfaces, such as membrane-bound transporters [e.g., ABC or SLC transporters] with extended molecular trajectories can be predicted to a very limited extent only. Certain computational tools exist for (multitarget) binding site comparison; however, they strongly depend on the quality and accuracy of the template structures (Jalencas & Mestres, 2013a; Zhang et al., 2017).
7. Multitarget agents have pharmacokinetic constraints that need to be overcome for therapeutic effectiveness (Morphy & Rankovic, 2006). The search for novel chemotypes that represent merged multitarget agents is key as these molecules are closer to drug likeness with greater likelihood to fulfill physicochemical parameters critical for pharmacokinetics (Morphy & Rankovic, 2006). However, even if desired scaffolds, fingerprints, or templates were discovered with preferred polypharmacological profiles, the optimization processes will consume precious resources to result in clinically usable candidates.

In conclusion, medicinal polypharmacology allows for the development of novel therapeutic strategies by multitarget disruption of crosstalk, feedback, and resistance of redundant pathways within the proteome. Additionally, it supports our understanding of the distinctive role of yet under-explored individual drug targets in a vastly growing opportunity space for target druggability. To harness the immense power of the polypharmacolome, two major goals are:

1. The identification of privileged ligands and their subjection to drug and/or target (class) repurposing and target hopping approaches to (i) synergize with effects coming from the modulation of multiple targets (Anighoro et al., 2014; Proschak et al., 2019); (ii) gain an anchor point to explore yet undruggable targets (Kim et al., 2014; Korcsmáros et al., 2007; Paolini et al., 2006); and (iii) use these anchor points for a fast targeted development of urgently needed drugs (e.g., pandemic events).
2. The identification of multitarget fingerprints ("superpatterns") to explore chemical and synthesis space to achieve both: (i) the discovery of structurally distinctive and functionally novel hit

molecules with improved polypharmacological profile (Stefan et al., 2022, Stefan et al., 2023). Structural distinctiveness represents originality which is a prerequisite for patents. Functional novelty (identification of alternative modes-of-action, e.g., activation, allosteric modulation, correction, potentiation, etc.) can particularly be discovered in (almost infinite) chemical space where the associated bioactivity space is multidimensional (Namasivayam, Stefan, Gorecki, et al., 2022), and thus, may contribute to advances in therapy; and (ii) the gain of crucial knowledge to circumvent off-target effects to profile drug safety including an accurate risk assessment (Anighoro et al., 2014).

The ensemble of (i) a large-scale biological assessment platform; (ii) structural biology techniques; and (iii) advanced computational ligand- as well as structure-based prediction methodologies will allow for the exploration and medical exploitation of yet undiscovered, under-studied, and under-explored drug targets of the future.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The information processed in this commentary has been derived from PubMed mainly. This article contains no data sets generated or analyzed during the current study.

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