Journal of Medicinal Chemistry

pubs.acs.org/jmc

Perspective

Is Target-Based Drug Discovery Efficient? Discovery and "Off-Target" Mechanisms of All Drugs

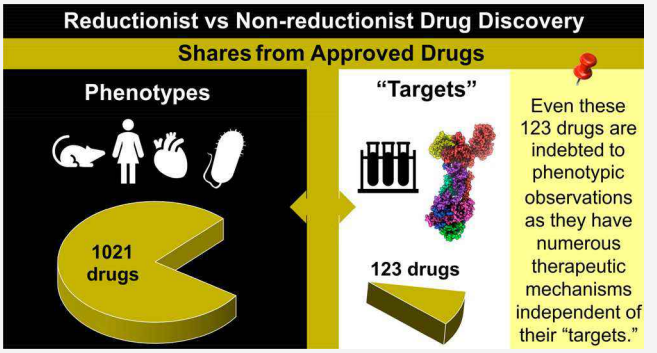
Arash Sadri*

Cite This: https://doi.org/10.1021/acs.jmedchem.2c01737

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Target-based drug discovery is the dominant paradigm of drug discovery; however, a comprehensive evaluation of its real-world efficiency is lacking. Here, a manual systematic review of about 32000 articles and patents dating back to 150 years ago demonstrates its apparent inefficiency. Analyzing the origins of all approved drugs reveals that, despite several decades of dominance, only 9.4% of small-molecule drugs have been discovered through "target-based" assays. Moreover, the therapeutic effects of even this minimal share cannot be solely attributed and reduced to their purported targets, as they depend on numerous off-target mechanisms unconsciously incorporated by phenotypic observations. The data suggest that reductionist target-based drug discovery may be a cause of the productivity crisis in drug discovery. An evidence-based approach to enhance efficiency seems to be prioritizing, in selecting and optimizing molecules, higher-level phenotypic observations that are closer to the sought-after therapeutic effects using tools like artificial intelligence and machine learning.



Downloaded via UNIV OF NORTH CAROLINA on September 21, 2023 at 21:39:02 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

SIGNIFICANCE

- This is the first systematic and comprehensive assessment of the real-world efficiency of target-based drug discovery.
- Merely 9.4% of approved small-molecule drugs have been discovered by this approach.
- Even these supposedly target-based drugs depend on numerous off-target mechanisms for their therapeutic effects.
- Reductionist target-based drug discovery has thus far been inefficient and maybe a cause of the productivity crisis.
- Approaches that prioritize higher-level observations are potentially more efficient based on both observational and theoretical evidence.

1. INTRODUCTION

1.1. Contemporary Drug Discovery Has Some Serious Problems. Drug discovery lies at an integral intersection where innovations and developments of diverse scientific fields and industries conjoin to translate into the ultimate purpose of improving health. However, the efficiency of discovering new drugs is so low that it would probably astonish researchers and practitioners in other domains.[1,2] The ratio of the drug candidates that gain approval to those that enter clinical studies is about 13% but can be as low as 0.4% for more complex CNS disorders and cancers.[3,4] Estimated research costs of introducing a new therapeutic to the market have soared up to 6.4 billion dollars with a mean of 1.3 billion dollars.[5] The translation of basic scientific research to clinical real-world impact has been denigrated as the "valley of death".[6] Such challenges have compelled many pharmaceutical companies, including Pfizer, Merck, GSK, AstraZeneca, and Amgen, to withdraw from neuroscience research at some point,[7] although its related disorders are a primary cause of disability worldwide,[8,9] impose immense societal costs,[10] and many of them have no cure. Moreover, many approved drugs that have been considered to be successful have been the subject of criticism by experts and available evidence. A considerable number are suggested to exert minimal effects,[11−18] offering almost no benefit compared to previously approved drugs,[18−22] or have been approved only based on surrogate end points[15,16,23−28] or flawed and limited evidence.[15−18,22,26,29−38] Compared to placebo, many approved drugs probably offer at best only marginal benefit and may even lower a patient's quality of life and survival.[17,22−24,39−44]

Adding to the oddity of this low productivity is the observation that productivity has declined significantly from several decades ago despite significant technological advance-

Received: October 27, 2022

© XXXX American Chemical Society

ments that have been developed and deployed in the most recent period. From 1950 to 2010, the number of drug approvals per billion dollars of research expenditure has halved every 9 years, a trend referred to as Eroom's Law.[45,46] Although, as was predicted earlier,[34] it appears that the trend has been reversing in recent years,[47,48] diagnosing the major causes of the low productivity of drug discovery and development is of paramount importance since it undermines the translation of all the progress we have made in advancing technology and enhancing biomedical knowledge into the ultimate goal of improving health.

1.2. Where Does the Problem Lie? Several factors have been proposed as causes of the productivity decline: exhaustion of "the more accessible and easily discoverable drugs" (the low-hanging fruit[1,46,49]), the cumulative pressure to surpass previous blockbuster drugs (the "better than the Beatles" problem),[1] the decreased tolerance for risk by drug regulatory agencies (the "cautious regulator" problem), the increase in human and technological investments (the "throw money at it" tendency), and the overestimation of the positive impacts of the scientific and technological advances, such as molecular biology and high-throughput screening, which has led to hastily abandoning previous methodologies (the "basic research-brute force" bias[46]). Many have also highlighted the reductionist tendency of the dominant methodology of drug discovery: target-based drug discovery.[45,46,49−61] Interestingly, this methodology was born at roughly the same time as the onset of this decline and has now dominated drug discovery approaches for several decades.[60] Most target-based drug discovery investigations are reductionist in nature since they are based on reducing the therapeutic effects that emerge from interacting with complex networks of cellular and extracellular components and their intricate feedback loops to the modulation of either a single or few proteins.[62] Notwithstanding, it is important to acknowledge that there have been attempts to move away from this extreme reductionism in target-based drug discovery by adopting polypharmacological approaches. Let us explore the evolution of drug discovery in order to better assess the criticisms against the focus on reductionism.

1.3. The Evolution of Drug Discovery. Drug discovery started when our ancestors began to recognize patterns between the substances they came across and their effects on the phenotypes they observed. For example, *Piptoporus betulinus* is a fungus whose several constituent substances have now been observed to be potent immunomodulator and antimicrobial agents.[63−67] Evidence, including an infected mummified human carrying this fungus, suggests its potential use in treating infectious diseases like trichuriasis around 5300 years ago[68−71] (also see refs 72−74). Further evidence indicates that the possible intentional use of effective drugs stretches back even further to 60000 years ago.[75−81] Even now, some of the most crucial drugs used in the clinic can be traced back to the therapeutics our ancestors discovered centuries ago, including morphine analogs (21 drugs), aspirin, digoxin, and many others (the historically used category of Figure 4 and Supporting Information 1).

After thousands of years and the cumulative growth of our knowledge and capabilities,[78] some pioneers of modern biomedical sciences, like François Magendie[82] and Claude Bernard,[83] began to unravel how these substances exerted their effects on phenotypes, i.e., their mechanism of action. The continuation of such investigations by trailblazing scientists like Rudolf Buchheim and Oswald Schmiedeberg[84,85] blossomed into the scientific discipline of pharmacology[86] (Figure 1). Afterward, in the 20th century, several highly prolific scientists

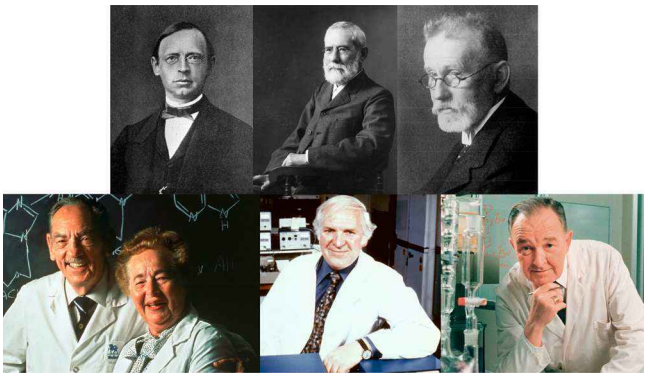


Figure 1. Some of the most important pioneers of pharmacology and rational drug discovery. Top row, from left to right: Rudolf Buchheim, Oswald Schmiedeberg, and Paul Ehrlich. Bottom row, from left to right: George Hitchings, Gertrude Elion, James Black, and Paul Janssen. The three images in the top row plus the photo of James Black in the bottom row are from Wikimedia Commons and are used under a CC BY 4.0 license. The images of George Hitchings and Gertrude Elion are from achievement.org/achiever/gertrude-elion. The image of Paul Janssen is from the Janssen Image Library, Janssen Global Services, LLC, used by permission.

not only significantly contributed to the development of the science of pharmacology[87] but also applied the knowledge of how molecules exert their effects on phenotypes to designing better drugs (Figure 1). Among these are Paul Ehrlich, who devised concepts like the magic bullet, chemotherapy, and chemoreceptor[88] and discovered salvarsan and neosalvarsan,[89] George Hitchings and Gertrude Elion, who used knowledge on metabolism pathways to discover mercaptopurine,[90] thioguanine,[91] azathioprine,[91] pyrimethamine,[92] allopurinol,[91] cotrimoxazole,[93] acyclovir,[94] and nelarabine,[95] James Black, who applied receptor theory[96] to discover the first-in-class medicines propranolol and cimetidine,[97] and Paul Janssen who discovered diphenoxylate,[98] difenoxin,[99] haloperidol,[100] droperidol,[100] fentanyl,[101] loperamide,[102] etomidate,[103] pimozide, sufentanil, alfentanil, mebendazole, miconazole, terconazole, and ketoconazole.[99]

This approach which attempted to use the available scientific knowledge, including pharmacological, pathological, and physiological aspects, to guide and focus the empirical screening of random substances and correlate with observations on their effects on phenotypes came to be known as *rational drug discovery*. Target-based drug discovery can be considered as a subsequent iteration of rational drug discovery that was born contemporaneously with the revolution of molecular biology and the development of technologies like X-ray crystallography, nuclear magnetic resonance imaging, computational chemistry, biotechnology, DNA sequencing, combinatorial chemistry, and high-throughput screening, that enabled the ever-finer dissection of biological processes to the point of the binding of molecules to a single protein.

Currently, target-based drug discovery heavily dominates drug discovery approaches in both academia and the pharmaceutical industry.[104−115] Drug candidates for complex disorders like OCD, depression, and Alzheimer's disease are being screened, selected, and optimized primarily based on their binding affinity for a single protein that is hypothesized to be

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

fundamentally related to the development of the disease.[116] Observing the therapeutic effects of molecules is primarily used for terminal filtering.[62]

1.4. Reductionism and Antireductionism. Reductionism has been a dominant attitude in sciences since the Scientific Revolution and the Industrial Revolution.[117] This approach gained further momentum in the later years of the 20th century and the initial years of this century[118] because of the technological progress that facilitated it.

In parallel with the dominance of reductionism over the past 70 years, antireductionism, which was even advocated by Aristotle,[119] has been spurred in diverse fields.[120−131] This has been driven by the disillusionment resulting from the failures of reductionism in unraveling complexity, such as the unfulfilled promises of the Human Genome Project.[118,130,132] Complex systems science has flourished[133−135] with dedicated institutions specializing in it, including the Santa Fe Institute,[136] the New England Complex Systems Institute, and Complexity Science Hub Vienna.[137] Recognition of the importance of complexity science was also reflected by awarding the 2021 Nobel Prize in Physics "for groundbreaking contributions to our understanding of complex systems".[138] Systems biology has also bloomed trying to pay more attention to the comprehensiveness of the components being studied and their interactions using computational and mathematical tools.[139,140] In drug discovery, antireductionism has grown in several approaches including systems pharmacology, network pharmacology,[141,142] and polypharmcology[143] and was given additional momentum after Swinney and Anthony showed that, despite the disproportionate dominance of reductionist target-based drug discovery, most of the first-in-class drugs approved between 1999 and 2008 were discovered by phenotypic approaches.[54] This could have inaugurated a rejuvenation of phenotypic drug discovery; alas, it is still being sidelined by a focus on target-based drug discovery[144,145] and is viewed merely as a complementary approach for discovering novel mechanisms of action and first-in-class drugs.[54,146]

1.5. Hypothesis: Target-Based Drug Discovery Is Inefficient. What is the relationship between the affinity of a molecule for a specific protein and its therapeutic effects on, for example, depressive disorders?[147] Can the tight binding of a molecule to a protein free the human body from such complex disorders? This question is the fundamental core of the criticisms that have been raised against the reductionism associated with target-based drug discovery. Besides the fact that plenty of these hypothesized "targets" may not even be relevant to the phenotypes they are attributed to,[116,148] most disorders and desired therapeutic effects seem to be too complex to be reducible to modulating the behavior of single proteins, except maybe monogenetic Mendelian disorders.[60] Moreover, it is established that our knowledge of the underlying pathology of many disorders is dwarfed by our ignorance about them.[149] This knowledge gap further hampers the feasibility of pinpointing a single protein to target in an attempt to counteract a specific pathology.

Despite the numerous criticisms that have been advanced against target-based drug discovery,[45,46,49−61] there is an absence of a comprehensive and systematic study that would be able to provide a relatively firm answer to the question: *Is target-based drug discovery an efficient, optimal, and rational approach?* Here, I attempt to provide an answer by examining the methodology of target-based drug discovery from several perspectives:

A. How many of the currently approved drugs are indebted to reductionist target-based drug discovery in contrast to less-reductionist approaches?
B. Even for the drugs discovered based on reductionist target-based drug discovery, can the therapeutic effects be reduced to the binding and modulation of the select proteins?
C. How does the binding of drugs to "therapeutic targets" with high affinity correlate with their therapeutic effects?
D. Does the methodology of target-based drug discovery stand on a sound theoretical foundation based on the available scientific knowledge?

2. EVIDENCE ON THE EFFICIENCY OF TARGET-BASED DRUG DISCOVERY

2.1. Contribution of Observing Therapeutic Effects vs Effects on Proteins to the Discovery of Approved Drugs.

2.1.1. Rationale. I hypothesized that a fundamental cause of drug discovery's decline is the transition to the reductionist methodology of target-based drug discovery that selects and optimizes structures primarily based on their binding to a few hypothetically relevant "target" proteins and usually uses *in vivo* and human data only as terminal filters. On the other hand, traditional drug discovery inevitably was a more empirical approach primarily relying on selecting and optimizing molecules based on their therapeutic effects on humans and other organisms like nonhuman animals (hereinafter referred to as animals), fungi, and bacteria because of the absence of the tools needed for reductionism that would enable directly assessing the effects of drugs at the lower levels associated with individual proteins.

While the aforementioned analysis conducted by Swinney and Anthony was seminal in revitalizing phenotypic drug discovery, the period they analyzed (1999−2008) was so limited that their conclusions, apart from being restricted to the suggestion that phenotypic drug discovery may be more efficient for discovering first-in-class drugs, were subsequently challenged by an analysis that had assessed a longer time frame.[150] Moreover, Swinney and Anthony's analysis did not cover the golden period of traditional drug discovery at all; thus, it is not suitable for comparing the real-world contributions of traditional and target-based drug discovery. Consequently, I expanded the analysis of Swinney and Anthony to include all approved drugs and tried to increase the accuracy and objectivity of the analysis.

2.1.2. Methods. I manually (not by automated methods like natural language processing) investigated the discovery origins of all drugs approved by the US FDA by the end of 2020, the list of which I had compiled using three databases: National Center for Advancing Translational Sciences (NCATS) Inxight Drugs (drugs.ncats.io),[151] Drugs@FDA (accessdata.fda.gov/scripts/cder/daf/index.cfm), and the Orange Book (fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book). In querying Inxight Drugs, I chose "US Approved OTC" OR "US Approved Rx" for the development status, "Approved" for the highest phase, "Principal Form" for substance form, and excluded treatment modalities of "Secondary," "Inactive Ingredient," "Diagnostic." From Drugs@FDA, I retrieved drugs with type 1 (New Molecular Entity) and type 7 ("Previously Marketed but Without an Approved NDA") applications among "Original NDA and Original BLA Approvals" and excluded the discontinued ones. I also added the nondiscontinued drugs

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

taken from the Orange Book if they were not already included. All of the retrieved drugs are listed in Supporting Information 1, yet I did not investigate the discovery origins of the following groups of drugs: diagnostic agents like contrast agents; nutrients, vitamins, and nutrient inorganic ions; secondary agents without therapeutic activity themselves, like mesna; antidotes; enantiopure or racemic formulations of previously approved drugs; prodrugs of previously approved drugs; excipients; drugs whose therapeutic effects depend more on the physical properties of molecules; e.g., surfactants, chelating agents, radiopharmaceuticals, photochemotherapeutics, and osmotic diuretics.

To maximize objectivity, it is important to settle upon simple and unambiguous definitions (Table 1). *Discovery origin* was defined as "the first observation that has related a therapeutic class to the therapeutic effect" and *therapeutic class* was defined as "a group of analogs (chemical and/or pharmacological[152]) along with their respective lead molecules which guided their discovery."[153] Drugs whose "discovery origin was observing the effects of molecules on proteins" were assigned to *target-based* and those whose "discovery origin was observing the effects of molecules on phenotypes" were assigned to *phenotype-based*. An example of the application of these definitions can be helpful in order to better gauge the objectivity of the conclusions. Captopril is known by many as one of the early drugs discovered "rationally." To objectively assign its discovery origin to phenotype-based or target-based, the definitions of these terms given above were followed exactly. In Supporting Information 1, these quotes from the discoverers of captopril themselves have been cited: "In 1968, Dr. Y.S. Bakhle demonstrated that dog lung ACE was inhibited by a mixture of peptides from the venom of the Brazilian viper *Bothrops jararaca*. [···] This exercise was not completely in vain; it showed how rare, indeed, were specific inhibitors of ACE, it also demonstrated that these, whether designed or stumbled upon, could be readily identified using a simple guinea pig ileum test system developed by Dr. Rubin and his colleagues. Success in this simple *in vitro* test was also highly predictive of activity *in vivo*, including antihypertensive activity. [···] The key result with this prototype compound, however, came in Dr. Rubin's guinea pig ileum test. Unlike the 2000 or so random compounds that we had previously tested, succinyl-L-proline had the properties of a specific ACE inhibitor: it inhibited contractile actions of angiotensin I and potentiated those of bradykinin, without having any effects on contractile actions of angiotensin II or those of several other smooth muscle agonists[154] (emphases added)." As is evident in the quote, although the discovery took place with a "target" protein in mind, the selections and "the first observation that has related a therapeutic class to the therapeutic effect" were completely based on "observing the effects of molecules on phenotypes."

Table 1. Concepts Used for Assessing the Contribution of Observing Therapeutic Effects vs Observing Effects on Proteins to the Discovery of Approved Drugs

concept	definition
Therapeutic class	A group of analogs along with their respective lead molecules which guided their discovery
Discovery origin	The first observation that has related a therapeutic class to its therapeutic effect
Target-based	Therapeutic classes whose discovery origin was observing the effects of molecules on proteins
Phenotype-based	Therapeutic classes whose discovery origin was observing the effects of molecules on phenotypes

It is worth noting that, according to the definitions provided above for therapeutic class and discovery origin, the discovery origins of all approved analog drugs are attributed to the discovery origin of their respective first-in-class drugs. While this may be subject to debate, by definition, analog and "me-too" drugs are based on the structure of their respective first-in-class drugs, and total dismissal of this would have led to an unfair comparison of the real-world contributions of target-based and phenotype-based drug discovery. Nonetheless, as is acknowledged later in the article, target-based drug discovery plays a key role in analog-based drug discovery. To identify a set of chemicals as analogs objectively, I used and cited the published literature (e.g., ref 152) and calculated feature trees as the molecular similarity measure using FTrees 6.3.[155]

Like Swinney and Anthony,[54] I counted biopharmaceuticals as a separate group, but I also further categorized them based on whether they are endogenous-based or not. I compared the share of phenotype-based and target-based categories among all the approved drugs and those approved after 1995, the approval year of the first "target-based" drug, saquinavir. I also further categorized the phenotype-based discovery origins into these: observing nonhuman or *ex vivo* phenotypes, observing phenotypes of humans, observing phenotypic effects of endogenous molecules, historically used compounds, sagaciously observed nonhuman or *ex vivo* phenotypes, mechanism of action-informed phenotypic observations.

In investigating the discovery origins, I highly prioritized the accounts of the initial reporting discovery papers (denoted as "From the discovery paper":) and afterward, other narrations from the discoverer(s) themselves (denoted as "From the discoverer(s)"). I tried to quote with the highest fidelity, exactly transferring styles and even incorrect spellings; except for most in-between-commas details and in-text citations (I have kept a few in case they would be informative).

In summation, in the analysis of the discovery origins, I tried to maximize objectivity, precision, and accuracy through several measures:

(1) Analyzing all drugs, not just drugs associated with a specific period.
(2) Entirely manual, rather than automated analysis.
(3) Basing decisions on simple definitions of discovery origin, therapeutic class, target-based, and phenotype-based.
(4) Referencing verbatim accounts of the original discovery papers and the discoverer(s) themselves.
(5) In cases where (4) was infeasible, referencing the published literature for the discovery process.
(6) Basing decisions of therapeutic classes on the published literature and FTrees.
(7) Detailed documentation of the paths followed to identify and assign each discovery origin.

2.1.3. Results and Discussion. Out of the 1310 US FDA-approved drugs, 69 were endogenous-based biopharmaceuticals and 97 were other biologic drugs. Out of the 1144 remaining small-molecule drugs, 123 (10.75%) were discovered by target-based drug discovery and 1021 (89.25%) by phenotype-based approaches. Despite the dominance of small-molecule target-based drug discovery in the last 40 years, it represents a meager share of the currently used drugs (123 drugs (9.39%)), in contrast to phenotype-based approaches (1021 (77.94%) vs) (Figure 2a). This disproportionate disparity holds up even when

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

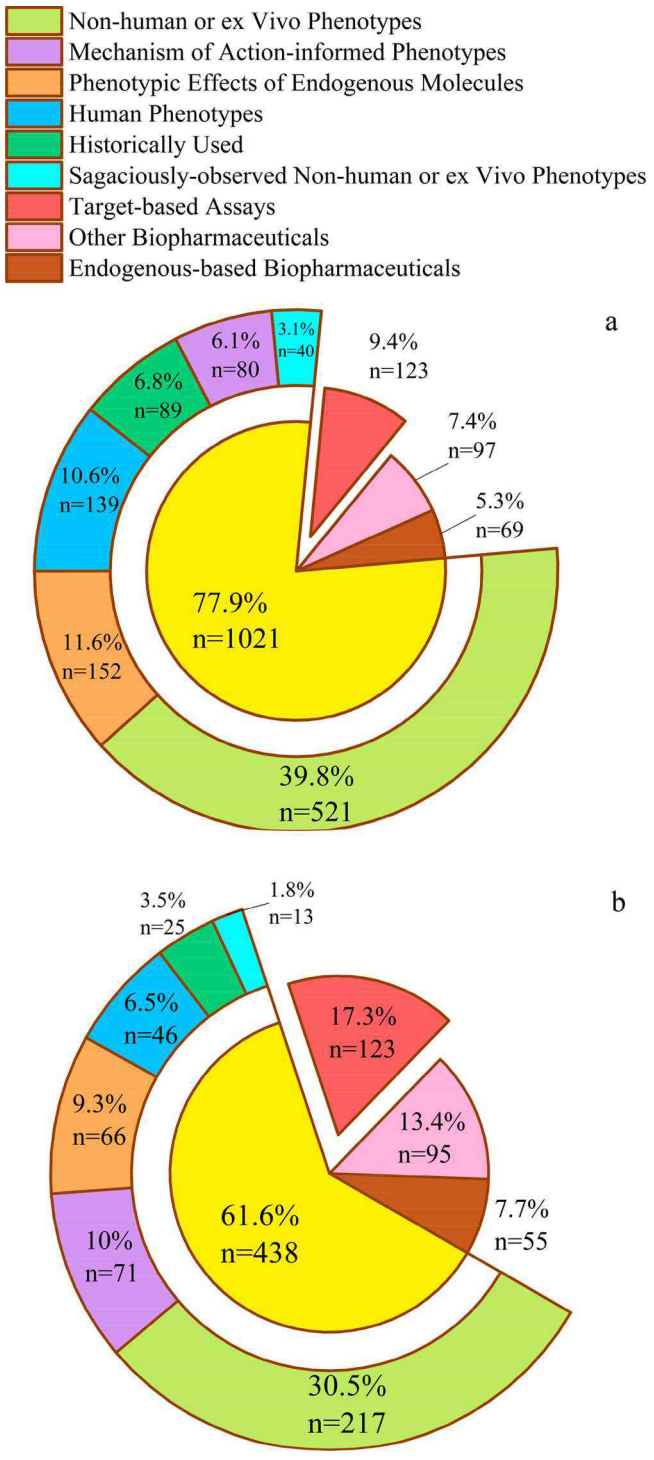


Figure 2. Shares of different approaches from the discovery origins of drugs. (a) All approved drugs; (b) drugs approved after 1995. All the drugs in each category are listed in Figure 4, and their detailed and manually extracted discovery origins are available in Supporting Information 1.

only the drugs approved after 1995 are taken into account (123 (17.30%) vs 438 (61.60%)) (Figure 2b). Although the share of target-based drug discovery from the drugs approved each year seems to have grown over time, there has not been a single year in which it was not surpassed by the share of phenotypic drug discovery (Figure 3).

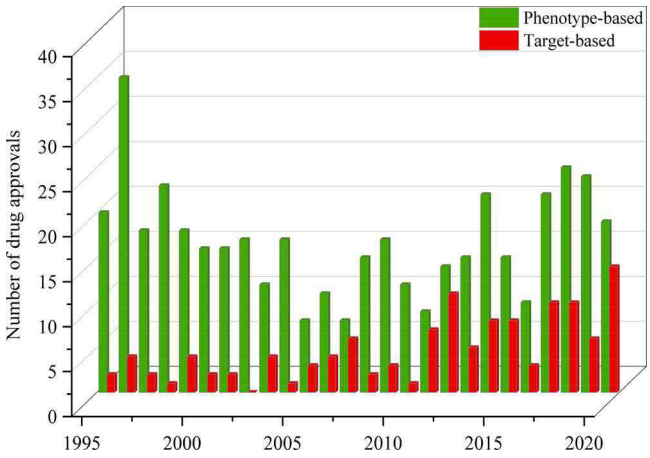


Figure 3. Number of drugs discovered by target-based or phenotype-based approaches and approved each year since 1995 (the approval year of the first target-based drug, saquinavir).

Reviewing the discovery origins provided in Supporting Information 1 demonstrates that, contrary to the textbook procedure of drug discovery which has been the standard of the past few decades,[62] a significant portion of the most important drugs used in the clinic have originated from approaches that many drug hunters nowadays would consider "otherworldly"[156] and "taken place on another planet".[156−158] Most of the approved drugs have originated from emphasizing and using highly predictive phenotypic models, like predictive animal models, *ex vivo* systems, or cultures of bacteria, fungi, and protozoa (about 700 drugs including most of the drugs in these categories: observing nonhuman or *ex vivo* phenotypes, mechanism of action-informed phenotypic observations, and observing phenotypic effects of endogenous molecules). This is evident in the discovery origins of many drugs including isoproterenol,[159] propranolol,[97] cimetidine,[97] ethosuximide,[160] purine analogs,[91] cyclosporine,[161] pentamidine,[162−165] omeprazole,[166,167] propofol,[168−170] paclitaxel,[171] topotecan,[172,173] ivermectin,[174,175] topiramate,[176,177] leflunomide,[178] sirolimus,[179] ezetimibe,[180] cinacalcet,[181] and tecovirimat.[182,183]

Many antimicrobial agents that were discovered by observing infected animals or the cultures of the microbes themselves, even during screening uncharacterized mixtures like soil samples, are other notable examples in this regard, like tetracyclines,[184] penicillins,[185] cephalosporins,[186] pyrimethamine,[92] chloroquine,[187] vancomycin,[188] rifampin,[189] clavulanic acid,[190] pretomanid,[191] retapamulin and lefamulin,[192,193] spinosad,[194] and bedaquiline.[195,196]

This attention to the predictivity of models was so high that in many cases, drug hunters used themselves as models and self-experimented with molecules, exemplified by lidocaine,[197] amphetamine,[198] cromolyn,[199] bisacodyl,[200] ingenol mebutate,[201] and bremelanotide.[202]

The drugs discovered based on serendipity and sagaciously observing nonhuman or *ex vivo* phenotypes can also be considered to be indebted to this attention toward predictive models, including bacitracin,[203,204] ticlopidine,[205] valproic acid,[206] warfarin,[207] meprobamate,[208] vinca alkaloids,[209] dipyridamole,[210] diazoxide,[211] cisplatin,[212,213] etomidate,[103] naftifine,[214] glatiramer acetate,[215,216] imiquimod,[217,218] thiazolidinediones,[219,220] levetiracetam and piracetam,[221] and dapagliflozin and empagliflozin.[222] Such serendipitous discoveries would be impossible in target-based drug discovery's biochemical affinity

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

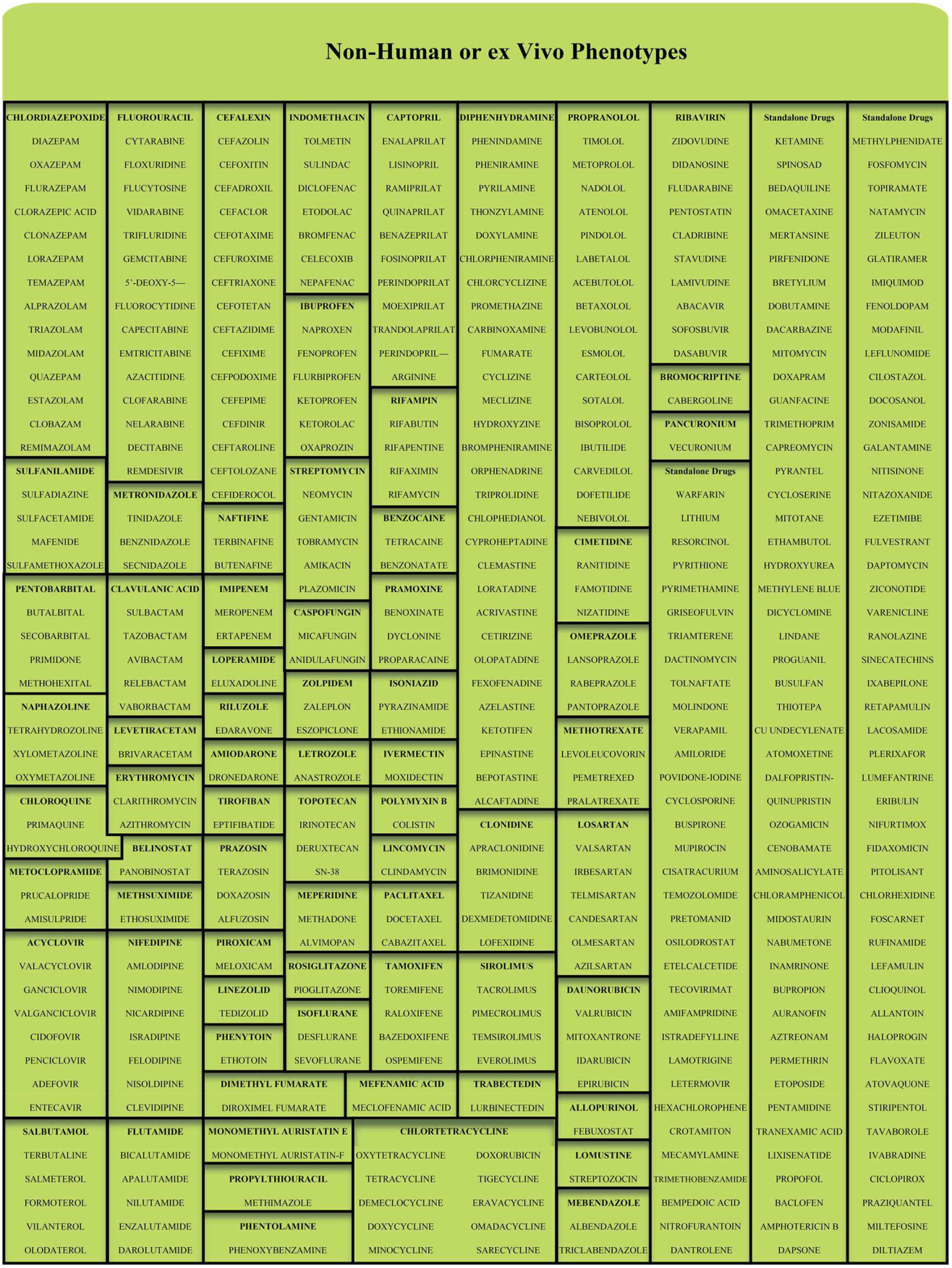


Figure 4. continued

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

Figure 4. continued

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

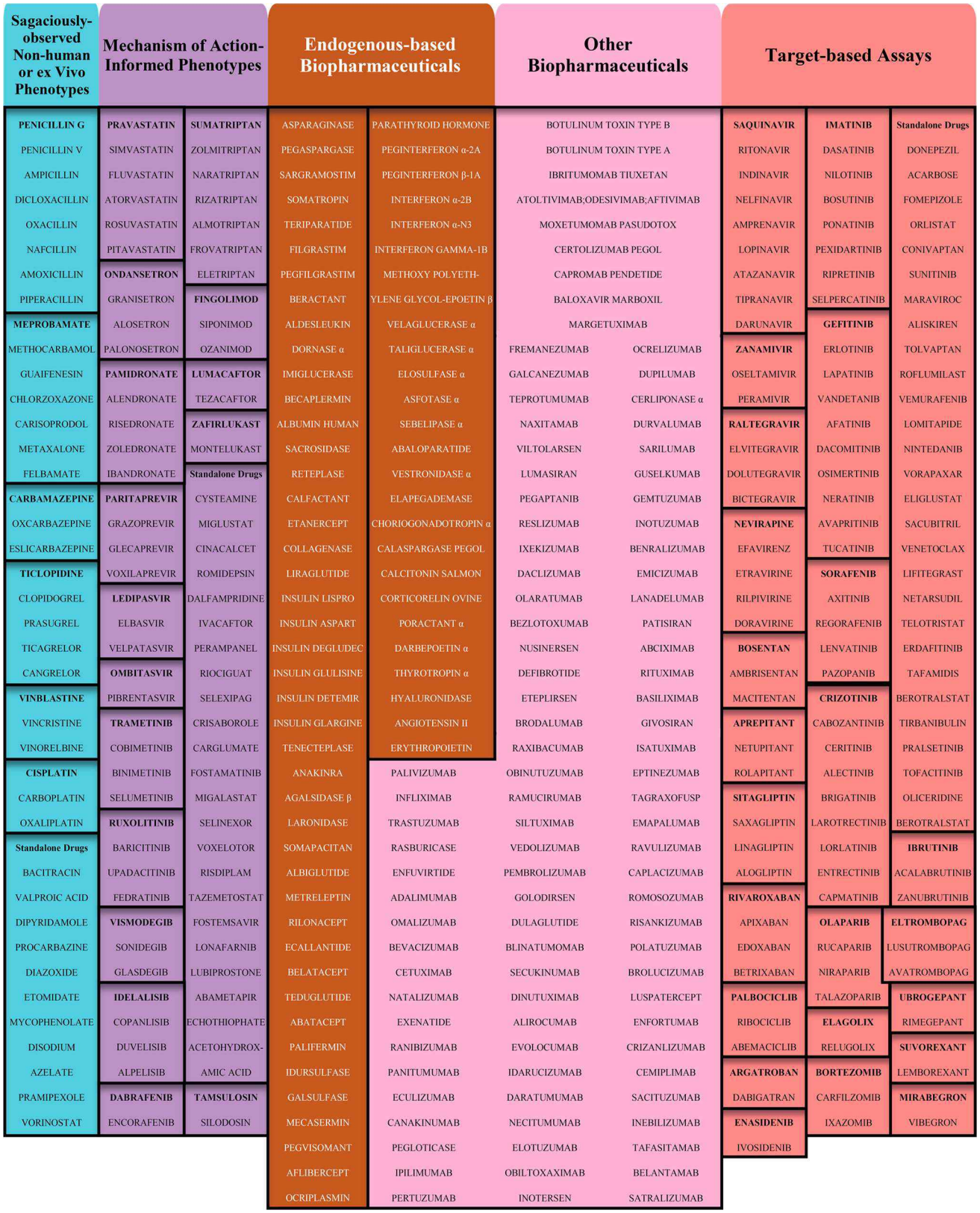


Figure 4. Discovery origins of all approved drugs. This is the detailed list of the drugs which have made up Figure 2a. Each rectangle represents a specific therapeutic class, and the color of each rectangle corresponds to the category as depicted in Figure 2 (which is also indicated in the headings above the therapeutic classes in this figure). Details of the discovery origins are available in Supporting Information 1.

assays where the output is merely the affinity of a molecule for a specific protein.

A minor portion of the discovery origins (the 10.6% human phenotypes plus the 6.8% historically used) can be traced back to serendipity and sagaciously observing the therapeutic effects

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

of substances in humans. Examples include chlorpromazine[223−225] (the prototype of almost all antipsychotics), imipramine[223,226,227] and iproniazide[228,229] (the prototypes of almost all antidepressants), acetaminophen,[230] corticosteroids,[231,232] disulfiram,[233] several diuretic[234] and diabetes medications,[211,235] methyldopa,[236] minoxidil,[237] flibanserin,[238] gemfibrozil,[239] nabilone,[240,241] anagrelide,[242] sildenafil,[243] azelaic acid,[244] hydroquinone,[245] and memantine.[246] It is fair to add to these cases the many drugs discovered based on historical observations, including metformin,[247] digoxin,[248] artemether,[249,250] podofilox,[251] ingenol mebutate,[201] fingolimod,[252,253] eribulin,[254,255] and spinosad.[194] These cases highlight the importance of sagacity in clinical settings.

The discovery origins of drugs suggest that another aspect that has undergone a notable transition during the evolution of drug discovery since the last century is a transition in the structure and functioning of drug discovery teams.[157,158] A few decades ago, drug discovery teams were small in number, comprising a few medicinal chemists and pharmacologists, all of whom were trying to answer the same question and who directly oversaw the relationships between chemical structures and modifications and their effects on phenotypes. Nowadays, drug discovery teams are significantly larger, and the goal of discovering a drug has been reduced and specialized into disconnected tasks.[256] The not-too-much-specialized structure of yestercentury's drug discovery teams enabled seamless two-way reiterative translation of phenotypic observations to structural selections and optimizations and observing the phenotypic outcomes of these optimizations. On the other hand, the specialized and fragmented structure of current drug discovery teams lends itself to the scheme of reductionist target-based drug discovery: one-way serial filtering and funneling in which phenotypic observations are primarily used only as terminal filters (e.g., see Figure 6 of ref 62).[46,56,57]

This insight can be inferred from the gleaned data that the "recent increase in productivity"[47,48] can be traced back more to the adaptation of the pharmaceutical industry to its failures rather than addressing their fundamental causes. For example, efforts have been redirected from the unaddressed challenge of complex CNS disorders toward the more reducible rare and monogenic disorders[7,48,49,257] or deriving analogs of drugs discovered decades ago, for example, sarecycline, eravacycline, omadacycline plazomicin, remimazolam, and lumateperone (Supporting Information 1). Even in some cases, drugs that were not brought forward to the market decades ago have been taken off the shelf and contribute to the apparent "increase in productivity." For example, rifamycin was originally discovered in 1963 using a phenotypic screen but was not developed further in the US; rather, it was instead optimized to rifampin which the US FDA approved in 1971.[189] Anyhow, in 2018, rifamycin itself was approved by the US FDA, and the drug was introduced to the US market.[258] Other similar examples include triclabendazole,[259] artesunate,[250] moxidectin,[260] and tafenoquine.[261] The peculiarity of these cases of returning to decades-old structures and molecules can be illuminated by heeding that the drug-like chemical space is estimated to be so vast, up to 10^{60} molecules,[262−264] that novel structures ought not to be scarce.

It is also fair to add to the disproportionate contribution of phenotypic observations the numerous postapproval labeled and off-label indications that have been added for many approved drugs. In many cases, such repurposings and added indications have been based on phenotypic observations made by astute clinicians.[265,266]

2.2. Are the Therapeutic Effects of "Target-Based" Drugs Reducible to Their Binding to a Single Protein?

2.2.1. Rationale. Although we have discovered that a disproportionate majority of the currently used drugs have been discovered by nonreductionist approaches that are now less prevalent, this is not definitive evidence that the reductionist approach of target-based drug discovery is inefficient because, as was cited earlier, this disparity may have been caused by other factors.

Another perspective from which we can assess target-based drug discovery is to question its role in the discovery of the drugs whose discovery origins we have identified as "target-based." This helps to investigate if the therapeutic effects of such drugs can really be reduced to the modulation of single proteins. We know that a majority of the drugs do not survive clinical phases because of a lack of efficacy, although many of them that have been discovered based on target-based drug discovery bind their targets with high affinity.[4] This implies that there may exist other variables that are consequential for the effectiveness of drugs, other than their binding to the targets with high affinity. One such variable is the degree of the relevance of the select target to the disorder. Interestingly, it has been shown that many of the supposed targets do not reliably relate to disorders.[116,267] Another possibility is that the therapeutic effects of drugs may emerge from suitable manipulation of a multitude of components in addition to the target. It is well-established in pharmacology that the therapeutic effects of many drugs are mediated by a multitude of mechanisms (see Supporting Information 3).[268−271] Moreover, it was recently shown that "off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials".[272−274] Having put all of these alongside the fact that even in target-based drug discovery, assessments of therapeutic effects play some role as terminal filters, it can be hypothesized that even for the "target-based" drugs, the therapeutic effects might not be entirely attributable to the scheme of target-based drug discovery. Therapeutic "off-target" mechanisms can be unconsciously and fortuitously selected by the phenotypic terminal filters. This hypothesis is strengthened by heeding that plenty of the approved drugs that we use in contemporary clinical practice have very modest discovery origins. They were discovered by observing their effects in humans or in vivo models either serendipitously or among a few hundred screened molecules (Supporting Information 1) rather than by systematically screening large libraries.[275]

In other words, attributing the discovery of the "target-based" drugs we identified in the previous section to target-based drug discovery and their affinity for a single "target" can be considered a case of survival bias.[46] Survival bias is the logical fallacy of focusing on the entities that have made it past some selection step and overlooking those that have not, typically because of their lack of visibility. When most of the drugs designed for binding to a single "target" with high affinity fail the efficacy phase of clinical trials, the efficacy of those that happen to pass this test should not be simply attributed to their high binding affinity.

2.2.2. Methods. To test the hypothesis that the therapeutic effects of many of the drugs discovered by the "target-based" approach are indebted to "off-target" mechanisms, I performed a systematic review (as in evidence-based medicine[276]) for each of the "target-based" drugs which were identified in the previous section. I searched PubMed and Embase with these queries: "[Drug]/pharmacology"[Majr] for PubMed and "Drug"/exp/

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

Table 2. Counts of "Off-Target" Therapeutic Mechanisms of "Target-Based" Drugs[a]

DONEPEZIL	40	BORTEZOMIB	69	ORLISTAT	10
ACARBOSE	14	CARFILZOMIB	2	RIMEGEPANT	1
ALISKIREN	12	EFAVIRENZ	2	ROFLUMILAST	9
RIVAROXABAN	7	NINTEDANIB	229	SACUBITRIL	2
EDOXABAN	1	GEFITINIB	111	TIRBANIBULIN	2
ZANAMIVIR	1	ERLOTINIB	109	VENETOCLAX	2
OSELTAMIVIR	1	LAPATINIB	16	SAQUINAVIR	11
FOMEPIZOLE	2	VANDETANIB	114	RITONAVIR	8
SITAGLIPTIN	13	AFATINIB	41	INDINAVIR	7
SAXAGLIPTIN	20	OSIMERTINIB	8	NELFINAVIR	8
LINAGLIPTIN	1	NERATINIB	4	LOPINAVIR	2
ALOGLIPTIN	1	SORAFENIB	140	ATAZANAVIR	1
ELTROMBOPAG	1	PAZOPANIB	107	MARAVIROC	3
ARGATROBAN	1	AXITINIB	102	ELTROMBOPAG	1
DABIGATRAN	2	REGORAFENIB	20	PALBOCICLIB	38
MIRABEGRON	2	LENVATINIB	10	RIBOCICLIB	14
DASATINIB	158	IMATINIB	78	ABEMACICLIB	17
NILOTINIB	63	CERITINIB	9	TALAZOPARIB	3
PONATINIB	13	OLAPARIB	4	CABOZANTINIB	5
BOSUTINIB	74	RUCAPARIB	17	ACALABRUTINIB	3
CRIZOTINIB	148	NIRAPARIB	2	VEMURAFENIB	18
TOFACITINIB	34	IBRUTINIB	40	SUNITINIB	270

[a]Details are available in Supporting Information 3. (The reason why the counts in Table 2 are different from the number of mechanisms listed for each drug in Supporting Information 3 is that the counts in Table 2 reflect the deduplicated counts of the mechanisms which also have been highlighted in Supporting Information 3).

mj/dd_pd for Embase. The retrieved citations were deduplicated using Systematic Review Assistant-Deduplication Module (SRA-DM)[277] (the retrieved citations from each database and their deduplicated sum are available for each drug in Supporting Information 2). I manually (not by automated methods such as natural language processing) reviewed[276] the citations and extracted mechanisms that were experimentally shown or suggested to mediate the effects related to the therapeutic effect for which the drug was initially approved but were not mediated by the "target(s)" the drug was discovered based on. To rule out the downstream effects of the binding of drugs to their "targets," I excluded from the extracted "off-target" mechanisms, those that were mediated by the first shell or the second shell interacting proteins. I retrieved these interactors from STRING v11[278] with these settings: "experiments" or "databases" for active interaction sources; highest confidence (0.900) for the minimum required interaction score; 500 for the maximum number of interactors in the first and the second shells. Those "off-target" mechanisms that were based on the direct binding of the drugs to the "off-target" proteins were exempt from this exclusion criterion. Because in many cases, several different studies had referred to the same mechanism for the therapeutic effect of one drug, I documented and cited all of these different studies but highlighted only one of such duplicates. The reason why the counts in Table 2 are different from the number of mechanisms listed for each drug in Supporting Information 3 is that the counts in Table 2 reflect the deduplicated counts of the mechanisms which are also mentioned in front of each drug in the tables of Supporting Information 3. To summarize, the extracted mechanisms needed to have these criteria:

(1) Based on the reviewed experimental pharmacological studies, they were proposed to mediate, to any extent, the therapeutic effects the drug was approved for.

(2) They depended neither on the "target(s)" the drug was discovered based on nor the first or second shell interacting proteins of these "target(s)", except where the mechanisms were based on direct binding of the drugs to these first or second shell interacting proteins.

2.2.3. Results and Discussion. The systematic review (which included a manual[276] review of 31027 unique articles) confirmed the hypothesis. Many "target-based" drugs have numerous "off-target" therapeutic mechanisms (Table 2 and Supporting Information 3). For example, donepezil, which was discovered and developed as an acetylcholinesterase inhibitor, was found to have 40 therapeutic mechanisms independent of acetylcholinesterase, including anti-inflammatory and immunomodulatory effects;[279−286] vasoprotective,[287−293] neuroprotective,[294−302] and antioxidant properties;[285,288,303,304] inhibiting neuronal apoptosis,[305−307] increasing neurogenesis via several pathways[308] like brain derived neurotrophic factor,[309] insulin-like growth factor 1,[310−312] and SRC;[313,314] stimulating oligodendrocyte differentiation and myelin-related gene expression;[315] direct effects on microtubule affinity regulating kinase 4,[316] nicotinic acetylcholine receptors,[317,318] sigma nonopioid intracellular receptor 1,[319−324] and calcium, potassium, and sodium channels,[298,299,307,325] downregulating miRNA-206;[326] preventing glutamate neurotoxicity;[327−331] protecting against oxygen−glucose deprivation-induced injury;[307,332−335] regulating serum adipokine levels;[336] increasing the expression of autoantibodies against amyloid beta;[337] increasing the activity of α-secretase and decreasing the activity of β-secretase;[338,339] reducing the production[339,340] and increasing the clearance of amyloid beta;[341,342] reducing the phosphorylation of tau;[340,343] and increasing the trafficking and activity of ADAM10 and ADAM17.[344]

Another example is crizotinib. Independent of inhibiting MET and ALK, it binds to 146 other kinases with considerable affinities,[345,346] induces oxidative DNA damage and apoptosis,[347−350] and has immunomodulatory effects through inhibit-

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

ing the macrophage stimulating 1 receptor and upregulating the major histocompatibility complex molecules.[348,351−353]

This implies that the contribution of target-based drug discovery to approved drugs is even far less than 9.4%. If it was solely up to the scheme of reductionist target-based drug discovery, none of these "off-target" therapeutic mechanisms would have existed. They have been unconsciously and blindly selected because of the terminal assessments of therapeutic effects and do not necessarily accompany all molecules selected based on their binding to single "targets." Notably, these counts are inevitably restricted to mechanisms that have been unraveled thus far; it is reasonable to expect that the actual "numbers" would be much higher.[354]

2.3. Is Binding the "Target" with High Affinity Even Relevant? *2.3.1. Rationale.* Now that we have observed that most drugs have been discovered by phenotypic observations and even the "target-based" drugs are not as "target-based" as claimed, how much is binding "targets" with high affinity, the holy grail of target-based drug discovery, relevant at all for the therapeutic effects of drugs? By selecting and filtering for molecules with higher binding affinities for a "target," target-based drug discovery is based on this presumption that drugs with therapeutic effects are enriched among molecules with higher binding affinities for the "target." A rough implication of this presumption is that the drugs which have already been approved probably have relatively higher binding affinities for the "target" that mediates their therapeutic effects, at least when their mechanisms of action are based on competitive antagonism and inhibition.

2.3.2. Methods. To test this presumption of target-based drug discovery that drugs with therapeutic effects are enriched among molecules with higher binding affinities for their "target," I investigated the percentile rank of each approved drug's affinity for each of its therapeutic "targets" among all ChEMBL[355] ligands of that "target." I retrieved the targets of approved drugs from "a comprehensive map of molecular drug targets" (Supporting Information S2 of ref 356, archived) which has compiled the "therapeutic targets" of approved drugs which are defined as "those proteins or other biomolecules (such as DNA, RNA, heparin, and peptides) to which the drug directly binds, and which are responsible for the therapeutic efficacy of the drug.[356]" I excluded drug-target pairs with these mechanisms of action: agonists, activators, biopharmaceuticals, channel-openers, modulators, activators, allosteric antagonists, partial agonists, inverse agonists, DNA and RNA inhibitors, "cell membrane inhibitors," releasing agents, and chelating agents. Then I retrieved the available binding measurements for the remaining "targets" from ChEMBL27[355] with these curations: measurements lacking a pChEMBL value or with pChEMBL values expressed in any relation other than "equal to" like "smaller than" or "bigger than" were excluded; measurements expressed in other than IC_{50} or K_i values were excluded; based on a previous study on the comparability of measures of inhibitory activity,[357] 0.30 was added to pChEMBL values of measurements expressed in IC_{50} values to make the measurements more comparable; pChEMBLs of molecules with more than one remaining measurement were averaged, and one final pCHEMBL was recorded for each ligand. After excluding "targets" with less than 100 remaining ligands, I calculated the percentile rank (inclusive) of the affinity of the approved drugs among the remaining ligands for each target. Percentile ranks of all salt and protonation alternative forms of each drug (available in ChEMBL) were averaged, weighted based on the count of measurements for each form.

2.3.3. Results and Discussion. While affinities of a notable number of approved drugs for their therapeutic "targets" are relatively low, most of them incline toward the highest percentile ranks (Figure 5). (The detailed data for all of the drug-target pairs are available in Supporting Information 4, and the summary data are available at Supporting Information 5.) This suggests that binding to "targets" with high affinity is relevant for therapeutic effects. Considering this alongside the minor contribution of target-based drug discovery to approved drugs and the numerous "off-target" therapeutic mechanisms of "target-based" drugs, it can be stated that binding to single "therapeutic targets" with high affinity is only a single aspect of a drug's therapeutic effect on phenotypes.

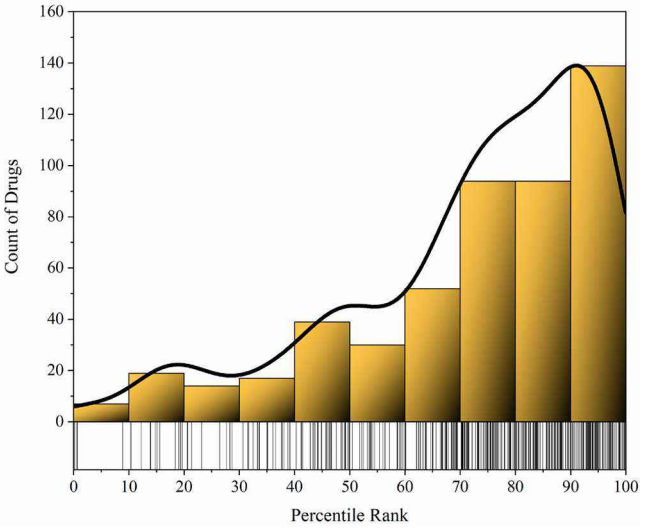


Figure 5. Percentile ranks of the affinity of approved drugs among all ChEMBL ligands of their therapeutic "targets."

2.4. Problems with the Theoretical Foundation of Target-Based Drug Discovery. We can reach a more definitive conclusion regarding the efficiency and rationality of target-based drug discovery by assessing the soundness of its theoretical basis.

2.4.1. Where Does the Reductionism of Target-Based Drug Discovery Come from? In an introductory speech on drug discovery and design I heard a few years ago, the human body was likened to a clock, a disorder was likened to a defect in a cogwheel of this clock, and the purpose of drug discovery was presented as designing a molecule which could bind this defective cogwheel. This simile showcases a deep-seated fallacy of target-based drug discovery: The functioning of the human body is presumed to be comparable to that of a machine. The machine mindset toward biological systems is a reductionist fallacy that has been pervasive for a few centuries.[358−363] It stems from our humane approach to designing and building systems. When we aim to design and build a specific system, while designing it, we design each part with specific functions in mind for that part in the eventual function of the whole system. Because of this, each function or dysfunction of a car or a spaceship can be traced back to specific parts by a *chain of tasks*. The fallacy of the machine mindset is its presupposition that this delineated chain of tasks between parts and functions is universal among all systems. Biological systems are not the result of the

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

same approach to designing systems. They are highly complex and the result of evolution by means of selection. Selection does not assign specific roles to parts. It only selects among the diverse ultimate outputs and phenotypes of systems created by random variations.

All organisms, similar to cities, the Internet, and the stock market, are *self-organizing*[364−366] complex systems. Their parts are not *chained* to their behaviors. Even though some elements may have accentuated roles in some functions or dysfunctions, there is usually no clear-cut and separable delineation.[363,367] This leads to several general distinctive features in complex systems compared to chained systems: extensive multifunctionality of different parts;[368] continuous and spectral, rather than clear-cut and binary-like causal relationships between the states of parts and systems' ultimate behaviors;[369] capability of "self-control" by frequent and extensive feedback between the individual parts and the whole system;[362,370,371] extensive redundancy;[372−374] vestigiality;[375] and degeneracy or multiple realizability, in which several nonidentical sets of processes yield identical ultimate outputs.[125,376−378]

Thus, a central problem with the theoretical framework of target-based drug discovery is that following the fallacy of the machine mindset and neglecting the differences between complex and chained systems, it has a too simplistic attitude toward the organization and function of biological processes. See ref 147 for a mathematical discussion of the implications of the complexities of biological systems and "the impossibility for a stimulus imposed on a single node of a network to generate a substantial modification of the general system behavior when in the presence of non-strictly linear causal chains."

2.4.2. Where Does the Efficiency of Higher-Level Observations Come from? We have presented a significant amount of evidence to support the contention that phenotypic drug discovery is more efficient than reductionist target-based drug discovery. But why is that? Is it only because of the fact that many disorders are not reducible to a single protein? If so, can drug discovery based on multiple targets, as in polypharmacological approaches,[143] be similarly efficient?

Fortunately, integrated information theory (IIT) provides a mathematical and formal framework[379] to investigate this.[380] Although this formalized theory, whose predictions are corroborated by empirical and mathematical evidence,[381−386] is under investigation and has received some criticism for its validity in explaining consciousness,[387,388] its applicability for investigating causal structures of diverse systems from the "intrinsic perspective" of systems themselves is well-documented.[382,383,389−393] Succinctly, IIT investigates "how the parts of the system, by being in a specific state, constrain the potential past and future states of the system itself".[390]

Based on IIT, it has been shown that describing the states of systems at spatiotemporally coarse-grained higher levels can increase information and intrinsic cause-effect power (Φ) (Figure 6).[378,389−391,394−397] This increase is mainly because of the increased captured specificity of a system's mechanisms at higher levels as noisy (indeterministic) and degenerate micro elements get grouped into more deterministic and less degenerate higher-level descriptions. Later, along with confirmation in a biological model, it was demonstrated that spatiotemporal higher-level descriptions can provide even more intrinsic cause-effect power through *black-boxing* compared to average-based coarse-graining, especially in systems with heterogeneous, integrated specialized parts, epitomized by organisms.[391,394] Black-boxing was first proposed in cybernetics

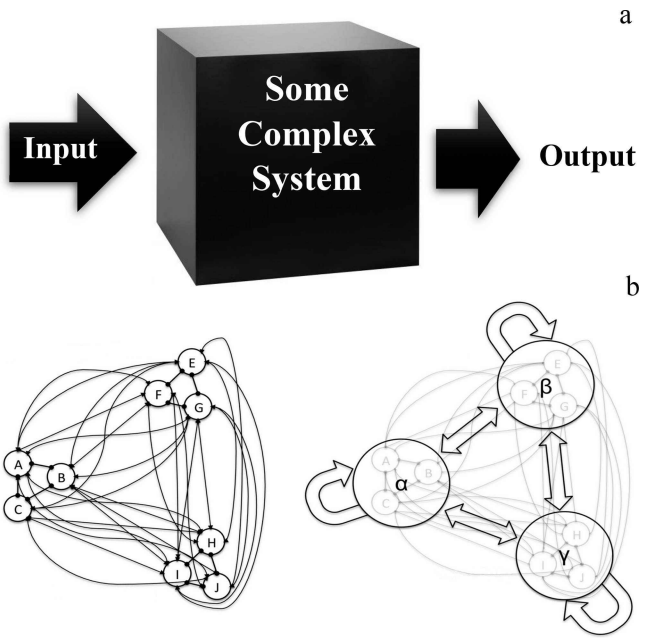


Figure 6. Two methods of going from lower to higher levels. (a) Black-boxing; (b) average-based coarse-graining; from ref 389. Copyright 2013 by National Academy of Sciences.

to enable the modeling of highly complicated and complex systems by hiding their inner workings and only taking into account their inputs and outputs.[398−400] It should be noted that, as one of the fathers of cybernetics, Ross Ashby, articulated, "Black Box theory is, however, even wider in application than these professional studies. The child who tries to open a door has to manipulate the handle (the input) so as to produce the desired movement at the latch (the output); and he has to learn how to control the one by the other without being able to see the internal mechanism that links them. In our daily lives we are confronted at every turn with systems whose internal mechanisms are not fully open to inspection, and which must be treated by the methods appropriate to the Black Box.[400]" It can be said that coarse-graining and black-boxing increase cause-effect power and informativeness by capturing simpler higher-level attractor states of highly complex lower levels[147,401] and parameter space compression.[402] References 403−416 present a few other examples of increased simplicity and informativeness at higher levels.

All of these imply that even if target-based drug discovery recorded the effects of molecules on all proteins and every other single component of the human body,[143,147] as in a hypothetical and impractically ideal polypharmacological target-based scheme, it would still have inferior efficiency compared to phenotypic drug discovery. Because it investigates the effects of molecules on the human body at higher levels (black-boxing), phenotypic drug discovery is endowed with superior cause-effect power and informativeness. This is notably crucial in the context of what question is the best to ask and what variable is the best to target in generative and predictive machine learning models used in drug discovery.[58,59]

3. TARGET-BASED DRUG DISCOVERY IS VALUABLE

Throughout the history of drug discovery, various technologies, including computational chemistry, high-throughput screening, and combinatorial chemistry, have emerged that, at first, garnered significant attention and optimism but, over time,

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

their limitations also came into focus. These tools have now become essential components integrated into many drug discovery campaigns, albeit with realistic expectations. The data analyzed in this study suggest that a similar awareness of the limitations of target-based drug discovery is needed in the field. However, it should be acknowledged that the numerous target-based tools which have been developed during the previous decades can be of immense assistance in the path forward.

First, some disorders, such as monogenetic Mendelian disorders, which can be reduced to single or a few proteins are, to varying extents, amenable to be approached by target-based drug discovery. The feasibility of reducing some disorders to a few proteins is also illustrated by the success of some monoclonal antibodies. Second, target-based drug discovery is an important asset in the context of analog-based drug discovery for modifying and refining structures. Analog-based drug discovery is itself a valuable tool for obtaining incremental, yet still important, improvements in medications.[153] Additionally, gathering sufficient and suitable higher-level data might be too inefficient and burdensome for some disorders. Among such burdens, the possible need to sacrifice a considerable number of animals is noteworthy, even though technologies like organoids, organs-on-chips, and *in silico* testing can mitigate this need. Target-based tools can greatly contribute in these cases. Another important role of target-based tools is analyzing the lower-level basis of therapeutic effects. The lower-level data obtained from target-based approaches can be employed in approaches like systems biology, systems pharmacology,[139−143,147] and multi-scale modeling[417] in order to help study how therapeutic effects emerge from lower-level phenomena. Such analyses can be of great value when they are appropriately integrated into drug discovery frameworks that try to derive benefit from both lower-level and higher-level data, like the framework suggested below.

4. CONCLUDING REMARKS

Based on the large amount of data that we have analyzed, the currently dominant reductionist approaches in drug discovery seem to be inefficient. Instead, prioritizing higher-level observations in selecting and optimizing molecules seems to be an evidence-based approach to increase efficiency. We have seen that rational drug discovery emerged from the attempts to guide and focus the empirical screening of random substances based on available scientific evidence. It can be said that reductionist target-based drug discovery is irrational in this sense as the available scientific evidence seems to contradict its methodology. The key problem and deviation in the transition from rational drug discovery to reductionist target-based drug discovery has been the extent of the employed reductionism. There is a large difference between rational drug discovery using the knowledge of the mechanism-of-action of drugs and, on the other side, the attempt of reductionist target-based drug discovery to reduce the therapeutic effects of drugs to single "target" proteins. For example, the five great pioneers of rational drug discovery mentioned earlier, Ehrlich, Hitchings, Elion, Black, and Janssen, four of whom have received Nobel Prizes in physiology or medicine, discovered all of those numerous approved drugs based on phenotypic observations,[89−95,97] despite all of the underlying hypotheses that they had developed and used to direct these observations[88,96,98−103] (see Supporting Information 1).

The important point is that, generally, therapeutic effects cannot be reduced to a molecule binding to a few proteins. This irreducibility was illustrated in section 1.6.2 and in Supporting Information 3 where we found out that many of the approved drugs with target-based origins benefit from numerous off-target mechanisms for their therapeutic effects. By solely focusing on a single component of therapeutic effects, reductionist target-based drug discovery severely limits its efficiency. In contrast, phenotypic observations have a more direct and closer connection to the ultimate sought-after therapeutic effects. By black-boxing[398−400] the immense complexity of the body and its disorders, phenotypic drug discovery can circumvent all of the complexities inside the body and directly aim for the ultimate goal, which is a therapeutic effect rather than a hypothetical, lower-level component of that goal. This more direct and closer connection can provide higher predictivity, which itself has a substantial effect on the approval rate.[49,58,59]

It might be argued against my criticisms that target-based drug discovery exploits the benefit of phenotypic observations in animals and humans, to varying extents (see ref 418 for an example). Indeed, this is true and was the basis of our investigations in section 1.6.2. However, as pointed out earlier, the problem is that phenotypic observations within target-based drug discovery do not primarily inform the design of structures since they are only used as terminal filters in a one-way serial funneling manner[46,56,57] (see Figure 6 of ref 62 for an illustration of this point). The structures of molecules are designed in the first place based on their binding affinity to the target and only filtered in the last steps based on their therapeutic effects. In contrast, in phenotypic drug discovery, molecules are selected based on directly observing the phenotypic effects of all molecules. As demonstrated in section 1.6.2 and Supporting Information 3, the binding of a molecule to single proteins is but one component of therapeutic effects, and there may be too weak a correlation between binding to a single target with high affinity and eliciting a therapeutic effect. Therefore, many drugs that are filtered out in the initial steps due to their low binding affinity may actually possess far more potent therapeutic effects than those that get selected based on their high binding affinity and are even subsequently selected in animal studies. In other words, the low predictivity of discovering drugs based on their binding affinity to a few proteins significantly limits and lowers the predictivity of the whole pipeline of a drug discovery framework whose cornerstone is the binding affinity of a molecule to a single protein instead of the therapeutic effects themselves.[49] This implicates any such approach, albeit some have tried to balance the reductionism of target-based drug discovery by considering factors other than binding a single target, like tissue exposure and the differences that any individual patient may have.[419,420]

The increased predictivity that higher-level observations can provide has important implications for the application of artificial intelligence and machine learning in drug discovery. The presented data suggest that, generally, these powerful technologies are not currently being used to answer the right question.[58,59] The ultimate goal is to design and select molecules with desired therapeutic effects on phenotypes, and the question needs to be posed commensurate with this objective.[49,50] Nevertheless, based on target-based drug discovery, this goal is segmented and reduced to ancillary[58] goals like designing molecules with higher affinities for a single "target";[421] ancillary goals which, based on the evidence presented here, may have little to do with that ultimate objective. Drawing upon our discussion in section 1.6.4, selecting and optimizing molecules based on therapeutic effects themselves, rather than a single component of these effects, can provide far more cause-effect

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

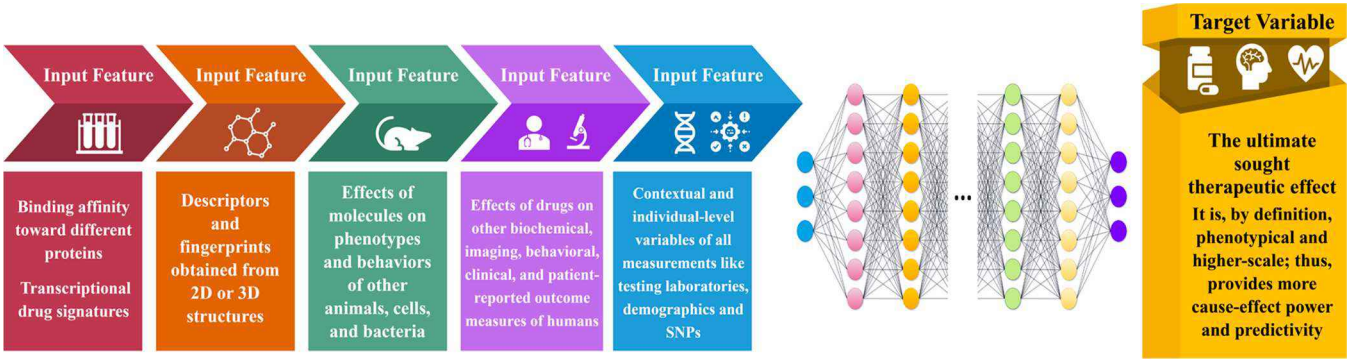


Figure 7. A preliminary proposal for a drug discovery approach which respects the primacy of therapeutic effects and gets benefit from both the tools which have been used in target-based drug discovery and the immense potential of artificial intelligence. Patterns can be recognized by various machine learning methods (e.g., deep neural networks as in this figure) between the structures of molecules and their aimed therapeutic effects. The data of the effects of drugs on lower levels and mesoscales and contextual and individual-level variables of the measurements can also be added to the input data to increase the accuracy of the recognized patterns and the trained model.

power. Apart from the rate of successfully demonstrating therapeutic efficacy in clinical studies and securing marketing approval,[49,58,59] this can greatly influence the magnitude of the effect size, the clinical significance, and the real-world value of approved drugs;[422,423] important aspects of approved drugs that, as we discussed early in the article, have been the subject of criticism by experts and available evidence.

As a very preliminary proposal, it is conceivable to develop machine learning models whose target variables would be measures of the therapeutic effect of molecules in humans or some highly predictive model. The input features of these models could be the diverse variables of the effects of drugs on lower levels; e.g., the binding affinity of drugs to various proteins, as in proteome-wide affinity fingerprints, transcriptional drug signatures, and descriptors and fingerprints obtained from the 2D or 3D structures of the molecules themselves (Figure 7). A potential starting point for building such models could be mining the animal and human data available in the published literature (and also unpublished data like electronic health data,[424−426] patient-reported outcomes,[427] and proprietary data). This immense trove of data that has been obtained at the expense of millions of lives, billions of dollars, and decades of research can be mined and capitalized through approaches like systematic review. Contextual and other individual-level variables can also be added to the input features to enhance accuracy. Of course, this framework is very preliminary, and the gathering of sufficient data with acceptable quality, both at lower and higher levels, might be impractical in many cases to build decent machine learning models. Nonetheless, such an approach, which may be termed *systematic review with cheminformatics meta-analysis*, can provide valuable initial qualitative insights even in these cases.[428]

We may hope that after becoming aware of the limitations of target-based drug discovery, having been armed with its capabilities and advanced technologies like machine learning and deep learning, high-content imaging, high-throughput phenotypic assays,[429,430] wearable biosensors,[431] Internet-of-things, organoids,[432,433] and electronic health data,[424−426] while also paying more attention to conceptual progress,[434] we will not only be able to surpass the current low productivity but even to supplant current gold-standard drugs with safer and far more effective alternatives.

5. LIMITATIONS

Emerging target-based approaches like protein-degrading technologies have the potential to alleviate the overall inefficiency of target-based drug discovery in the future; however, because of their recent emergence, they were not represented in this analysis.

Concerning section 1.6.1, it must be noted that there are no established criteria and definitions to determine which drugs should be classified as target-based or phenotype-based. Consequently, the definitions provided here might be contested. For instance, one could argue that any drug discovered with a specific "target" in mind should be considered target-based. It should be remembered that terms like target-based, phenotype-based, discovery origin, and drug-class are all abstract and arbitrary concepts and constructs, and any attempt to find concrete definitions in the outside world may be futile. Given the lack of pre-established definitions, the definitions used in this analysis are inevitably subjective. Nevertheless, I have tried my best to provide simple definitions that would be pragmatic and maximally useful for our purpose and also would provide the most objectivity in the categorizations.[435] These criteria also align with those employed in the seminal study of Swinney and Anthony.[54] Furthermore, since the process of drug discovery is highly complex and unique for each approved drug, attempting to fit it into discrete and concise categories can introduce subjectivity in both defining and assigning the categories,[436,437] I have tried to mitigate this binary bias by trying to fully document the path I went through to identify and assign each discovery origin. I also highlighted (in yellow) the parts which better display the rationale behind the assigned labels. These facilitate remaining conscious of the whole process of the discovery of each drug beyond the discrete labels and their statistics.

I was not able to find the discovery origins of several drugs. In some cases, the discovery origin was not unambiguously identifiable, and it was not recorded what observation first identified a relationship between a therapeutic class and its therapeutic effect. The discovery origins of those drugs whose accurate discovery accounts were not found but were undoubtedly discovered based on phenotypical observations, according to their discovery year and the trends of the discovery year, were categorized as nonhuman or *ex vivo* phenotype. There were instances where I found a discovery-related paper, for example in PubMed, but could not find its full-text webpage. Since feature trees are biology-agnostic, establishing a static

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

cutoff limit for defining analogs was not feasible. For example, although mechlorethamine and chlorambucil have near-identical pharmacophores, their distinct auxophores result in low global similarity. Consistent with the seminal study of Swinney and Anthony, biologics were excluded from the comparison of drug discovery approaches. I have attributed the discovery origins of all me-too drugs to the discovery origins of their leading first-in-class drugs. Confirmation bias may have influenced my search for discovery origins. I have included drugs that have received accelerated conditional approval.

Concerning section 1.6.2, the mechanisms of organisms' behaviors are hardly localizable.[363,367,438] Even state-of-the-art methods like using si-RNA to illuminate the mechanism-of-action of drugs have many flaws,[439−441] as do animal studies using pharmacological tool compounds to investigate the mechanisms of drugs. Many studies that I used in investigating the "off-target" therapeutic mechanisms of "target-based" drugs were of this kind. The relevance of some of the "off-target" mechanisms I have counted to the therapeutic effects of the drugs is based on general association rather than explicit evidence, particularly those derived from kinome inhibition assays. Furthermore, despite my best efforts, it is possible that some mechanisms that have been counted as independent therapeutic mechanisms may still be traced back to the same underlying mechanism.

As for section 1.6.3, while ChEMBL compiles ligands for each protein without imposing restrictions based on low or high affinity, it is plausible to hypothesize that the ligands retrieved from ChEMBL for each protein are enriched with molecules exhibiting higher affinities compared to randomly selected ligands whose affinities to that protein have not been measured. As a result, it is reasonable to hypothesize that the percentile ranks of the affinity of the approved drugs among random molecules would be higher than among the ChEMBL ligands for each protein.

■ ASSOCIATED CONTENT

Data Availability Statement

All relevant data are available in the Supporting Information section of the article. In Supporting Information 1, the titles of the drugs are hyperlinked to their web pages on Inxight Drugs[151] or DrugBank.[442] These links have been archived, mostly between the 16th and 18th of June 2021, and can be accessed via Wayback Machine (web.archive.org). Below most target-tables in Supporting Information 2, there is a permalink to the STRING protein−protein interaction network for that target, as well as other relevant files. Code Availability: The analysis workflow used in section 2.3 is available at https://kni.me/s/qI6JhDcsvL4JPmfB.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c01737.

Supporting Information 1: detailed discovery origins of all approved drugs (PDF)

Supporting Information 2: retrieved citations for the systematic review of "off-target" therapeutic mechanisms of target-based drugs (ZIP)

Supporting Information 3: "off-target" therapeutic mechanisms of "target-based" drugs (PDF)

Supporting Information 4: detailed data of the analysis of the percentile ranks of the affinity of approved drugs among all ChEMBL ligands of their therapeutic targets (ZIP)

Supporting Information 5: summary data of the analysis of the percentile ranks of the affinity of approved drugs among all ChEMBL ligands of their therapeutic targets (XLSX)

■ AUTHOR INFORMATION

Corresponding Author

Arash Sadri − *Lyceum Scientific Charity, Tehran, Iran 1415893697; Interdisciplinary Neuroscience Research Program (INRP), Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran 1417755331; Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran 1417614411;* orcid.org/0000-0002-3726-243X; Email: arashsadri@lyceum.charity

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jmedchem.2c01737

Notes

The author declares the following competing financial interest(s): I declare that I have two patent applications relevant to this manuscript.

Biography

Arash Sadri has recently completed his Doctor of Pharmacy (PharmD) program at Tehran University of Medical Sciences (2014−2022). Following his dream of discovering drugs, Arash has developed a keen interest in cheminformatics, computer-aided drug design, computational biology, and systems pharmacology. He has invented a new binding affinity prediction approach called Consensually Docked 5D-QSAR and serves as a research consultant at Aras Pharmaceutical. Additionally, Arash has founded Lyceum Scientific Charity to uphold two core principles of science: the pursuit of truth above all else and serving the public good.

■ ACKNOWLEDGMENTS

I appreciate the valuable discussions I have had with my friends, Sepideh Paknezhad, Ramtin Abdzadeh, Mohammadali Niazi, Mohammad Saber, and Saman Ghods. I express my gratitude to Professor Latifeh Navidpour for her kindness, patience, and helpful comments. I am thankful to Professor Azadeh Ebrahim-Habibi and Professor Shahin Akhondzadeh for their kind support. I appreciate the collaboration I have had with the Iranian Pharmaceutical Students Association (IPhSA), Tehran, Iran. Finally, I deeply thank Aida Aliaskari for her kind assistance in preparing the presented materials.

■ REFERENCES

(1) Pammolli, F.; Magazzini, L.; Riccaboni, M. The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discovery* **2011**, *10*, 428−438.

(2) Schuhmacher, A.; Hinder, M.; von Stegmann Und Stein, A.; Hartl, D.; Gassmann, O. Analysis of pharma R&D productivity - a new perspective needed. *Drug Discovery Today* **2023**, *28*, No. 103726.

(3) Cummings, J. L.; Morstorf, T.; Zhong, K. Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimers Res. Ther.* **2014**, *6*, 37.

(4) Wong, C. H.; Siah, K. W.; Lo, A. W. Estimation of clinical trial success rates and related parameters. *Biostatistics* **2019**, *20*, 273−286.

(5) Wouters, O. J.; McKee, M.; Luyten, J. Estimated research and development investment needed to bring a new medicine to market, 2009−2018. *JAMA* **2020**, *323*, 844−853.

(6) Coller, B. S.; Califf, R. M. Traversing the valley of death: A guide to assessing prospects for translational success. *Sci. Transl. Med.* **2009**, *1*, No. 10cm19.
(7) Jacob, B. Big pharma backed away from brain drugs. Is a return in sight? *BioPharma Dive*, 2020. https://www.biopharmadive.com/news/pharma-neuroscience-retreat-return-brain-drugs/570250/, http://web.archive.org/web/20210802144618/http://web.archive.org/screenshot/https://www.biopharmadive.com/news/pharma-neuroscience-retreat-return-brain-drugs/570250/.
(8) GBD 2019 Mental Disorders Collaborators.. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990−2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **2022**, *9*, 137−150.
(9) Arias, D.; Saxena, S.; Verguet, S. Quantifying the global burden of mental disorders and their economic value. *EClinicalMedicine* **2022**, *54*, No. 101675.
(10) Christensen, M. K.; Lim, C. C. W.; Saha, S.; Plana-Ripoll, O.; Cannon, D.; Presley, F.; Weye, N.; Momen, N. C.; Whiteford, H. A.; Iburg, K. M.; McGrath, J. J. The cost of mental disorders: a systematic review. *Epidemiol Psychiatr Sci.* **2020**, *29*, No. e161.
(11) Leucht, S.; Helfer, B.; Gartlehner, G.; Davis, J. M. How effective are common medications: A perspective based on meta-analyses of major drugs. *BMC Med.* **2015**, *13*, 253.
(12) Moncrieff, J.; Kirsch, I. Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. *Contemp. Clin. Trials* **2015**, *43*, 60−62.
(13) Kirsch, I. Placebo effect in the treatment of depression and anxiety. *Front Psychiatry* **2019**, *10*, 407.
(14) Ioannidis, J. P. Effectiveness of antidepressants: An evidence myth constructed from a thousand randomized trials? *Philos. Ethics Humanit. Med.* **2008**, *3*, 14.
(15) Smith, C. E. P.; Prasad, V. Assessment of new molecular entities approved for cancer treatment in 2020. *JAMA Netw. Open* **2021**, *4*, No. e2112558.
(16) Grössmann, N.; Robausch, M.; Rosian, K.; Wild, C.; Simon, J. Monitoring evidence on overall survival benefits of anticancer drugs approved by the European Medicines Agency between 2009 and 2015. *Eur. J. Cancer* **2019**, *110*, 1−7.
(17) Ribeiro, T. B.; Colunga-Lozano, L. E.; Araujo, A. P. V.; Bennett, C. L.; Hozo, I.; Djulbegovic, B. Single-arm clinical trials that supported FDA accelerated approvals have modest effect sizes and were at high risk of bias. *J. Clin. Epidemiol.* **2022**, *148*, 193−195.
(18) Zhang, Y.; Naci, H.; Wagner, A. K.; Xu, Z.; Yang, Y.; Zhu, J.; Ji, J.; Shi, L.; Guan, X. Overall Survival Benefits of Cancer Drugs Approved in China From 2005 to 2020. *JAMA Netw. Open* **2022**, *5*, No. e2225973.
(19) Ward, D. J.; Slade, A.; Genus, T.; Martino, O. I.; Stevens, A. J. How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001−2012. *BMJ. Open* **2014**, *4*, No. e006235.
(20) Haslam, A.; Gill, J.; Prasad, V. The response rate of alternative treatments for drugs approved on the basis of response rate. *Int. J. Cancer* **2021**, *148*, 713−722.
(21) Fojo, T.; Mailankody, S.; Lo, A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: The John Conley lecture. *JAMA Otolaryngol Head Neck Surg* **2014**, *140*, 1225−1236.
(22) Wieseler, B.; McGauran, N.; Kaiser, T. New drugs: Where did we go wrong and what can we do better? *BMJ.* **2019**, *366*, l4340.
(23) Rupp, T.; Zuckerman, D. Quality of life, overall survival, and costs of cancer drugs approved based on surrogate endpoints. *JAMA Int. Med.* **2017**, *177*, 276−277.
(24) Chen, E. Y.; Raghunathan, V.; Prasad, V. An overview of cancer drugs approved by the US Food and Drug Administration based on the surrogate end point of response rate. *JAMA Int. Med.* **2019**, *179*, 915−921.
(25) Chen, E. Y.; Haslam, A.; Prasad, V. FDA acceptance of surrogate end points for cancer drug approval: 1992−2019. *JAMA Int. Med.* **2020**, *180*, 912−914.
(26) Pease, A. M.; Krumholz, H. M.; Downing, N. S.; Aminawung, J. A.; Shah, N. D.; Ross, J. S. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: Systematic review. *BMJ.* **2017**, *357*, j1680.
(27) Alabaku, O.; Laffey, T. N.; Suh, K.; Li, M. Trends in endpoint use in pivotal trials and efficacy for US Food and Drug Administration-approved solid tumor therapies, 1995−2021. *J. Manag Care Spec Pharm.* **2022**, *28*, 1219−1223.
(28) Maeda, H.; Shingai, R.; Takeda, K.; Hara, A.; Murai, Y.; Ofuchi, M. Assessment of Surrogate End Point Trends in Clinical Trials to Approve Oncology Drugs From 2001 to 2020 in Japan. *JAMA Netw. Open* **2023**, *6*, No. e238875.
(29) Hilal, T.; Gonzalez-Velez, M.; Prasad, V. Limitations in clinical trials leading to anticancer drug approvals by the US Food and Drug Administration. *JAMA Int. Med.* **2020**, *180*, 1108−1115.
(30) Scher, K. S.; Hurria, A. Under-representation of older adults in cancer registration trials: Known problem, little progress. *J. Clin. Oncol.* **2012**, *30*, 2036−2038.
(31) Hilal, T.; Sonbol, M. B.; Prasad, V. Analysis of control arm quality in randomized clinical trials leading to anticancer drug approval by the US Food and Drug Administration. *JAMA Oncol* **2019**, *5*, 887−892.
(32) Cherla, A.; Naci, H.; Kesselheim, A. S.; Gyawali, B.; Mossialos, E. Assessment of coverage in England of cancer drugs qualifying for US Food and Drug Administration accelerated approval. *JAMA Int. Med.* **2021**, *181*, 490−498.
(33) Del Paggio, J. C.; Tannock, I. F. The fragility of phase 3 trials supporting FDA-approved anticancer medicines: A retrospective analysis. *Lancet Oncol.* **2019**, *20*, 1065−1069.
(34) Sharp, J.; Prasad, V. An estimate of rate of deviation from NCCN guideline recommendations for central nervous system imaging in trials forming basis for drug approval in first line advanced non-small cell lung cancer (NSCLC). *BMC Cancer* **2022**, *22*, 70.
(35) Gloy, V.; Schmitt, A. M.; Düblin, P.; Hirt, J.; Axfors, C.; Kuk, H.; Pereira, T. V.; Locher, C.; Caquelin, L.; Walter-Claudi, M.; Lythgoe, M. P.; Herbrand, A.; Kasenda, B.; Hemkens, L. G. The evidence base of US Food and Drug Administration approvals of novel cancer therapies from 2000 to 2020. *Int. J. Cancer* **2023**, *152*, 2474−2484.
(36) Feldman, D.; Avorn, J.; Kesselheim, A. S. Use of Extrapolation in New Drug Approvals by the US Food and Drug Administration. *JAMA Netw. Open* **2022**, *5*, No. e227958.
(37) Olivier, T.; Haslam, A.; Prasad, V. Post-progression treatment in cancer randomized trials: a cross-sectional study of trials leading to FDA approval and published trials between 2018 and 2020. *BMC Cancer* **2023**, *23*, 448.
(38) Johnston, J. L.; Ross, J. S.; Ramachandran, R. US Food and Drug Administration Approval of Drugs Not Meeting Pivotal Trial Primary End Points, 2018−2021. *JAMA Int. Med.* **2023**, *183*, 376−380.
(39) Davis, C.; Naci, H.; Gurpinar, E.; Poplavska, E.; Pinto, A.; Aggarwal, A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: Retrospective cohort study of drug approvals 2009−13. *BMJ.* **2017**, *359*, j4530.
(40) Temel, J. S.; Greer, J. A.; Muzikansky, A.; Gallagher, E. R.; Admane, S.; Jackson, V. A.; Dahlin, C. M.; Blinderman, C. D.; Jacobsen, J.; Pirl, W. F.; Billings, J. A.; Lynch, T. J. Early palliative care for patients with metastatic non−small-cell lung cancer. *N. Engl. J. Med.* **2010**, *363*, 733−742.
(41) Maeda, H.; Khatami, M. Analyses of repeated failures in cancer therapy for solid tumors: Poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs. *Clinical and Translational Medicine* **2018**, *7*, 11−11.
(42) Cohen, D. Cancer drugs: High price, uncertain value. *BMJ.* **2017**, *359*, j4543.
(43) Gøtzsche, P. C.; Young, A. H.; Crace, J. Does long term use of psychiatric drugs cause more harm than good? *BMJ.* **2015**, *350*, h2435.
(44) Andrews, P. W.; Thomson, J. A., Jr.; Amstadter, A.; Neale, M. C. Primum non nocere: An evolutionary analysis of whether antidepressants do more harm than good. *Front. Psychol.* **2012**, *3*, 117.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(45) Wurtman, R. J.; Bettiker, R. L. The slowing of treatment discovery, 1965−1995. *Nat. Med.* **1995**, *1*, 1122−1125.
(46) Scannell, J. W.; Blanckley, A.; Boldon, H.; Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discovery* **2012**, *11*, 191−200.
(47) Pammolli, F.; Righetto, L.; Abrignani, S.; Pani, L.; Pelicci, P. G.; Rabosio, E. The endless frontier? The recent increase of R&D productivity in pharmaceuticals. *J. Transl. Med.* **2020**, *18*, 162.
(48) Ringel, M. S.; Scannell, J. W.; Baedeker, M.; Schulze, U. Breaking Eroom's law. *Nat. Rev. Drug Discovery* **2020**, *19*, 833−834.
(49) Scannell, J. W.; Bosley, J. When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One* **2016**, *11*, No. e0147215.
(50) Horrobin, D. F. Modern biomedical research: An internally self-consistent universe with little contact with medical reality? *Nat. Rev. Drug Discovery* **2003**, *2*, 151−154.
(51) Horrobin, D. F. Innovation in the pharmaceutical industry. *J. R. Soc. Med.* **2000**, *93*, 341−345.
(52) Horrobin, D. F. Realism in drug discovery-could Cassandra be right? *Nat. Biotechnol.* **2001**, *19*, 1099−1100.
(53) Persson, C. G. A.; Erjefält, J. S.; Uller, L.; Andersson, M.; Greiff, L. Unbalanced research. *Trends Pharmacol. Sci.* **2001**, *22*, 538−541.
(54) Swinney, D. C.; Anthony, J. How were new medicines discovered? *Nat. Rev. Drug Discovery* **2011**, *10*, 507−519.
(55) Le Fanu, J. *The Rise and Fall of Modern Medicine*, revised ed.; Basic Books: New York, 2012; p xviii, 590 pages.
(56) Rees, J. Complex disease and the new clinical sciences. *Science* **2002**, *296*, 698−700.
(57) Rees, J. The fundamentals of clinical discovery. *Perspect. Biol. Med.* **2004**, *47*, 597−607.
(58) Bender, A.; Cortés-Ciriano, I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 1: Ways to make an impact, and why we are not there yet. *Drug Discovery Today* **2021**, *26*, 511−524.
(59) Bender, A.; Cortes-Ciriano, I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 2: a discussion of chemical and biological data. *Drug Discovery Today* **2021**, *26*, 1040−1052.
(60) Sams-Dodd, F. Target-based drug discovery: Is something wrong? *Drug Discovery Today* **2005**, *10*, 139−147.
(61) Moffat, J. G.; Rudolph, J.; Bailey, D. Phenotypic screening in cancer drug discovery - past, present and future. *Nat. Rev. Drug Discovery* **2014**, *13*, 588−602.
(62) Hughes, J. P.; Rees, S.; Kalindjian, S. B.; Philpott, K. L. Principles of early drug discovery. *Br. J. Pharmacol.* **2011**, *162*, 1239−1249.
(63) Kawecki, Z.; Kaczor, J.; Karpińska, T.; Sujak, I.; Kandefer-Szerszeń, M. Studies of RNA isolated from Piptoporus betulinus as interferon inducer. *Arch. Immunol. Ther. Exp. (Warsz.)* **1978**, *26*, 517−522.
(64) Kandefer-Szerszeń, M.; Kawecki, Z.; Guz, M. Fungal nucleic acids as interferon inducers. *Acta Microbiol. Polym.* **1979**, *28*, 277−291.
(65) Sułkowska-Ziaja, K.; Szewczyk, A.; Galanty, A.; Gdula-Argasińska, J.; Muszyńska, B. Chemical composition and biological activity of extracts from fruiting bodies and mycelial cultures of Fomitopsis betulina. *Mol. Biol. Rep.* **2018**, *45*, 2535−2544.
(66) Schlegel, B.; Luhmann, U.; Härtl, A.; Gräfe, U. Piptamine, a new antibiotic produced by Piptoporus betulinus Lu 9−1. *J. Antibiot. (Tokyo)* **2000**, *53*, 973−974.
(67) Doskocil, I.; Havlik, J.; Verlotta, R.; Tauchen, J.; Vesela, L.; Macakova, K.; Opletal, L.; Kokoska, L.; Rada, V. In vitro immunomodulatory activity, cytotoxicity and chemistry of some central European polypores. *Pharm. Biol.* **2016**, *54*, 2369−2376.
(68) Capasso, L. 5300 years ago, the Ice Man used natural laxatives and antibiotics. *Lancet* **1998**, *352*, 1864.
(69) Peintner, U.; Pöder, R.; Pümpel, T. The iceman's fungi. *Mycol. Res.* **1998**, *102*, 1153−1162.
(70) Zink, A.; Samadelli, M.; Gostner, P.; Piombino-Mascali, D. Possible evidence for care and treatment in the Tyrolean Iceman. *Int. J. Paleopathol* **2019**, *25*, 110−117.
(71) Nerlich, A. G.; Egarter Vigl, E.; Fleckinger, A.; Tauber, M.; Peschel, O. Der Mann aus dem Eis: Lebensszenario und Pathologische Befunde aus 30 Jahren Forschung an der Gletschermumie„ Ötzi". *Der Pathologe* **2021**, *42*, 530−539.
(72) Harrison, F.; Roberts, A. E.; Gabrilska, R.; Rumbaugh, K. P.; Lee, C.; Diggle, S. P. A 1,000-year-old antimicrobial remedy with antistaphylococcal activity. *mBio* **2015**, *6*, No. e01129.
(73) Bassett, E. J.; Keith, M. S.; Armelagos, G. J.; Martin, D. L.; Villanueva, A. R. Tetracycline-labeled human bone from ancient Sudanese Nubia (A.D. 350). *Science* **1980**, *209*, 1532−1534.
(74) Nelson, M. L.; Dinardo, A.; Hochberg, J.; Armelagos, G. J. Mass spectroscopic characterization of tetracycline in the skeletal remains of an ancient population from Sudanese Nubia 350−550 CE. *Am. J. Phys. Anthropol.* **2010**, *143*, 151−154.
(75) Solecki, R. S. Shanidar IV, a Neanderthal flower burial in northern Iraq. *Science* **1975**, *190*, 880−881.
(76) Lietava, J. Medicinal plants in a Middle Paleolithic grave Shanidar IV? *J. Ethnopharmacol.* **1992**, *35*, 263−266.
(77) Guerra-Doce, E. Psychoactive substances in prehistoric times: Examining the archaeological evidence. *Time and Mind* **2015**, *8*, 91−112.
(78) Sneader, W. *Drug Discovery: A History*; Wiley: Chichester, 2005. DOI: 10.1002/0470015535, https://archive.org/details/drugdiscoveryhis0000snea.
(79) Merlin, M. D. Archaeological evidence for the tradition of psychoactive plant use In the old world. *Econ. Bot.* **2003**, *57*, 295−323.
(80) Guerra-Doce, E. The origins of inebriation: Archaeological evidence of the consumption of fermented beverages and drugs in prehistoric Eurasia. *J. Archaeol. Method Theory* **2015**, *22*, 751−782.
(81) Zlas, J.; Stark, H.; Seligman, J.; Levy, R.; Werker, E.; Breuer, A.; Mechoulam, R. Early medical use of cannabis. *Nature* **1993**, *363*, 215−215.
(82) Magendie, F. *Formulary for the Preparation and Employment of Several New Remedies*; T. and G. Underwood, 1829. https://archive.org/details/formularyforprep00mage.
(83) Bernard, C. Études physiologiques sur quelques poisons Américains: I. Le curare. *Revue des Deux Mondes (1829−1971)* **1864**, *53*, 164−190.
(84) Kuschinsky, G. The influence of Dorpat on the emergence of pharmacology as a distinct discipline. *J. Hist. Med. Allied Sci.* **1968**, *23*, 258−271.
(85) Muscholl, E. Second W.D.M. Paton Memorial Lecture. The evolution of experimental pharmacology as a biological science: the pioneering work of Buchheim and Schmiedeberg. *Br. J. Pharmacol.* **1995**, *116*, 2155−2159.
(86) Leake, C. D. The scientific status of pharmacology. *Science* **1961**, *134*, 2069−2079.
(87) Rubin, R. P. A brief history of great discoveries in pharmacology: in celebration of the centennial anniversary of the founding of the American Society of Pharmacology and Experimental Therapeutics. *Pharmacol. Rev.* **2007**, *59*, 289−359.
(88) Parascandola, J. The theoretical basis of Paul Ehrlich's chemotherapy. *J. Hist. Med. Allied Sci.* **1981**, *36*, 19−43.
(89) Ehrlich, P. *The Collected Papers of Paul Ehrlich*; Pergamon: 1960; Vol. III: Chemotherapy. DOI: 10.1016/C2013-0-01636-2. Publications of Paul Ehrlich are also available freely at https://www.pei.de/EN/institute/paul-ehrlich/publications/publications-of-paul-ehrlich-node.html (25 August 2022). http://web.archive.org/web/20220825160634/https://www.pei.de/EN/institute/paul-ehrlich/publications/publications-of-paul-ehrlich-node.html.
(90) Elion, G. B.; Burgi, E.; Hitchings, G. H. Studies on condensed pyrimidine systems. IX. The synthesis of some 6-substituted purines. *J. Am. Chem. Soc.* **1952**, *74*, 411−414.
(91) Elion, G. B. The purine path to chemotherapy. *Science* **1989**, *244*, 41−47.
(92) Falco, E. A.; Goodwin, L. G.; Hitchings, G. H.; Rollo, I. M.; Russell, P. B. 2:4-diaminopyrimidines- a new series of antimalarials. *Br. J. Pharmacol. Chemother.* **1951**, *6*, 185−200.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(93) Hitchings, G. H. Biochemical background of trimethoprim-sulphamethoxazole. *Med. J. Aust.* **1973**, *1* (Suppl), 5−9.
(94) Elion, G. B. Acyclovir: Discovery, mechanism of action, and selectivity. *J. Med. Virol.* **1993**, *41* (Suppl 1), 2−6.
(95) Koenig, R. The legacy of great science: the work of Nobel Laureate Gertrude Elion lives on. *Oncologist* **2006**, *11*, 961−965.
(96) Quirke, V. Putting theory into practice: James Black, receptor theory and the development of the beta-blockers at ICI, 1958−1978. *Med. Hist.* **2006**, *50*, 69−92.
(97) Black, J. Drugs from emasculated hormones: The principle of syntopic antagonism. *Science* **1989**, *245*, 486−493.
(98) Black, J. A personal perspective on Dr. Paul Janssen. *J. Med. Chem.* **2005**, *48*, 1687−1688.
(99) van Gestel, S.; Schuermans, V. Thirty-three years of drug discovery and research with Dr. Paul Janssen. *Drug Dev. Res.* **1986**, *8*, 1−13.
(100) Janssen, P. A. J.; Van De Westeringh, C.; Jageneau, A. H. M.; Demoen, P. J. A.; Hermans, B. K. F.; Van Daele, G. H. P.; Schellekens, K. H. L.; Van Der Eycken, C. A. M.; Niemegeers, C. J. E. Chemistry and pharmacology of CNS depressants related to 4-(4-hydroxy-phenylpiperidino)butyrophenone. I. Synthesis and screening data in mice. *J. Med. Pharm. Chem.* **1959**, *1*, 281−297.
(101) Janssen, P. A. J.; Gardocki, J. F. Method for producing analgesia. US3141823A, 1962/09/04, 1964.
(102) Stokbroekx, R. A.; Vandenberk, J.; Van Heertum, A. H. M. T.; Van Laar, G. M. L. W.; Van der Aa, M. J. M. C.; Van Bever, W. F. M.; Janssen, P. A. J. Synthetic antidiarrheal agents. 2,2-Diphenyl-4-(4′-aryl-4′-hydroxypiperidino)butyramides. *J. Med. Chem.* **1973**, *16*, 782−786.
(103) Godefroi, E. F.; Janssen, P. A.; Vandereycken, C. A.; Vanheertum, A. H.; Niemegeers, C. J. Dl-1-(1-arylalkyl)imidazole-5-carboxylate esters. A novel type of hypnotic agents. *J. Med. Chem.* **1965**, *8*, 220−223.
(104) Sumitomo dainippon pharma and exscientia joint development new drug candidate created using artificial intelligence (AI) begins clinical trial. https://investors.exscientia.ai/press-releases/press-release-details/2020/sumitomo-dainippon-pharma-and-exscientia-joint-development-new-drug-candidate-created-using-artificial-intelligence-ai-begins-clinical-trial/Default.aspx, http://web.archive.org/web/20211005123058/https://investors.exscientia.ai/press-releases/press-release-details/2020/sumitomo-dainippon-pharma-and-exscientia-joint-development-new-drug-candidate-created-using-artificial-intelligence-ai-begins-clinical-trial/Default.aspx (5 October 2021). https://investors.exscientia.ai/press-releases/press-release-details/2020/sumitomo-dainippon-pharma-and-exscientia-joint-development-new-drug-candidate-created-using-artificial-intelligence-ai-begins-clinical-trial/Default.aspx, http://web.archive.org/web/20211005123058/https://investors.exscientia.ai/press-releases/press-release-details/2020/sumitomo-dainippon-pharma-and-exscientia-joint-development-new-drug-candidate-created-using-artificial-intelligence-ai-begins-clinical-trial/Default.aspx.
(105) Zhavoronkov, A.; Ivanenkov, Y. A.; Aliper, A.; Veselov, M. S.; Aladinskiy, V. A.; Aladinskaya, A. V.; Terentiev, V. A.; Polykovskiy, D. A.; Kuznetsov, M. D.; Asadulaev, A.; Volkov, Y.; Zholus, A.; Shayakhmetov, R. R.; Zhebrak, A.; Minaeva, L. I.; Zagribelnyy, B. A.; Lee, L. H.; Soll, R.; Madge, D.; Xing, L.; Guo, T.; Aspuru-Guzik, A. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat. Biotechnol.* **2019**, *37*, 1038−1040.
(106) Fink, E. A.; Xu, J.; Hübner, H.; Braz, J. M.; Seemann, P.; Avet, C.; Craik, V.; Weikert, D.; Schmidt, M. F.; Webb, C. M.; Tolmachova, N. A.; Moroz, Y. S.; Huang, X. P.; Kalyanaraman, C.; Gahbauer, S.; Chen, G.; Liu, Z.; Jacobson, M. P.; Irwin, J. J.; Bouvier, M.; Du, Y.; Shoichet, B. K.; Basbaum, A. I.; Gmeiner, P. Structure-based discovery of nonopioid analgesics acting through the α(2A)-adrenergic receptor. *Science* **2022**, *377*, No. eabn7065.
(107) Kaplan, A. L.; Confair, D. N.; Kim, K.; Barros-Álvarez, X.; Rodriguiz, R. M.; Yang, Y.; Kweon, O. S.; Che, T.; McCorvy, J. D.; Kamber, D. N.; Phelan, J. P.; Martins, L. C.; Pogorelov, V. M.; DiBerto, J. F.; Slocum, S. T.; Huang, X. P.; Kumar, J. M.; Robertson, M. J.; Panova, O.; Seven, A. B.; Wetsel, A. Q.; Wetsel, W. C.; Irwin, J. J.; Skiniotis, G.; Shoichet, B. K.; Roth, B. L.; Ellman, J. A. Bespoke library docking for 5-HT(2A) receptor agonists with antidepressant activity. *Nature* **2022**, *610*, 582−591.
(108) Wei, T. T.; Chandy, M.; Nishiga, M.; Zhang, A.; Kumar, K. K.; Thomas, D.; Manhas, A.; Rhee, S.; Justesen, J. M.; Chen, I. Y.; Wo, H. T.; Khanamiri, S.; Yang, J. Y.; Seidl, F. J.; Burns, N. Z.; Liu, C.; Sayed, N.; Shie, J. J.; Yeh, C. F.; Yang, K. C.; Lau, E.; Lynch, K. L.; Rivas, M.; Kobilka, B. K.; Wu, J. C. Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation. *Cell* **2022**, *185*, 1676−1693.
(109) Layton, M. E.; Kern, J. C.; Hartingh, T. J.; Shipe, W. D.; Raheem, I.; Kandebo, M.; Hayes, R. P.; Huszar, S.; Eddins, D.; Ma, B.; Fuerst, J.; Wollenberg, G. K.; Li, J.; Fritzen, J.; McGaughey, G. B.; Uslaner, J. M.; Smith, S. M.; Coleman, P. J.; Cox, C. D. Discovery of MK-8189, a highly potent and selective PDE10A inhibitor for the treatment of schizophrenia. *J. Med. Chem.* **2023**, *66*, 1157−1171.
(110) Wei, L.; Qi, X.; Yu, X.; Zheng, Y.; Luo, X.; Wei, Y.; Ni, P.; Zhao, L.; Wang, Q.; Ma, X.; Deng, W.; Guo, W.; Hu, X.; Li, T. 3,4-Dihydrobenzo[e][1,2,3]oxathiazine 2,2-dioxide analogs act as potential AMPA receptor potentiators with antidepressant activity. *Eur. J. Med. Chem.* **2023**, *251*, No. 115252.
(111) Dong, Y.; Lu, J.; Zhang, S.; Chen, L.; Wen, J.; Wang, F.; Mao, Y.; Li, L.; Zhang, J.; Liao, S.; Dong, L. Design, synthesis and bioevaluation of 1,2,4-thiadiazolidine-3,5-dione derivatives as potential GSK-3β inhibitors for the treatment of Alzheimer's disease. *Bioorg. Chem.* **2023**, *134*, No. 106446.
(112) Peyressatre, M.; Arama, D. P.; Laure, A.; González-Vera, J. A.; Pellerano, M.; Masurier, N.; Lisowski, V.; Morris, M. C. Identification of quinazolinone analogs targeting CDK5 kinase activity and glioblastoma cell proliferation. *Frontiers in Chemistry* **2020**, *8*. DOI: 10.3389/fchem.2020.00691.
(113) Savardi, A.; Borgogno, M.; Narducci, R.; La Sala, G.; Ortega, J. A.; Summa, M.; Armirotti, A.; Bertorelli, R.; Contestabile, A.; De Vivo, M.; Cancedda, L. Discovery of a small molecule drug candidate for selective NKCC1 inhibition in brain disorders. *Chem.* **2020**, *6*, 2073−2096.
(114) Jang, W. D.; Jeon, S.; Kim, S.; Lee, S. Y. Drugs repurposed for COVID-19 by virtual screening of 6,218 drugs and cell-based assay. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, *118*. DOI: 10.1073/pnas.2024302118 https://ncbi.nlm.nih.gov/pmc/articles/PMC8325362.
(115) Luttens, A.; Gullberg, H.; Abdurakhmanov, E.; Vo, D. D.; Akaberi, D.; Talibov, V. O.; Nekhotiaeva, N.; Vangeel, L.; De Jonghe, S.; Jochmans, D.; Krambrich, J.; Tas, A.; Lundgren, B.; Gravenfors, Y.; Craig, A. J.; Atilaw, Y.; Sandström, A.; Moodie, L. W. K.; Lundkvist, Å.; van Hemert, M. J.; Neyts, J.; Lennerstrand, J.; Kihlberg, J.; Sandberg, K.; Danielson, U. H.; Carlsson, J. Ultralarge Virtual Screening Identifies SARS-CoV-2 Main Protease Inhibitors with Broad-Spectrum Activity against Coronaviruses. *J. Am. Chem. Soc.* **2022**, *144*, 2905−2920. https://ncbi.nlm.nih.gov/pmc/articles/PMC8848513 and J.C. have submitted a patent application on the compounds.
(116) Prinz, F.; Schlange, T.; Asadullah, K. Believe it or not: How much can we rely on published data on potential drug targets? *Nat. Rev. Drug Discovery* **2011**, *10*, 712.
(117) Andersen, H. The history of reductionism versus holistic approaches to scientific research. *Endeavour* **2001**, *25*, 153−156.
(118) Morange, M. *The Black Box of Biology: A History of the Molecular Revolution*; Harvard University Press: Cambridge, MA, 2020.
(119) Aristotle. *Metaphysics*. 350 BCE. http://classics.mit.edu//Aristotle/metaphysics.html, https://archive.org/details/aristotlesmetaph0001aris, https://archive.org/details/aristotlesmetaph0002aris.
(120) Gazzaniga, M. S. Neuroscience and the correct level of explanation for understanding mind. An extraterrestrial roams through some neuroscience laboratories and concludes earthlings are not grasping how best to understand the mind-brain interface. *Trends Cogn. Sci.* **2010**, *14*, 291−292.
(121) Lazebnik, Y. Can a biologist fix a radio?—Or, what I learned while studying apoptosis. *Cancer Cell* **2002**, *2*, 179−182.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(122) Mayr, E. *What Makes Biology Unique? Considerations on the Autonomy of a Scientific Discipline*; Cambridge University Press: Harvard University, MA, 2004. DOI: 10.1017/CBO9780511617188.
(123) Anderson, P. W. More is different. *Science* **1972**, *177*, 393−396.
(124) Nurse, P. Life, logic and information. *Nature* **2008**, *454*, 424−426.
(125) Krakauer, J. W.; Ghazanfar, A. A.; Gomez-Marin, A.; MacIver, M. A.; Poeppel, D. Neuroscience needs behavior: Correcting a reductionist bias. *Neuron* **2017**, *93*, 480−490.
(126) Ahn, A. C.; Tewari, M.; Poon, C. S.; Phillips, R. S. The limits of reductionism in medicine: Could systems biology offer an alternative? *PLoS Med.* **2006**, *3*, No. e208.
(127) Uttal, W. R. *The New Phrenology: The Limits of Localizing Cognitive Processes in the Brain*; MIT Press, 2003.
(128) Prigogine, I.; Stengers, I. *Order Out of Chaos: Man's New Dialogue with Nature*; Bantam, 1984. https://archive.org/details/orderoutofchaosm00prig/page/54.
(129) Dupré, J. *The Disorder of Things: Metaphysical Foundations of the Disunity of Science*; Harvard University Press, 1993. Also see DOI: 10.1080/00455091.1995.10717410.
(130) Gould, S. J. Humbled by the genome's mysteries. *New York Times*, 2001. https://www.nytimes.com/2001/02/19/opinion/humbled-by-the-genome-s-mysteries.html, https://web.archive.org/web/20210610073950/https://www.nytimes.com/2001/02/19/opinion/humbled-by-the-genome-s-mysteries.html.
(131) Macklem, P. T. Emergent phenomena and the secrets of life. *J. Appl. Physiol (1985)* **2008**, *104*, 1844−1846.
(132) Joyner, M. J.; Paneth, N. Promises, promises, and precision medicine. *J. Clin. Invest.* **2019**, *129*, 946−948.
(133) Waldrop, M. M. *The Emerging Science at the Edge of Order and Chaos*; Simon & Schuste, 1992. https://archive.org/details/complexityemergi00wald.
(134) Hooker, C. *Philosophy of Complex Systems*; Elsevier, 2011. DOI: 10.1016/C2009-0-06625-2.
(135) Corning, P. A. The re-emergence of "emergence": A venerable concept in search of a theory. *Complexity* **2002**, *7*, 18−30.
(136) Krakauer, D. C. *Worlds Hidden in Plain Sight: The Evolving Idea of Complexity at the Santa Fe Institute 1984−2019*; Santa Fe Institute of Science, 2019. https://www.sfipress.org/books/worlds-hidden-in-plain-sight.
(137) Leinfellner, K. The Idea Factory: Complexity Science Hub Vienna. https://www.csh.ac.at/we-proudly-present-5-years-csh-the-report/, http://web.archive.org/web/20210716141958/https://www.csh.ac.at/we-proudly-present-5-years-csh-the-report/ (16 July 2021). https://www.csh.ac.at/we-proudly-present-5-years-csh-the-report/, http://web.archive.org/web/20210716141958/https://www.csh.ac.at/we-proudly-present-5-years-csh-the-report/.
(138) SFI applauds first Nobel Prize for complex systems research. https://santafe.edu/news-center/news/sfi-applauds-first-nobel-prize-complex-systems-research, https://web.archive.org/web/20211028184127/https://santafe.edu/news-center/news/sfi-applauds-first-nobel-prize-complex-systems-research (28 October 2021). https://santafe.edu/news-center/news/sfi-applauds-first-nobel-prize-complex-systems-research, https://web.archive.org/web/20211028184127/https://santafe.edu/news-center/news/sfi-applauds-first-nobel-prize-complex-systems-research.
(139) Ma'ayan, A. Complex systems biology. *J. R. Soc. Interface* **2017**, *14*, No. 20170391.
(140) Green, S. *Philosophy of Systems Biology: Perspectives from Scientists and Philosophers*.; Springer: 2017. DOI: 10.1007/978-3-319-47000-9.
(141) Geerts, H.; Wikswo, J.; van der Graaf, P. H.; Bai, J. P. F.; Gaiteri, C.; Bennett, D.; Swalley, S. E.; Schuck, E.; Kaddurah-Daouk, R.; Tsaioun, K.; Pelleymounter, M. Quantitative Systems Pharmacology for Neuroscience Drug Discovery and Development: Current Status, Opportunities, and Challenges. *CPT: Pharmacometrics & Systems Pharmacology* **2020**, *9*, 5−20.
(142) Azer, K.; Kaddi, C. D.; Barrett, J. S.; Bai, J. P. F.; McQuade, S. T.; Merrill, N. J.; Piccoli, B.; Neves-Zaph, S.; Marchetti, L.; Lombardo, R.; Parolo, S.; Immanuel, S. R. C.; Baliga, N. S. History and future perspectives on the discipline of quantitative systems pharmacology modeling and its applications. *Front. Physiol.* **2021**, *12*, No. 637999.
(143) Csermely, P.; Agoston, V.; Pongor, S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol. Sci.* **2005**, *26*, 178−182.
(144) Haasen, D.; Schopfer, U.; Antczak, C.; Guy, C.; Fuchs, F.; Selzer, P. How phenotypic screening influenced drug discovery: lessons from five years of practice. *Assay Drug Dev. Technol.* **2017**, *15*, 239−246.
(145) Swinney, D. C. Phenotypic drug discovery: History, evolution, future. In *Phenotypic Drug Discovery*; Royal Society of Chemistry, 2020; pp 1−19. DOI: 10.1039/9781839160721-00001.
(146) Vincent, F.; Nueda, A.; Lee, J.; Schenone, M.; Prunotto, M.; Mercola, M. Phenotypic drug discovery: recent successes, lessons learned and new directions. *Nat. Rev. Drug Discovery* **2022**, *21*, 899.
(147) Tun, K.; Menghini, M.; D'Andrea, L.; Dhar, P.; Tanaka, H.; Giuliani, A. Why so few drug targets: a mathematical explanation? *Curr. Comput. Aided Drug Des.* **2011**, *7*, 206−213.
(148) Begley, C. G.; Ellis, L. M. Raise standards for preclinical cancer research. *Nature* **2012**, *483*, 531−533.
(149) Nemeroff, C. B. The state of our understanding of the pathophysiology and optimal treatment of depression: Glass half full or half empty? *Am. J. Psychiatry* **2020**, *177*, 671−685.
(150) Eder, J.; Sedrani, R.; Wiesmann, C. The discovery of first-in-class drugs: Origins and evolution. *Nat. Rev. Drug Discovery* **2014**, *13*, 577−587.
(151) Siramshetty, V. B.; Grishagin, I.; Nguyen, Đ. T.; Peryea, T.; Skovpen, Y.; Stroganov, O.; Katzel, D.; Sheils, T.; Jadhav, A.; Mathé, E. A.; Southall, N. T. NCATS Inxight Drugs: a comprehensive and curated portal for translational research. *Nucleic Acids Res.* **2022**, *50*, D1307−D1316.
(152) Fischer, J. n.; Ganellin, C. R. *Analogue-based Drug Discovery*. Wiley-VCH: Weinheim, 2006; p xxxi, 575 p. DOI: 10.1002/3527608001.
(153) Aronson, J. K.; Green, A. R. Me-too pharmaceutical products: History, definitions, examples, and relevance to drug shortages and essential medicines lists. *Br. J. Clin. Pharmacol.* **2020**, *86*, 2114−2122.
(154) Cushman, D. W.; Ondetti, M. A. History of the design of captopril and related inhibitors of angiotensin converting enzyme. *Hypertension* **1991**, *17*, 589−592.
(155) Rarey, M.; Dixon, J. S. Feature trees: A new molecular similarity measure based on tree matching. *J. Comput. Aided Mol. Des.* **1998**, *12*, 471−490. https://www.biosolveit.de/products/#FTrees, http://web.archive.org/web/20210125063205/https://www.biosolveit.de/wp-content/uploads/2021/01/FTrees.pdf (25 January 2021)
(156) Lowe, D. The mysterious origins of the quinolones. https://www.science.org/content/blog-post/mysterious-origins-quinolones, http://web.archive.org/web/20210923081446/https://www.science.org/content/blog-post/mysterious-origins-quinolones (23 September 2021). https://www.science.org/content/blog-post/mysterious-origins-quinolones, http://web.archive.org/web/20210923081446/https://www.science.org/content/blog-post/mysterious-origins-quinolones.
(157) Flynn, J. In two generations, drug research sees a big shift. *Wall Street J.* **2004**. https://www.wsj.com/articles/SB107644751774825922, also see https://www.science.org/content/blog-post/old-days-some-older-than-others (9 September 2021), http://web.archive.org/web/20210909121804/https://www.science.org/content/blog-post/old-days-some-older-than-others.
(158) Lombardino, J. G.; Lowe, J. A. The role of the medicinal chemist in drug discovery — then and now. *Nat. Rev. Drug Discovery* **2004**, *3*, 853−862.
(159) Konzett, H. On the discovery of isoprenaline. *Trends Pharmacol. Sci.* **1981**, *2*, 47−49.
(160) Fromm, G. H. Antiepileptic actions of ethosuximide. In *Drugs for the Control of Epilepsy Actions on Neuronal Networks Involved in Seizure Disorders*, Faingold, C. L.; Fromm, G. H., Eds. CRC: 1992. DOI: 10.1201/9780429262623.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(161) Borel, J. F.; Kis, Z. L.; Beveridge, T. The history of the discovery and development of cyclosporine (Sandimmune®). In *The Search for Anti-Inflammatory Drugs*; Merluzzi, V. J.; Adams, J., Eds.; Birkhäuser: Boston, 1995; pp 27−63. DOI: 10.1007/978-1-4615-9846-6_2.
(162) Steverding, D. The development of drugs for treatment of sleeping sickness: A historical review. *Parasit. Vectors* **2010**, *3*, 15.
(163) King, H.; Lourie, E. M.; Yorke, W. New trypanocidal substances. *Lancet* **1937**, *230*, 1360−1363.
(164) Lourie, E. M.; Yorke, W. Studies in chemotherapy XXI.—The trypanocidal action of certain aromatic diamidines. *Ann. Trop. Med. Parasitol.* **1939**, *33*, 289−304.
(165) Yorke, W.; Adams, A. R. D.; Murgatroyd, F. Studies in chemotherapy I. A method for maintaining pathogenic trypanosomes alive in vitro at 37° C. for 24 h. *Ann. Trop. Med. Parasitol.* **1929**, *23*, 501−518.
(166) Olbe, L.; Carlsson, E.; Lindberg, P. A proton-pump inhibitor expedition: The case histories of omeprazole and esomeprazole. *Nat. Rev. Drug Discovery* **2003**, *2*, 132−139.
(167) Pascaud, X. B. L.; Malen, C.; Danree, B. New thiocarboxamides derivatives with specific gastric antisecretory properties. *J. Med. Chem.* **1971**, *14*, 244−246.
(168) James, R.; Glen, J. B. Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. *J. Med. Chem.* **1980**, *23*, 1350−1357.
(169) Glen, J. B. I. The discovery and development of propofol anesthesia: The 2018 Lasker-DeBakey clinical medical research award. *JAMA* **2018**, *320*, 1235−1236.
(170) Glen, J. B. Animal studies of the anaesthetic activity of ICI 35 868. *Br. J. Anaesth.* **1980**, *52*, 731−742.
(171) Wani, M. C.; Horwitz, S. B. Nature as a remarkable chemist: A personal story of the discovery and development of Taxol. *Anticancer Drugs* **2014**, *25*, 482−487.
(172) Wall, M. E.; Wani, M. C. Camptothecin and taxol: From discovery to clinic. *J. Ethnopharmacol.* **1996**, *51*, 239−253. discussion 253−234.
(173) Martino, E.; Della Volpe, S.; Terribile, E.; Benetti, E.; Sakaj, M.; Centamore, A.; Sala, A.; Collina, S. The long story of camptothecin: From traditional medicine to drugs. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 701−707.
(174) Burg, R. W.; Miller, B. M.; Baker, E. E.; Birnbaum, J.; Currie, S. A.; Hartman, R.; Kong, Y. L.; Monaghan, R. L.; Olson, G.; Putter, I.; Tunac, J. B.; Wallick, H.; Stapley, E. O.; Oiwa, R.; Omura, S. Avermectins, new family of potent anthelmintic agents: Producing organism and fermentation. *Antimicrob. Agents Chemother.* **1979**, *15*, 361−367.
(175) Campbell, W. C. Lessons from the history of ivermectin and other antiparasitic agents. *Annu. Rev. Anim. Biosci.* **2016**, *4*, 1−14.
(176) Maryanoff, B. E. Phenotypic assessment and the discovery of topiramate. *ACS Med. Chem. Lett.* **2016**, *7*, 662−665.
(177) Maryanoff, B. E. 2009 Edward E Smissman Award. Pharmaceutical ″gold″ from neurostabilizing agents: Topiramate and successor molecules. *J. Med. Chem.* **2009**, *52*, 3431−3440.
(178) Bartlett, R. R.; Schleyerbach, R. Immunopharmacological profile of a novel isoxazol derivative, HWA 486, with potential antirheumatic activity — I. Disease modifying action on adjuvant arthritis of the rat. *Int. J. Immunopharmacol.* **1985**, *7*, 7−18.
(179) Douros, J.; Suffness, M. New antitumor substances of natural origin. *Cancer Treat. Rev.* **1981**, *8*, 63−87.
(180) Salisbury, B. G; Davis, H. R; Burrier, R. E; Burnett, D. A; Boykow, G.; Caplen, M. A.; Clemmons, A. L; Compton, D. S; Hoos, L. M; McGregor, D. G; Schnitzer-Polokoff, R.; Smith, A. A; Weig, B. C; Zilli, D. L; Clader, J. W; Sybertz, E. J Hypocholesterolemic activity of a novel inhibitor of cholesterol absorption, SCH 48461. *Atherosclerosis* **1995**, *115*, 45−63.
(181) Nemeth, E. F. Misconceptions about calcimimetics. *Ann. N.Y. Acad. Sci.* **2006**, *1068*, 471−476.
(182) Grosenbach, D. W.; Jordan, R.; Hruby, D. E. Development of the small-molecule antiviral ST-246 as a smallpox therapeutic. *Future Virol.* **2011**, *6*, 653−671.
(183) Yang, G.; Pevear, D. C.; Davies, M. H.; Collett, M. S.; Bailey, T.; Rippen, S.; Barone, L.; Burns, C.; Rhodes, G.; Tohan, S.; Huggins, J. W.; Baker, R. O.; Buller, R. L.; Touchette, E.; Waller, K.; Schriewer, J.; Neyts, J.; DeClercq, E.; Jones, K.; Hruby, D.; Jordan, R. An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. *J. Virol.* **2005**, *79*, 13139−13149.
(184) Nelson, M. L.; Levy, S. B. The history of the tetracyclines. *Ann. N.Y. Acad. Sci.* **2011**, *1241*, 17−32.
(185) Swann, J. P. The search for synthetic penicillin during World War II. *Br. J. Hist. Sci.* **1983**, *16*, 154−190.
(186) Abraham, E. P. A glimpse of the early history of the cephalosporins. *Rev. Infect. Dis.* **1979**, *1*, 99−105.
(187) Coatney, G. R. Pitfalls in a discovery: The chronicle of chloroquine. *Am. J. Trop. Med. Hyg.* **1963**, *12*, 121−128.
(188) Levine, D. P. Vancomycin: A history. *Clin. Infect. Dis.* **2006**, *42* (Suppl1), S5−S12.
(189) Sensi, P. History of the development of rifampin. *Rev. Infect. Dis.* **1983**, *5* (Suppl3), S402−S406.
(190) Brown, A. G.; Butterworth, D.; Cole, M.; Hanscomb, G.; Hood, J. D.; Reading, C.; Rolinson, G. N. Naturally-occurring beta-lactamase inhibitors with antibacterial activity. *J. Antibiot. (Tokyo)* **1976**, *29*, 668−669.
(191) Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barry, C. E.; Baker, W. R. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* **2000**, *405*, 962−966.
(192) Novak, R. Are pleuromutilin antibiotics finally fit for human use? *Ann. N.Y. Acad. Sci.* **2011**, *1241*, 71−81.
(193) Kavanagh, F.; Hervey, A.; Robbins, W. J. Antibiotic substances from basidiomycetes: VIII. Pleurotus multilus (Fr.) Sacc. and Pleurotus passeckerianus pilat. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 570−574.
(194) Thompson, G. D.; Dutton, R.; Sparks, T. C. Spinosad - a case study: An example from a natural products discovery programme. *Pest Manag. Sci.* **2000**, *56*, 696−702.
(195) Matteelli, A.; Carvalho, A. C.; Dooley, K. E.; Kritski, A. TMC207: The first compound of a new class of potent anti-tuberculosis drugs. *Future Microbiol.* **2010**, *5*, 849−858.
(196) Barry, C. E., 3rd. Unorthodox approach to the development of a new antituberculosis therapy. *N. Engl. J. Med.* **2009**, *360*, 2466−2467.
(197) Gordh, T.; Gordh, T. E.; Lindqvist, K.; Warner, D. S. Lidocaine: The origin of a modern local anesthetic. 1949. *Anesthesiology* **2010**, *113*, 1433−1437.
(198) Hicks, J. Fast times: The life, death, and rebirth of amphetamine. https://www.sciencehistory.org/distillations/fast-times-the-life-death-and-rebirth-of-amphetamine, http://web.archive.org/web/20210125103639/https://www.sciencehistory.org/distillations/fast-times-the-life-death-and-rebirth-of-amphetamine (25 January 2021). https://www.sciencehistory.org/distillations/fast-times-the-life-death-and-rebirth-of-amphetamine, http://web.archive.org/web/20210125103639/https://www.sciencehistory.org/distillations/fast-times-the-life-death-and-rebirth-of-amphetamine.
(199) Howell, J. Roger Altounyan and the discovery of cromolyn (sodium cromoglycate). *J. Allergy Clin. Immunol.* **2005**, *115*, 882−885.
(200) Whorton, J. C. The phenolphthalein follies: Purgation and the pleasure principle in the early twentieth century. *Pharm. Hist.* **1993**, *35*, 3−24.
(201) Ogbourne, S. M.; Parsons, P. G. The value of nature's natural product library for the discovery of new chemical entities: The discovery of ingenol mebutate. *Fitoterapia* **2014**, *98*, 36−44.
(202) Hadley, M. E. Discovery that a melanocortin regulates sexual functions in male and female humans. *Peptides* **2005**, *26*, 1687−1689.
(203) Nguyen, R.; Khanna, N. R.; Safadi, A. O. Bacitracin topical. In *StatPearls*, January **2020** ed.; Treasure Island (FL), 2020. https://www.ncbi.nlm.nih.gov/books/NBK536993/.
(204) Johnson, B. A.; Anker, H.; Meleney, F. L. Bacitracin: A new antibiotic produced by a member of the B. subtilis group. *Science* **1945**, *102*, 376−377.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(205) Maffrand, J.-P. The story of clopidogrel and its predecessor, ticlopidine: Could these major antiplatelet and antithrombotic drugs be discovered and developed today? *C. R. Chim.* **2012**, *15*, 737−743.
(206) Löscher, W. The discovery of valproate. In *Valproate*, Löscher, W., Ed.; Birkhäuser: Basel, 1999; pp 1−3. DOI: 10.1007/978-3-0348-8759-5_1.
(207) Pirmohamed, M. Warfarin: Almost 60 years old and still causing problems. *Br. J. Clin. Pharmacol.* **2006**, *62*, 509−511.
(208) Ramchandani, D.; Lopez-Munoz, F.; Alamo, C. Meprobamate-tranquilizer or anxiolytic? A historical perspective. *Psychiatr. Q.* **2006**, *77*, 43−53.
(209) Duffin, J. Poisoning the spindle: Serendipity and discovery of the anti-tumor properties of the Vinca alkaloids. *Can. Bull. Med. Hist.* **2000**, *17*, 155−192.
(210) Eisert, W. G. Dipyridamole in antithrombotic treatment. *Adv. Cardiol.* **2012**, *47*, 78−86.
(211) Black, J. Diazoxide and the treatment of hypoglycemia: An historical review. *Ann. N.Y. Acad. Sci.* **1968**, *150*, 194−203.
(212) Kerpel-Fronius, S. Cisplatin and its analogues for cancer chemotherapy. In *Analogue-based Drug Discovery*, Fischer, J.; Ganellin, C. R., Eds.; Wiley, 2006; Vol. *1*, pp 385−394. DOI: 10.1002/3527608001.ch19.
(213) Rosenberg, B.; Vancamp, L.; Krigas, T. Inhibition of cell division in Escherichia coli by electrolysis products from a platinum electrode. *Nature* **1965**, *205*, 698−699.
(214) Stutz, A. Synthesis and structure-activity correlations within allylamine antimycotics. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 46−62.
(215) Weinstock-Guttman, B.; Nair, K. V.; Glajch, J. L.; Ganguly, T. C.; Kantor, D. Two decades of glatiramer acetate: From initial discovery to the current development of generics. *J. Neurol. Sci.* **2017**, *376*, 255−259.
(216) Teitelbaum, D.; Meshorer, A.; Hirshfeld, T.; Arnon, R.; Sela, M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *Eur. J. Immunol.* **1971**, *1*, 242−248.
(217) Halcomb, R. L. TLR-7 agonists for the treatment of viral hepatitis. In *Successful Strategies for the Discovery of Antiviral Drugs*, Desai, M. C., Meanwell, N. A., Eds.; The Royal Society of Chemistry, 2013; pp 365−383. DOI: 10.1039/9781849737814-00365.
(218) Rhodes, J. Discovery of immunopotentiatory drugs: Current and future strategies. *Clin. Exp. Immunol.* **2002**, *130*, 363−369.
(219) Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on antidiabetic agents. I. Synthesis of 5-[4-(2-methyl-2-phenylpropoxy)-benzyl]thiazolidine-2,4-dione (AL-321) and related compounds. *Chem. Pharm. Bull.* **1982**, *30*, 3563−3573.
(220) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on antidiabetic agents. II. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives. *Chem. Pharm. Bull.* **1982**, *30*, 3580−3600.
(221) Giurgea, C. E. The nootropic concept and its prospective implications. *Drug Dev. Res.* **1982**, *2*, 441−446.
(222) Jörgens, V. Josef von Mering: the baron who discovered SGLT inhibition. *In Unveiling Diabetes - Historical Milestones in Diabetology*; Jörgens, V., Porta, M., Eds.; Karger, 2020; Vol. *29*, pp 134−141. DOI: 10.1159/000506566.
(223) Kirsch, D. R.; Ogas, O. *The Drug Hunters: The Improbable Quest to Discover New Medicines*; Arcade: New York, 2017.
(224) Ban, T. A. Fifty years chlorpromazine: A historical perspective. *Neuropsychiatr. Dis. Treat.* **2007**, *3*, 495−500.
(225) Lopez-Munoz, F.; Alamo, C.; Cuenca, E.; Shen, W. W.; Clervoy, P.; Rubio, G. History of the discovery and clinical introduction of chlorpromazine. *Ann. Clin. Psychiatry* **2005**, *17*, 113−135.
(226) Cahn, C. Roland Kuhn, 1912−2005. *Neuropsychopharmacology* **2006**, *31*, 1096−1096.
(227) Fangmann, P.; Assion, H.-J.; Juckel, G.; González, C. Á.; López-Muñoz, F. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: Tricyclics and tetracyclics. *J. Clin. Psychopharmacol* **2008**, *28*, 1−4.
(228) Selikoff, I. J.; Robitzek, E. H.; Ornstein, G. G. Treatment of pulmonary tuberculosis with hydrazide derivatives of isonicotinic acid. *J. Am. Med. Assoc.* **1952**, *150*, 973−980.
(229) Lopez-Munoz, F.; Alamo, C.; Juckel, G.; Assion, H. J. Half a century of antidepressant drugs: On the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part I: Monoamine oxidase inhibitors. *J. Clin. Psychopharmacol.* **2007**, *27*, 555−559.
(230) Brune, K.; Renner, B.; Tiegs, G. Acetaminophen/paracetamol: A history of errors, failures and false decisions. *Eur. J. Pain* **2015**, *19*, 953−965.
(231) Hench, P. S. Effect of jaundice on rheumatoid arthritis. *Br. Med. J.* **1938**, *2*, 394−398.
(232) Still, G. F.; Garrod, A. E. On a form of chronic joint disease in children. *Med. Chir. Trans.* **1897**, *80*, 47−59.
(233) Pattanayak, R. D.; Sagar, R.; Pal, A. Tracing the journey of disulfiram: From an unintended discovery to a treatment option for alcoholism. *J. Ment. Health Human Behav.* **2015**, *20*, 41−43.
(234) Lang, H.; Hropot, M. Discovery and development of diuretic agents. In *Diuretics*, Greger, R. F.; Knauf, H.; Mutschler, E., Eds.; Springer: Berlin, Heidelberg, 1995; Vol. *117*, pp 141−172. DOI: 10.1007/978-3-642-79565-7_4.
(235) Li, J. J. *Laughing gas, Viagra, and Lipitor: The Human Stories Behind the Drugs We Use*; Oxford University Press, 2006. DOI: 10.1093/oso/9780195300994.001.0001, https://archive.org/details/laughinggasviagr0000liji.
(236) Sjoerdsma, A. Methyldopa. *Br. J. Clin. Pharmacol.* **1982**, *13*, 45−49.
(237) Zins, G. R. The history of the development of minoxidil. *Clin. Dermatol.* **1988**, *6*, 132−147.
(238) Dooley, E. M.; Miller, M. K.; Clayton, A. H. Flibanserin: From bench to bedside. *Sex Med. Rev.* **2017**, *5*, 461−469.
(239) Oliver, M. The clofibrate saga: A retrospective commentary. *Br. J. Clin. Pharmacol.* **2012**, *74*, 907−910.
(240) Sallan, S. E.; Zinberg, N. E.; Frei, E., 3rd. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N. Engl. J. Med.* **1975**, *293*, 795−797.
(241) Abel, E. L. *Marihuana: The First Twelve Thousand Years*; Springer, 1980. DOI: 10.1007/978-1-4899-2189-5.
(242) Silverstein, M. N.; Petitt, R. M.; Solberg, L. A., Jr; Fleming, J. S.; Knight, R. C.; Schacter, L. P. Anagrelide: a new drug for treating thrombocytosis. *N. Engl. J. Med.* **1988**, *318*, 1292−1294.
(243) Osterloh, I. H. The discovery and development of Viagra (sildenafil citrate). In *Sildenafil*, Dunzendorfer, U., Ed.; Birkhäuser: Basel, 2004; pp 1−13. DOI: 10.1007/978-3-0348-7945-3_1.
(244) Breathnach, A. Azelaic acid: A new agent in the treatment of acne: History, metabolism and biochemistry. *J. Dermatol. Treat.* **1989**, *1*, 7−10.
(245) Nordlund, J. J. Hyperpigmentation: Its historical treatment and the development of hydroquinone. *J. Pigmentory Dis.* **2015**, *2*, No. 1000221.
(246) Alam, S.; Lingenfelter, K. S.; Bender, A. M.; Lindsley, C. W. Classics in chemical neuroscience: Memantine. *ACS Chem. Neurosci.* **2017**, *8*, 1823−1829.
(247) Bailey, C. J. Metformin: Historical overview. *Diabetologia* **2017**, *60*, 1566−1576.
(248) Wray, S.; Eisner, D. A.; Allen, D. G. Two hundred years of the foxglove. *Med. Hist. Suppl.* **1985**, *29*, 132−150.
(249) Klayman, D. L. Qinghaosu (artemisinin): An antimalarial drug from China. *Science* **1985**, *228*, 1049−1055.
(250) Meiyi, Z.; Guoqiao, L.; Ying, L.; Zelin, L.; Xu, L.; Dianxi, N.; Jingyan, W.; Xiuqing, J.; Linrong, S.; Tianwei, L.; Linrong, S. Discovery of qinghaosu (artemisinin)—history of research and development of artemisinin-based antimalarials. In *Artemisinin-Based and Other Antimalarials*, Guoqiao, L.; Ying, L.; Zelin, L.; Meiyi, Z., Eds.; Academic Press, 2018; pp 1−67. DOI: 10.1016/b978-0-12-813133-6.00001-9.
(251) Imbert, T. F. Discovery of podophyllotoxins. *Biochimie* **1998**, *80*, 207−222.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(252) Chiba, K.; Adachi, K. Discovery of fingolimod, the sphingosine 1-phosphate receptor modulator and its application for the therapy of multiple sclerosis. *Future Med. Chem.* **2012**, *4*, 771−781.
(253) Chiba, K. Discovery of fingolimod based on the chemical modification of a natural product from the fungus, Isaria sinclairii. *J. Antibiot. (Tokyo)* **2020**, *73*, 666−678.
(254) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. Norhalichondrin A: An antitumor polyether macrolide from a marine sponge. *J. Am. Chem. Soc.* **1985**, *107*, 4796−4798.
(255) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. Okadaic acid, a cytotoxic polyether from two marine sponges of the genus Halichondria. *J. Am. Chem. Soc.* **1981**, *103*, 2469−2471.
(256) Silver, L. L. Challenges of antibacterial discovery. *Clin. Microbiol. Rev.* **2011**, *24*, 71−109.
(257) Shih, H. P.; Zhang, X.; Aronov, A. M. Drug discovery effectiveness from the standpoint of therapeutic mechanisms and indications. *Nat. Rev. Drug Discovery* **2018**, *17*, 19−33.
(258) FDA approves new drug to treat travelers' diarrhea. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-travelers-diarrhea, http://web.archive.org/web/20210709134846/https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-travelers-diarrhea (9 July 2021). https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-travelers-diarrhea, http://web.archive.org/web/20210709134846/https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-travelers-diarrhea.
(259) Boray, J. C.; Crowfoot, P. D.; Strong, M. B.; Allison, J. R.; Schellenbaum, M.; Von Orelli, M.; Sarasin, G. Treatment of immature and mature Fasciola hepatica infections in sheep with triclabendazole. *Vet. Rec.* **1983**, *113*, 315−317.
(260) Rock, D.; DeLay, R.; Gliddon, M. Chemistry, pharmacology and safety of the macrocyclic lactones: moxidectin. In *Macrocyclic Lactones in Antiparasitic Therapy*, Vercruysse, J.; Rew, R. S., Eds.; CABI, 2002; pp 75−96. DOI: 10.1079/9780851996172.0075.
(261) Peters, W. The evolution of tafenoquine−antimalarial for a new millennium? *J. R. Soc. Med.* **1999**, *92*, 345−352.
(262) Bohacek, R. S.; McMartin, C.; Guida, W. C. The art and practice of structure-based drug design: a molecular modeling perspective. *Med. Res. Rev.* **1996**, *16*, 3−50.
(263) Fink, T.; Bruggesser, H.; Reymond, J. L. Virtual exploration of the small-molecule chemical universe below 160 Da. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 1504−1508.
(264) Drew, K. L.; Baiman, H.; Khwaounjoo, P.; Yu, B.; Reynisson, J. Size estimation of chemical space: how big is it? *J. Pharm. Pharmacol.* **2012**, *64*, 490−495.
(265) Demonaco, H. J.; Ali, A.; Hippel, E. The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy* **2006**, *26*, 323−332.
(266) Edwards, A. What are the odds of finding a COVID-19 drug from a lab repurposing screen? *J. Chem. Inf. Model.* **2020**, *60*, 5727−5729.
(267) Begley, C. G.; Ellis, L. M. Drug development: Raise standards for preclinical cancer research. *Nature* **2012**, *483*, 531−533.
(268) Amelio, I.; Lisitsa, A.; Knight, R. A.; Melino, G.; Antonov, A. V. Polypharmacology of approved anticancer drugs. *Curr. Drug Targets* **2017**, *18*, 534−543.
(269) Casarotto, P. C.; Girych, M.; Fred, S. M.; Kovaleva, V.; Moliner, R.; Enkavi, G.; Biojone, C.; Cannarozzo, C.; Sahu, M. P.; Kaurinkoski, K.; Brunello, C. A.; Steinzeig, A.; Winkel, F.; Patil, S.; Vestring, S.; Serchov, T.; Diniz, C.; Laukkanen, L.; Cardon, I.; Antila, H.; Rog, T.; Piepponen, T. P.; Bramham, C. R.; Normann, C.; Lauri, S. E.; Saarma, M.; Vattulainen, I.; Castrén, E. Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. *Cell* **2021**, *184*, 1299−1313.
(270) Wetzel, C.; Lonneman, M.; Wu, C. Polypharmacological drug actions of recently FDA approved antibiotics. *Eur. J. Med. Chem.* **2021**, *209*, No. 112931.
(271) Ryszkiewicz, P.; Malinowska, B.; Schlicker, E. Polypharmacology: promises and new drugs in 2022. *Pharmacol. Rep.* **2023**, *75*, 755−770.
(272) Lin, A.; Giuliano, C. J.; Palladino, A.; John, K. M.; Abramowicz, C.; Yuan, M. L.; Sausville, E. L.; Lukow, D. A.; Liu, L.; Chait, A. R.; Galluzzo, Z. C.; Tucker, C.; Sheltzer, J. M. Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. *Sci. Transl. Med.* **2019**, *11*, No. eaaw8412.
(273) Kettle, J. G.; Alwan, H.; Bista, M.; Breed, J.; Davies, N. L.; Eckersley, K.; Fillery, S.; Foote, K. M.; Goodwin, L.; Jones, D. R.; Käck, H.; Lau, A.; Nissink, J. W.; Read, J.; Scott, J. S.; Taylor, B.; Walker, G.; Wissler, L.; Wylot, M. Potent and selective inhibitors of MTH1 probe its role in cancer cell survival. *J. Med. Chem.* **2016**, *59*, 2346−2361.
(274) Papeo, G. MutT homolog 1 (MTH1): the silencing of a target. *J. Med. Chem.* **2016**, *59*, 2343−2345.
(275) Sadybekov, A. V.; Katritch, V. Computational approaches streamlining drug discovery. *Nature* **2023**, *616*, 673−685.
(276) Tawfik, G. M.; Dila, K. A. S.; Mohamed, M. Y. F.; Tam, D. N. H.; Kien, N. D.; Ahmed, A. M.; Huy, N. T. A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Trop. Med. Health* **2019**, *47*, 46.
(277) Rathbone, J.; Carter, M.; Hoffmann, T.; Glasziou, P. Better duplicate detection for systematic reviewers: Evaluation of Systematic Review Assistant-Deduplication Module. *Syst. Rev.* **2015**, *4*, 6.
(278) Szklarczyk, D.; Gable, A. L.; Lyon, D.; Junge, A.; Wyder, S.; Huerta-Cepas, J.; Simonovic, M.; Doncheva, N. T.; Morris, J. H.; Bork, P.; Jensen, L. J.; Mering, C. V. STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res.* **2019**, *47*, D607−D613.
(279) Arikawa, M.; Kakinuma, Y.; Noguchi, T.; Todaka, H.; Sato, T. Donepezil, an acetylcholinesterase inhibitor, attenuates LPS-induced inflammatory response in murine macrophage cell line RAW 264.7 through inhibition of nuclear factor kappa B translocation. *Eur. J. Pharmacol.* **2016**, *789*, 17−26.
(280) Kim, H. G.; Moon, M.; Choi, J. G.; Park, G.; Kim, A. J.; Hur, J.; Lee, K. T.; Oh, M. S. Donepezil inhibits the amyloid-beta oligomer-induced microglial activation in vitro and in vivo. *Neurotoxicology* **2014**, *40*, 23−32.
(281) Goschorska, M.; Baranowska-Bosiacka, I.; Gutowska, I.; Tarnowski, M.; Piotrowska, K.; Metryka, E.; Safranow, K.; Chlubek, D. Effect of acetylcholinesterase inhibitors donepezil and rivastigmine on the activity and expression of cyclooxygenases in a model of the inflammatory action of fluoride on macrophages obtained from THP-1 monocytes. *Toxicology* **2018**, *406*−*407*, 9−20.
(282) Guo, H. B.; Cheng, Y. F.; Wu, J. G.; Wang, C. M.; Wang, H. T.; Zhang, C.; Qiu, Z. K.; Xu, J. P. Donepezil improves learning and memory deficits in APP/PS1 mice by inhibition of microglial activation. *Neuroscience* **2015**, *290*, 530−542.
(283) Haraguchi, Y.; Mizoguchi, Y.; Ohgidani, M.; Imamura, Y.; Murakawa-Hirachi, T.; Nabeta, H.; Tateishi, H.; Kato, T. A.; Monji, A. Donepezil suppresses intracellular Ca2+ mobilization through the PI3K pathway in rodent microglia. *J. Neuroinflammation* **2017**, *14*. DOI: 10.1186/s12974-017-1033-0.
(284) Hwang, J.; Hwang, H.; Lee, H. W.; Suk, K. Microglia signaling as a target of donepezil. *Neuropharmacology* **2010**, *58*, 1122−1129.
(285) Makitani, K.; Nakagawa, S.; Izumi, Y.; Akaike, A.; Kume, T. Inhibitory effect of donepezil on bradykinin-induced increase in the intracellular calcium concentration in cultured cortical astrocytes. *J. Pharmacol. Sci.* **2017**, *134*, 37−44.
(286) Reale, M.; Iarlori, C.; Gambi, F.; Feliciani, C.; Isabella, L.; Gambi, D. The acetylcholinesterase inhibitor, Donepezil, regulates a Th2 bias in Alzheimer's disease patients. *Neuropharmacology* **2006**, *50*, 606−613.
(287) Doganay, G.; Khodr, B.; Georgiou, G.; Khalil, Z. Pharmacological manipulation of the vasoconstrictive effects of amyloid-beta peptides by donepezil and rivastigmine. *Curr. Alzheimer Res.* **2006**, *3*, 137−145.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(288) Lataro, R. M.; Silva, M. A. B.; Mestriner, F. L.; Cau, S. B. A.; Tostes, R. C. A.; Salgado, H. C. Chronic treatment with acetylcholinesterase inhibitors attenuates vascular dysfunction in spontaneously hypertensive rats. *Am. J. Hypertens* **2019**, *32*, 579−587.
(289) Kinoshita, H.; Nakahata, K.; Hama-Tomioka, K.; Ishida, Y.; Matsuda, N.; Hatakeyama, N.; Haba, M.; Kondo, T.; Hatano, Y. Cholinesterase inhibitor donepezil dilates cerebral parenchymal arterioles via the activation of neuronal nitric oxide synthase. *Anesthesiology* **2008**, *109*, 124−129.
(290) Fujiki, M.; Kobayashi, H.; Uchida, S.; Inoue, R.; Ishii, K. Neuroprotective effect of donepezil, a nicotinic acetylcholine-receptor activator, on cerebral infarction in rats. *Brain Res.* **2005**, *1043*, 236−241.
(291) Nakano, S.; Asada, T.; Matsuda, H.; Uno, M.; Takasaki, M. Donepezil hydrochloride preserves regional cerebral blood flow in patients with Alzheimer's disease. *J. Nucl. Med.* **2001**, *42*, 1441−1445.
(292) Min, D.; Mao, X.; Wu, K.; Cao, Y.; Guo, F.; Zhu, S.; Xie, N.; Wang, L.; Chen, T.; Shaw, C.; Cai, J. Donepezil attenuates hippocampal neuronal damage and cognitive deficits after global cerebral ischemia in gerbils. *Neurosci. Lett.* **2012**, *510*, 29−33.
(293) Mortazavian, S. M.; Parsaee, H.; Mousavi, S. H.; Tayarani-Najaran, Z.; Ghorbani, A.; Sadeghnia, H. R. Acetylcholinesterase inhibitors promote angiogenesis in chick chorioallantoic membrane and inhibit apoptosis of endothelial cells. *Int. J. Alzheimers Dis.* **2013**, *2013*, No. 121068.
(294) Kotani, S.; Yamauchi, T.; Teramoto, T.; Ogura, H. Donepezil, an acetylcholinesterase inhibitor, enhances adult hippocampal neurogenesis. *Chem. Biol. Interact.* **2008**, *175*, 227−230.
(295) Atef, M. M.; El-Sayed, N. M.; Ahmed, A. A. M.; Mostafa, Y. M. Donepezil improves neuropathy through activation of AMPK signalling pathway in streptozotocin-induced diabetic mice. *Biochem. Pharmacol.* **2019**, *159*, 1−10.
(296) Kapai, N. A.; Solntseva, E. I.; Skrebitskii, V. G. Donepezil eliminates suppressive effects of beta-amyloid peptide (1−42) on long-term potentiation in the hippocampus. *Bull. Exp. Biol. Med.* **2010**, *149*, 33−36.
(297) Kapai, N. A.; Bukanova, J. V.; Solntseva, E. I.; Skrebitsky, V. G. Donepezil in a narrow concentration range augments control and impaired by beta-amyloid peptide hippocampal LTP in NMDAR-independent manner. *Cell. Mol. Neurobiol.* **2012**, *32*, 219−226.
(298) Solntseva, E. I.; Bukanova, J. V.; Marchenko, E.; Skrebitsky, V. G. Donepezil is a strong antagonist of voltage-gated calcium and potassium channels in molluscan neurons. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2007**, *144*, 319−326.
(299) Yu, B.; Hu, G. Y. Donepezil blocks voltage-gated ion channels in rat dissociated hippocampal neurons. *Eur. J. Pharmacol.* **2005**, *508*, 15−21.
(300) Zhou, X.; Xiao, W.; Su, Z.; Cheng, J.; Zheng, C.; Zhang, Z.; Wang, Y.; Wang, L.; Xu, B.; Li, S.; Yang, X.; Pui Man Hoi, M. Hippocampal proteomic alteration in triple transgenic mouse model of Alzheimer's disease and implication of PINK 1 regulation in donepezil treatment. *J. Proteome Res.* **2019**, *18*, 1542−1552.
(301) Noh, M. Y.; Koh, S. H.; Kim, Y.; Kim, H. Y.; Cho, G. W.; Kim, S. H. Neuroprotective effects of donepezil through inhibition of GSK-3 activity in amyloid-β-induced neuronal cell death. *J. Neurochem.* **2009**, *108*, 1116−1125.
(302) Kimura, M.; Komatsu, H.; Ogura, H.; Sawada, K. Comparison of donepezil and memantine for protective effect against amyloid-beta(1−42) toxicity in rat septal neurons. *Neurosci. Lett.* **2005**, *391*, 17−21.
(303) Goschorska, M.; Gutowska, I.; Baranowska-Bosiacka, I.; Piotrowska, K.; Metryka, E.; Safranow, K.; Chlubek, D. Influence of acetylcholinesterase inhibitors used in Alzheimer's disease treatment on the activity of antioxidant enzymes and the concentration of glutathione in THP-1 macrophages under fluoride-induced oxidative stress. *Int. J. Env. Res. Public Health* **2019**, *16*, 10.
(304) Umukoro, S.; Adewole, F. A.; Eduviere, A. T.; Aderibigbe, A. O.; Onwuchekwa, C. Free radical scavenging effect of donepezil as the possible contribution to its memory enhancing activity in mice. *Drug Res.* **2014**, *64*, 236−239.
(305) Li, Y. X.; Ye, Z. H.; Chen, T.; Jia, X. F.; He, L. The effects of donepezil on phencyclidine-induced cognitive deficits in a mouse model of schizophrenia. *Pharmacol., Biochem. Behav.* **2018**, *175*, 69−76.
(306) Tsuchiya, K.; Tajima, H.; Yamada, M.; Takahashi, H.; Kuwae, T.; Sunaga, K.; Katsube, N.; Ishitani, R. Disclosure of a pro-apoptotic glyceraldehyde-3-phosphate dehydrogenase promoter: Anti-dementia drugs depress its activation in apoptosis. *Life Sci.* **2004**, *74*, 3245−3258.
(307) Yuan, H.; Wang, W. P.; Feng, N.; Wang, L.; Wang, X. L. Donepezil attenuated oxygen-glucose deprivation insult by blocking Kv2.1 potassium channels. *Eur. J. Pharmacol.* **2011**, *657*, 76−83.
(308) Page, M.; Pacico, N.; Ourtioualous, S.; Deprez, T.; Koshibu, K. Procognitive compounds promote neurite outgrowth. *Pharmacology* **2015**, *96*, 131−136.
(309) Jian, W. X.; Zhang, Z.; Zhan, J. H.; Chu, S. F.; Peng, Y.; Zhao, M.; Wang, Q.; Chen, N. H. Donepezil attenuates vascular dementia in rats through increasing BDNF induced by reducing HDAC6 nuclear translocation. *Acta Pharmacol. Sin.* **2020**, *41*, 588−598.
(310) Narimatsu, N.; Harada, N.; Kurihara, H.; Nakagata, N.; Sobue, K.; Okajima, K. Donepezil improves cognitive function in mice by increasing the production of insulin-like growth factor-I in the hippocampus. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 2−12.
(311) Obermayr, R. P.; Mayerhofer, L.; Knechtelsdorfer, M.; Mersich, N.; Huber, E. R.; Geyer, G.; Tragl, K. H. The age-related down-regulation of the growth hormone/insulin-like growth factor-1 axis in the elderly male is reversed considerably by donepezil, a drug for Alzheimer's disease. *Exp. Gerontol.* **2005**, *40*, 157−163.
(312) Zhu, Z.; Zhang, L.; Cui, Y.; Li, M.; Ren, R.; Li, G.; Sun, X.; Li, Q. Functional compensation and mechanism of choline acetyltransferase in the treatment of cognitive deficits in aged dementia mice. *Neuroscience* **2020**, *442*, 41−53.
(313) Man, J.; Cui, K.; Fu, X.; Zhang, D.; Lu, Z.; Gao, Y.; Yu, L.; Li, N.; Wang, J. Donepezil promotes neurogenesis via Src signaling pathway in a rat model of chronic cerebral hypoperfusion. *Brain Res.* **2020**, *1736*, No. 146782.
(314) Oda, T.; Kume, T.; Katsuki, H.; Niidome, T.; Sugimoto, H.; Akaike, A. Donepezil potentiates nerve growth factor-induced neurite outgrowth in PC12 cells. *J. Pharmacol. Sci.* **2007**, *104*, 349−354.
(315) Imamura, O.; Arai, M.; Dateki, M.; Ogata, T.; Uchida, R.; Tomoda, H.; Takishima, K. Nicotinic acetylcholine receptors mediate donepezil-induced oligodendrocyte differentiation. *J. Neurochem.* **2015**, *135*, 1086−1098.
(316) Shamsi, A.; Anwar, S.; Mohammad, T.; Alajmi, M. F.; Hussain, A.; Rehman, M. T.; Hasan, G. M.; Islam, A.; Hassan, M. I. MARK4 inhibited by AChE inhibitors, donepezil and rivastigmine tartrate: Insights into alzheimer's disease therapy. *Biomolecules* **2020**, *10*, 789.
(317) Di Angelantonio, S.; Bernardi, G.; Mercuri, N. B. Donepezil modulates nicotinic receptors of substantia nigra dopaminergic neurones. *Br. J. Pharmacol.* **2004**, *141*, 644−652.
(318) Takada-Takatori, Y.; Kume, T.; Ohgi, Y.; Fujii, T.; Niidome, T.; Sugimoto, H.; Akaike, A. Mechanisms of α7-nicotinic receptor up-regulation and sensitization to donepezil induced by chronic donepezil treatment. *Eur. J. Pharmacol.* **2008**, *590*, 150−156.
(319) Hashimoto, K. Potential role of the sigma-1 receptor chaperone in the beneficial effects of donepezil in dementia with lewy bodies. *Clin. Psychopharmacol. Neurosci.* **2013**, *11*, 43−44.
(320) Ishikawa, M.; Sakata, M.; Ishii, K.; Kimura, Y.; Oda, K.; Toyohara, J.; Wu, J.; Ishiwata, K.; Iyo, M.; Hashimoto, K. High occupancy of σ1 receptors in the human brain after single oral administration of donepezil: A positron emission tomography study using [11C]SA4503. *Int. J. Neuropsychopharmacol.* **2009**, *12*, 1127−1131.
(321) Ishima, T.; Nishimura, T.; Iyo, M.; Hashimoto, K. Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by donepezil: Role of sigma-1 receptors and IP3 receptors. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2008**, *32*, 1656−1659.
(322) Meunier, J.; Ieni, J.; Maurice, T. The anti-amnesic and neuroprotective effects of donepezil against amyloid B25−35 peptide-induced toxicity in mice involve an interaction with the σ1 receptor. *Br. J. Pharmacol.* **2006**, *149*, 998−1012.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(323) Kunitachi, S.; Fujita, Y.; Ishima, T.; Kohno, M.; Horio, M.; Tanibuchi, Y.; Shirayama, Y.; Iyo, M.; Hashimoto, K. Phencyclidine-induced cognitive deficits in mice are ameliorated by subsequent subchronic administration of donepezil: Role of sigma-1 receptors. *Brain Res.* **2009**, *1279*, 189−196.
(324) Maurice, T.; Meunier, J.; Feng, B.; Ieni, J.; Monaghan, D. T. Interaction with σ1 protein, but not N-Methyl-D-aspartate receptor, is involved in the pharmacological activity of donepezil. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 606−614.
(325) Guo, T. T.; Wang, W. P.; Wang, X. L. Mechanism of donepezil protecting neurons by inhibiting sodium channel and NMDA receptor channel. *Chin. Pharm. J.* **2017**, *52*, 2166−2171.
(326) Wang, C. N.; Wang, Y. J.; Wang, H.; Song, L.; Chen, Y.; Wang, J. L.; Ye, Y.; Jiang, B. The anti-dementia effects of donepezil involve miR-206−3p in the hippocampus and cortex. *Biol. Pharm. Bull.* **2017**, *40*, 465−472.
(327) Shen, H.; Kihara, T.; Hongo, H.; Wu, X.; Kem, W. R.; Shimohama, S.; Akaike, A.; Niidome, T.; Sugimoto, H. Neuroprotection by donepezil against glutamate excitotoxicity involves stimulation of α7 nicotinic receptors and internalization of NMDA receptors. *Br. J. Pharmacol.* **2010**, *161*, 127−139.
(328) Akaike, A.; Takada-Takatori, Y.; Kume, T.; Izumi, Y. Mechanisms of neuroprotective effects of nicotine and acetylcholinesterase inhibitors: Role of α4 and α7 receptors in neuroprotection. *J. Mol. Neurosci.* **2010**, *40*, 211−216.
(329) Arias, E.; Gallego-Sandín, S.; Villarroya, M.; García, A. G.; López, M. G. Unequal neuroprotection afforded by the acetylcholinesterase inhibitors galantamine, donepezil, and rivastigmine in SHSY5Y neuroblastoma cells: Role of nicotinic receptors. *J. Pharmacol. Exp. Ther.* **2005**, *315*, 1346−1353.
(330) Takada-Takatori, Y.; Kume, T.; Ohgi, Y.; Izumi, Y.; Niidome, T.; Fujii, T.; Sugimoto, H.; Akaike, A. Mechanism of neuroprotection by donepezil pretreatment in rat cortical neurons chronically treated with donepezil. *J. Neurosci. Res.* **2008**, *86*, 3575−3583.
(331) Akaike, A.; Katsuki, H.; Kume, T.; Takada-Takatori, Y. Neuroprotective action of donepezil mediated by neuronal nicotinic receptors. *Psychogeriatrics* **2006**, *6*, S47−S56.
(332) Kim, E.; Park, M.; Jeong, J.; Kim, H.; Lee, S. K.; Lee, E.; Oh, B. H.; Namkoong, K. Cholinesterase inhibitor donepezil increases mitochondrial biogenesis through AMP-activated protein kinase in the hippocampus. *Neuropsychobiology* **2016**, *73*, 81−91.
(333) Akasofu, S.; Kosasa, T.; Kimura, M.; Kubota, A. Protective effect of donepezil in a primary culture of rat cortical neurons exposed to oxygen-glucose deprivation. *Eur. J. Pharmacol.* **2003**, *472*, 57−63.
(334) Akasofu, S.; Sawada, K.; Kosasa, T.; Hihara, H.; Ogura, H.; Akaike, A. Donepezil attenuates excitotoxic damage induced by membrane depolarization of cortical neurons exposed to veratridine. *Eur. J. Pharmacol.* **2008**, *588*, 189−197.
(335) Zhang, T.; Tian, F.; Wang, J.; Zhou, S.; Dong, X.; Guo, K.; Jing, J.; Zhou, Y.; Chen, Y. Donepezil attenuates high glucose-accelerated senescence in human umbilical vein endothelial cells through SIRT1 activation. *Cell Stress Chaperones* **2015**, *20*, 787−792.
(336) Pákáski, M.; Fehér, A.; Juhász, A.; Drótos, G.; Fazekas, O. C.; Kovács, J.; Janka, Z.; Kálmán, J. Serum adipokine levels modified by donepezil treatment in Alzheimer's disease. *J. Alzheimer's Dis.* **2013**, *38*, 371−377.
(337) Conti, E.; Tremolizzo, L.; Santarone, M. E.; Tironi, M.; Radice, I.; Zoia, C. P.; Aliprandi, A.; Salmaggi, A.; Dominici, R.; Casati, M.; Appollonio, I.; Ferrarese, C. Donepezil modulates the endogenous immune response: Implications for Alzheimer's disease. *Hum. Psychopharmacol.* **2016**, *31*, 296−303.
(338) Dong, G. S.; Li, X.; Jiang, Q. H.; Yang, H. Q. [Effects of donepezil treatment on platelets alpha and beta secretase activities in Alzheimer's disease patients]. *Zhonghua Yi Xue Za Zhi* **2011**, *91*, 3341−3345.
(339) Takada-Takatori, Y.; Nakagawa, S.; Kimata, R.; Nao, Y.; Mizukawa, Y.; Urushidani, T.; Izumi, Y.; Akaike, A.; Tsuchida, K.; Kume, T. Donepezil modulates amyloid precursor protein endocytosis and reduction by up-regulation of SNX33 expression in primary cortical neurons. *Sci. Rep.* **2019**, *9*, 11922.
(340) Talib, L. L.; Hototian, S. R.; Joaquim, H. P. G.; Forlenza, O. V.; Gattaz, W. F. Increased iPLA2 activity and levels of phosphorylated GSK3B in platelets are associated with donepezil treatment in Alzheimer's disease patients. *Eur. Arch. Psychiatry Clin. Neurosci.* **2015**, *265*, 701−706.
(341) Mohamed, L. A.; Qosa, H.; Kaddoumi, A. Age-related decline in brain and hepatic clearance of amyloid-beta is rectified by the cholinesterase inhibitors donepezil and rivastigmine in rats. *ACS Chem. Neurosci.* **2015**, *6*, 725−736.
(342) Ye, C. Y.; Lei, Y.; Tang, X. C.; Zhang, H. Y. Donepezil attenuates Aβ-associated mitochondrial dysfunction and reduces mitochondrial Aβ accumulation in vivo and in vitro. *Neuropharmacology* **2015**, *95*, 29−36.
(343) Noh, M. Y.; Koh, S. H.; Kim, S. M.; Maurice, T.; Ku, S. K.; Kim, S. H. Neuroprotective effects of donepezil against Aβ42-induced neuronal toxicity are mediated through not only enhancing PP2A activity but also regulating GSK-3β and nAChRs activity. *J. Neurochem.* **2013**, *127*, 562−574.
(344) Zimmermann, M.; Gardoni, F.; Marcello, E.; Colciaghi, F.; Borroni, B.; Padovani, A.; Cattabeni, F.; Di Luca, M. Acetylcholinesterase inhibitors increase ADAM10 activity by promoting its trafficking in neuroblastoma cell lines. *J. Neurochem.* **2004**, *90*, 1489−1499.
(345) Davis, M. I.; Hunt, J. P.; Herrgard, S.; Ciceri, P.; Wodicka, L. M.; Pallares, G.; Hocker, M.; Treiber, D. K.; Zarrinkar, P. P. Comprehensive analysis of kinase inhibitor selectivity. *Nat. Biotechnol.* **2011**, *29*, 1046−1051.
(346) Troutman, S.; Moleirinho, S.; Kota, S.; Nettles, K.; Fallahi, M.; Johnson, G. L.; Kissil, J. L. Crizotinib inhibits NF2-associated schwannoma through inhibition of focal adhesion kinase 1. *Oncotarget* **2016**, *7*, 54515−54525.
(347) Dai, X.; Guo, G.; Zou, P.; Cui, R.; Chen, W.; Chen, X.; Yin, C.; He, W.; Vinothkumar, R.; Yang, F.; Zhang, X.; Liang, G. (S)-crizotinib induces apoptosis in human non-small cell lung cancer cells by activating ROS independent of MTH1. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 120.
(348) Megiorni, F.; McDowell, H. P.; Camero, S.; Mannarino, O.; Ceccarelli, S.; Paiano, M.; Losty, P. D.; Pizer, B.; Shukla, R.; Pizzuti, A.; Clerico, A.; Dominici, C. Crizotinib-induced antitumour activity in human alveolar rhabdomyosarcoma cells is not solely dependent on ALK and MET inhibition. *J. Exp. Clin. Cancer Res.* **2015**, *34*. DOI: 10.1186/s13046-015-0228-4 https://ncbi.nlm.nih.gov/pmc/articles/PMC4596370.
(349) Ji, J.; Chen, W.; Lian, W.; Chen, R.; Yang, J.; Zhang, Q.; Weng, Q.; Khan, Z.; Hu, J.; Chen, X.; Zou, P.; Chen, X.; Liang, G. (S)-crizotinib reduces gastric cancer growth through oxidative DNA damage and triggers pro-survival akt signal. *Cell Death Dis.* **2018**, *9*, 660.
(350) Hamedani, F. S.; Cinar, M.; Mo, Z.; Cervania, M. A.; Amin, H. M.; Alkan, S. Crizotinib (PF-2341066) induces apoptosis due to downregulation of pSTAT3 and BCL-2 family proteins in NPM-ALK+ anaplastic large cell lymphoma. *Leuk. Res.* **2014**, *38*, 503−508.
(351) Vladimer, G. I.; Snijder, B.; Krall, N.; Bigenzahn, J. W.; Huber, K. V. M.; Lardeau, C. H.; Sanjiv, K.; Ringler, A.; Berglund, U. W.; Sabler, M.; de la Fuente, O. L.; Knöbl, P.; Kubicek, S.; Helleday, T.; Jäger, U.; Superti-Furga, G. Global survey of the immunomodulatory potential of common drugs. *Nat. Chem. Biol.* **2017**, *13*, 681−690.
(352) Liu, P.; Zhao, L.; Pol, J.; Levesque, S.; Petrazzuolo, A.; Pfirschke, C.; Engblom, C.; Rickelt, S.; Yamazaki, T.; Iribarren, K.; Senovilla, L.; Bezu, L.; Vacchelli, E.; Sica, V.; Melis, A.; Martin, T.; Xia, L.; Yang, H.; Li, Q.; Chen, J.; Durand, S.; Aprahamian, F.; Lefevre, D.; Broutin, S.; Paci, A.; Bongers, A.; Minard-Colin, V.; Tartour, E.; Zitvogel, L.; Apetoh, L.; Ma, Y.; Pittet, M. J.; Kepp, O.; Kroemer, G. Crizotinib-induced immunogenic cell death in non-small cell lung cancer. *Nat. Commun.* **2019**, *10*, 1486.
(353) Zhou, Y.; Zhao, C.; Gery, S.; Braunstein, G. D.; Okamoto, R.; Alvarez, R.; Miles, S. A.; Doan, N. B.; Said, J. W.; Gu, J.; Phillip Koeffler, H. Off-target effects of c-MET inhibitors on thyroid cancer cells. *Mol. Cancer Ther.* **2014**, *13*, 134−143.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(354) Mestres, J.; Gregori-Puigjané, E.; Valverde, S.; Solé, R. V. The topology of drug-target interaction networks: implicit dependence on drug properties and target families. *Mol. Biosyst.* **2009**, *5*, 1051−1057.
(355) Mendez, D.; Gaulton, A.; Bento, A. P.; Chambers, J.; De Veij, M.; Felix, E.; Magarinos, M. P.; Mosquera, J. F.; Mutowo, P.; Nowotka, M.; Gordillo-Maranon, M.; Hunter, F.; Junco, L.; Mugumbate, G.; Rodriguez-Lopez, M.; Atkinson, F.; Bosc, N.; Radoux, C. J.; Segura-Cabrera, A.; Hersey, A.; Leach, A. R. ChEMBL: Towards direct deposition of bioassay data. *Nucleic Acids Res.* **2019**, *47*, D930−D940.
(356) Santos, R.; Ursu, O.; Gaulton, A.; Bento, A. P.; Donadi, R. S.; Bologa, C. G.; Karlsson, A.; Al-Lazikani, B.; Hersey, A.; Oprea, T. I.; Overington, J. P. A comprehensive map of molecular drug targets. *Nat. Rev. Drug Discovery* **2017**, *16*, 19−34.
(357) Kalliokoski, T.; Kramer, C.; Vulpetti, A.; Gedeck, P. Comparability of mixed IC(5)(0) data - a statistical analysis. *PLoS One* **2013**, *8*, No. e61007.
(358) Polanyi, M. Life's irreducible structure. *Science* **1968**, *160*, 1308−1312.
(359) Des Chene, D. *Spirits and Clocks: Machine and Organism in Descartes*; Cornell University Press: Ithaca, N.Y.; London, 2001. DOI: 10.7591/9781501723728.
(360) Nicholson, D. J. Is the cell really a machine? *J. Theor. Biol.* **2019**, *477*, 108−126.
(361) Bongard, J.; Levin, M. Living things are not (20th century) machines: Updating mechanism metaphors in light of the modern science of machine behavior. *Frontiers in Ecology and Evolution* **2021**, *9*, 147.
(362) Holm, S.; Serban, M. *Philosophical Perspectives on the Engineering Approach in Biology: Living Machines?*; Routledge, 2020. DOI: 10.4324/9781351212243.
(363) Levy, A. Machine-likeness and explanation by decomposition. *Philosopher's Imprint* **2014**, *14*, 1−15.
(364) Nicolis, G.; Prigogine, I. *Self-Organization in Nonequilibrium Systems*; Wiley, 1977.
(365) Ashby, W. R. Principles of the self-organizing system. In *Facets of Systems Science*, Klir, G. J., Ed. Springer: Boston, MA, 1991; pp 521−536. DOI: 10.1007/978-1-4899-0718-9_38.
(366) Kauffman, S. A. *The Origins of Order: Self-organization and Selection in Evolution*. Oxford University Press: 1993; p xviii, 709 p. also see DOI: 10.1007/978-94-015-8054-0_8 and DOI: 10.1142/9789814415743_0003.
(367) Bechtel, W.; Richardson, R. C. *Discovering Complexity: Decomposition and Localization as Strategies in Scientific Research*; MIT Press, 2010.
(368) Piatigorsky, J. *Gene Sharing and Evolution: The Diversity of Protein Functions*; Harvard University Press, 2009. DOI: 10.4159/9780674042124.
(369) Gao, A.; Shrinivas, K.; Lepeudry, P.; Suzuki, H. I.; Sharp, P. A.; Chakraborty, A. K. Evolution of weak cooperative interactions for biological specificity. *Proc. Natl. Acad. Sci. U.S.A* **2018**, *115*, E11053−E11060.
(370) Winning, J.; Bechtel, W. Rethinking causality in biological and neural mechanisms: Constraints and control. *Mind. Mach* **2018**, *28*, 287−310.
(371) Calabrese, E. J.; Mattson, M. P. How does hormesis impact biology, toxicology, and medicine? *NPJ. Aging Mech Dis* **2017**, *3*, 13.
(372) Milo, D. S. *Good Enough: The Tolerance for Mediocrity in Nature and Society*; Harvard University Press, 2019. DOI: 10.4159/9780674240049.
(373) Fischer, A.; Rausell, A. Primary immunodeficiencies suggest redundancy within the human immune system. *Sci. Immunol.* **2016**, *1*. DOI: 10.1126/sciimmunol.aah5861.
(374) Conant, G. C.; Wagner, A. Duplicate genes and robustness to transient gene knock-downs in Caenorhabditis elegans. *Proc. Biol. Sci.* **2004**, *271*, 89−96.
(375) Senter, P.; Moch, J. G. A critical survey of vestigial structures in the postcranial skeletons of extant mammals. *PeerJ.* **2015**, *3*, No. e1439.
(376) Edelman, G. M.; Gally, J. A. Degeneracy and complexity in biological systems. *Proc. Natl. Acad. Sci. U.S.A* **2001**, *98*, 13763−13768.
(377) Figdor, C. Neuroscience and the multiple realization of cognitive functions. *Philos. Sci.* **2010**, *77*, 419−456.
(378) Klein, B.; Hoel, E. The emergence of informative higher scales in complex networks. *Complexity* **2020**, *2020*, No. 8932526.
(379) Kleiner, J.; Tull, S. The mathematical structure of integrated information theory. *Frontiers in Applied Mathematics and Statistics* **2021**, *6*, 74.
(380) Oizumi, M.; Albantakis, L.; Tononi, G. From the phenomenology to the mechanisms of consciousness: Integrated Information Theory 3.0. *PLoS Comput. Biol.* **2014**, *10*, No. e1003588.
(381) Casali, A. G.; Gosseries, O.; Rosanova, M.; Boly, M.; Sarasso, S.; Casali, K. R.; Casarotto, S.; Bruno, M. A.; Laureys, S.; Tononi, G.; Massimini, M. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci. Transl. Med.* **2013**, *5*, No. 198ra105.
(382) Popiel, N. J. M.; Khajehabdollahi, S.; Abeyasinghe, P. M.; Riganello, F.; Nichols, E. S.; Owen, A. M.; Soddu, A. The emergence of integrated information, complexity, and 'consciousness' at criticality. *Entropy* **2020**, *22*, 339.
(383) Marshall, W.; Kim, H.; Walker, S. I.; Tononi, G.; Albantakis, L. How causal analysis can reveal autonomy in models of biological systems. *Philos. Trans A Math Phys. Eng. Sci.* **2017**, *375*, 20160358.
(384) Massimini, M.; Ferrarelli, F.; Huber, R.; Esser, S. K.; Singh, H.; Tononi, G. Breakdown of cortical effective connectivity during sleep. *Science* **2005**, *309*, 2228−2232.
(385) Ferrarelli, F.; Massimini, M.; Sarasso, S.; Casali, A.; Riedner, B. A.; Angelini, G.; Tononi, G.; Pearce, R. A. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. *Proc. Natl. Acad. Sci. U.S.A* **2010**, *107*, 2681−2686.
(386) Casarotto, S.; Comanducci, A.; Rosanova, M.; Sarasso, S.; Fecchio, M.; Napolitani, M.; Pigorini, A.; A, G. C.; Trimarchi, P. D.; Boly, M.; Gosseries, O.; Bodart, O.; Curto, F.; Landi, C.; Mariotti, M.; Devalle, G.; Laureys, S.; Tononi, G.; Massimini, M. Stratification of unresponsive patients by an independently validated index of brain complexity. *Ann. Neurol.* **2016**, *80*, 718−729.
(387) Merker, B.; Williford, K.; Rudrauf, D. The integrated information theory of consciousness: A case of mistaken identity. *Behav. Brain Sci.* **2022**, *45*, No. e41.
(388) Melloni, L.; Mudrik, L.; Pitts, M.; Koch, C. Making the hard problem of consciousness easier. *Science* **2021**, *372*, 911−912.
(389) Hoel, E. P.; Albantakis, L.; Tononi, G. Quantifying causal emergence shows that macro can beat micro. *Proc. Natl. Acad. Sci. U.S.A* **2013**, *110*, 19790−19795.
(390) Hoel, E. P.; Albantakis, L.; Marshall, W.; Tononi, G. Can the macro beat the micro? Integrated information across spatiotemporal scales. *Neurosci Conscious* **2016**, *2016*, No. niw012.
(391) Marshall, W.; Albantakis, L.; Tononi, G. Black-boxing and cause-effect power. *PLoS Comput. Biol.* **2018**, *14*, No. e1006114.
(392) Albantakis, L.; Tononi, G. The intrinsic cause-effect power of discrete dynamical systems—from elementary cellular automata to adapting animats. *Entropy* **2015**, *17*, 5472−5502.
(393) Barrett, A. B.; Mediano, P. A. The phi measure of integrated information is not well-defined for general physical systems. *J. Consciousness Stud.* **2019**, *26*, 11−20.
(394) Hoel, E. P. When the map is better than the territory. *Entropy* **2017**, *19*, 188.
(395) Klein, B.; Hoel, E.; Swain, A.; Griebenow, R.; Levin, M. Evolution and emergence: higher order information structure in protein interactomes across the tree of life. *Integr. Biol. (Camb.)* **2021**, *13*, 283−294.
(396) Leung, A.; Tsuchiya, N. Emergence of integrated information at macro timescales in real neural recordings. *Entropy (Basel)* **2022**, *24*, 625.
(397) Grasso, M.; Albantakis, L.; Lang, J. P.; Tononi, G. Causal reductionism and causal structures. *Nat. Neurosci.* **2021**, *24*, 1348−1355.
(398) Petrick, E. R. Building the black box: Cyberneticians and complex systems. *Science, Technology, & Human Values* **2020**, *45*, 575−595.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

(399) Bunge, M. A general black box theory. *Philos. Sci.* **1963**, *30*, 346−358.
(400) Ashby, W. R. *An Introduction to Cybernetics*. Wiley: London, 1956. https://archive.org/details/introductiontocy00ashb/page/86.
(401) Huang, S.; Eichler, G.; Bar-Yam, Y.; Ingber, D. E. Cell fates as high-dimensional attractor states of a complex gene regulatory network. *Phys. Rev. Lett.* **2005**, *94*, No. 128701.
(402) Wolpert, D.; Libby, E.; Grochow, J. A.; Dedeo, S. The many faces of state space compression. In *From Matter to Life: Information and Causality*, Ellis, G. F. R.; Davies, P. C. W.; Walker, S. I., Eds. Cambridge University Press: Cambridge, 2017; pp 199−243. DOI: 10.1017/9781316584200.010.
(403) Machta, B. B.; Chachra, R.; Transtrum, M. K.; Sethna, J. P. Parameter space compression underlies emergent theories and predictive models. *Science* **2013**, *342*, 604−607.
(404) Sáenz, P. J.; Pucci, G.; Turton, S. E.; Goujon, A.; Rosales, R. R.; Dunkel, J.; Bush, J. W. M. Emergent order in hydrodynamic spin lattices. *Nature* **2021**, *596*, 58−62.
(405) Batterman, R. W. Emergence, singularities, and symmetry breaking. *Found. Phys.* **2011**, *41*, 1031−1050.
(406) Bain, J. Emergence in effective field theories. *European Journal for Philosophy of Science* **2013**, *3*, 257−273.
(407) Castellani, E. Reductionism, emergence, and effective field theories. *Studies in History and Philosophy of Science Part B: Studies in History and Philosophy of Modern Physics* **2002**, *33*, 251−267.
(408) Barrett, C. L.; Herring, C. D.; Reed, J. L.; Palsson, B. O. The global transcriptional regulatory network for metabolism in Escherichia coli exhibits few dominant functional states. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 19103−19108.
(409) Ruiz, R. F. G.; Vernon, A. R. Emergence of simple patterns in many-body systems: from macroscopic objects to the atomic nucleus. *European Physical Journal A* **2020**, *56*, 136.
(410) van Zuiden, B. C.; Paulose, J.; Irvine, W. T.; Bartolo, D.; Vitelli, V. Spatiotemporal order and emergent edge currents in active spinner materials. *Proc. Natl. Acad. Sci. U.S.A* **2016**, *113*, 12919−12924.
(411) Newman, D. V. Emergence and strange attractors. *Philos. Sci.* **1996**, *63*, 245−261.
(412) Andriano, V.; Bacciotti, A.; Beccari, G. Global stability and external stability of dynamical systems. *Nonlinear Analysis: Theory, Methods & Applications* **1997**, *28*, 1167−1185.
(413) Transtrum, M. K.; Machta, B. B.; Brown, K. S.; Daniels, B. C.; Myers, C. R.; Sethna, J. P. Perspective: Sloppiness and emergent theories in physics, biology, and beyond. *J. Chem. Phys.* **2015**, *143*, No. 010901.
(414) Read, P. L.; Young, R. M. B.; Kennedy, D. The turbulent dynamics of Jupiter's and Saturn's weather layers: Order out of chaos? *Geoscience Letters* **2020**, *7*, 10.
(415) Chvykov, P.; Berrueta, T. A.; Vardhan, A.; Savoie, W.; Samland, A.; Murphey, T. D.; Wiesenfeld, K.; Goldman, D. I.; England, J. L. Low rattling: A predictive principle for self-organization in active collectives. *Science* **2021**, *371*, 90−95.
(416) Tallapragada, P.; Sudarsanam, S. A globally stable attractor that is locally unstable everywhere. *AIP Advances* **2017**, *7*, No. 125012.
(417) Zhang, J. D.; Sach-Peltason, L.; Kramer, C.; Wang, K.; Ebeling, M. Multiscale modelling of drug mechanism and safety. *Drug Discovery Today* **2020**, *25*, 519−534.
(418) Manglik, A.; Lin, H.; Aryal, D. K.; McCorvy, J. D.; Dengler, D.; Corder, G.; Levit, A.; Kling, R. C.; Bernat, V.; Hübner, H.; Huang, X. P.; Sassano, M. F.; Giguère, P. M.; Löber, S.; Da, D.; Scherrer, G.; Kobilka, B. K.; Gmeiner, P.; Roth, B. L.; Shoichet, B. K. Structure-based discovery of opioid analgesics with reduced side effects. *Nature* **2016**, *537*, 185−190.
(419) Morgan, P.; Brown, D. G.; Lennard, S.; Anderton, M. J.; Barrett, J. C.; Eriksson, U.; Fidock, M.; Hamrén, B.; Johnson, A.; March, R. E.; Matcham, J.; Mettetal, J.; Nicholls, D. J.; Platz, S.; Rees, S.; Snowden, M. A.; Pangalos, M. N. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. *Nat. Rev. Drug Discovery* **2018**, *17*, 167−181.
(420) Sun, D.; Gao, W.; Hu, H.; Zhou, S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm. Sin B* **2022**, *12*, 3049−3062.
(421) Li, Y.; Pei, J.; Lai, L. Structure-based de novo drug design using 3D deep generative models. *Chem. Sci.* **2021**, *12*, 13664−13675.
(422) Aarts, S.; Winkens, B.; van Den Akker, M. The insignificance of statistical significance. *Eur. J. Gen Pract* **2012**, *18*, 50−52.
(423) Leung, W. C. Balancing statistical and clinical significance in evaluating treatment effects. *Postgrad. Med. J.* **2001**, *77*, 201−204.
(424) Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials. https://rethinkingclinicaltrials.org/, http://web.archive.org/web/20210820131717/https://rethinkingclinicaltrials.org/ (20 August 2021). https://rethinkingclinicaltrials.org/, http://web.archive.org/web/20210820131717/https://rethinkingclinicaltrials.org/.
(425) Nguyen, M.; Jankovic, I.; Kalesinskas, L.; Baiocchi, M.; Chen, J. H. Machine learning for initial insulin estimation in hospitalized patients. *J. Am. Med. Inform Assoc* **2021**, *28*, 2212.
(426) Sheu, Y. H.; Magdamo, C.; Miller, M.; Das, S.; Blacker, D.; Smoller, J. W. AI-assisted prediction of differential response to antidepressant classes using electronic health records. *NPJ. Digit Med.* **2023**, *6*, 73.
(427) Frost, J.; Okun, S.; Vaughan, T.; Heywood, J.; Wicks, P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. *J. Med. Internet Res.* **2011**, *13*, No. e6.
(428) Sadri, A. Method, Software, Database, and System for the Most Efficient Phenotypic Drug Discovery Using Predictive and Generative Artificial Intelligence. WO2023/084472A2, 2022/11/14, 2023.
(429) Stokes, J. M.; Yang, K.; Swanson, K.; Jin, W.; Cubillos-Ruiz, A.; Donghia, N. M.; MacNair, C. R.; French, S.; Carfrae, L. A.; Bloom-Ackermann, Z.; Tran, V. M.; Chiappino-Pepe, A.; Badran, A. H.; Andrews, I. W.; Chory, E. J.; Church, G. M.; Brown, E. D.; Jaakkola, T. S.; Barzilay, R.; Collins, J. J. A deep learning approach to antibiotic discovery. *Cell* **2020**, *180*, 688−702.
(430) Lin, X.; Duan, X.; Jacobs, C.; Ullmann, J.; Chan, C. Y.; Chen, S.; Cheng, S. H.; Zhao, W. N.; Poduri, A.; Wang, X.; Haggarty, S. J.; Shi, P. High-throughput brain activity mapping and machine learning as a foundation for systems neuropharmacology. *Nat. Commun.* **2018**, *9*, 5142.
(431) Li, X.; Dunn, J.; Salins, D.; Zhou, G.; Zhou, W.; Schüssler-Fiorenza Rose, S. M.; Perelman, D.; Colbert, E.; Runge, R.; Rego, S.; Sonecha, R.; Datta, S.; McLaughlin, T.; Snyder, M. P. Digital health: Tracking physiomes and activity using wearable biosensors reveals useful health-related information. *PLoS Biol.* **2017**, *15*, No. e2001402.
(432) Park, S. E.; Georgescu, A.; Huh, D. Organoids-on-a-chip. *Science* **2019**, *364*, 960−965.
(433) National Academies of Sciences Engineering and Medicine. *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance*; National Academies Press: Washington, D.C., 2021. DOI: 10.17226/26078.
(434) Huszagh, V. A.; Infante, J. P. The hypothetical way of progress. *Nature* **1989**, *338*, 109.
(435) Brigandt, I. How to philosophically tackle kinds without talking about "natural kinds". *Can. J. Philos.* **2020**, 1−24.
(436) Fisher, M.; Keil, F. C. The binary bias: A systematic distortion in the integration of information. *Psychol. Sci.* **2018**, *29*, 1846−1858.
(437) van Deemter, K. *Not Exactly: In Praise of Vagueness*; Oxford University Press: 2010. https://archive.org/details/notexactlyinprai0000deem.
(438) Chicharro, D.; Ledberg, A. When two become one: The limits of causality analysis of brain dynamics. *PLoS One* **2012**, *7*, No. e32466.
(439) El-Brolosy, M. A.; Stainier, D. Y. R. Genetic compensation: A phenomenon in search of mechanisms. *PLoS Genet.* **2017**, *13*, No. e1006780.
(440) Anderson, J. L.; Mulligan, T. S.; Shen, M. C.; Wang, H.; Scahill, C. M.; Tan, F. J.; Du, S. J.; Busch-Nentwich, E. M.; Farber, S. A. mRNA processing in mutant zebrafish lines generated by chemical and

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX

CRISPR-mediated mutagenesis produces unexpected transcripts that escape nonsense-mediated decay. *PLoS Genet.* **2017**, *13*, No. e1007105.
(441) Zimmer, A. M.; Pan, Y. K.; Chandrapalan, T.; Kwong, R. W. M.; Perry, S. F. Loss-of-function approaches in comparative physiology: Is there a future for knockdown experiments in the era of genome editing? *J. Exp. Biol.* **2019**, *222*. DOI: 10.1242/jeb.175737.
(442) Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M. DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Res.* **2018**, *46*, D1074−D1082.

https://doi.org/10.1021/acs.jmedchem.2c01737
J. Med. Chem. XXXX, XXX, XXX−XXX