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PERSPECTIVES

Finding Promiscuous Old Drugs for New Uses

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ABSTRACT From research published in the last six years we have identified 34 studies that have screened libraries of FDA-approved drugs against various whole cell or target assays. These studies have each identified one or more compounds with a suggested new bioactivity that had not been described previously. We now show that 13 of these drugs were active against more than one additional disease, thereby suggesting a degree of promiscuity. We also show that following compilation of all the studies, 109 molecules were identified by screening *in vitro*. These molecules appear to be statistically more hydrophobic with a higher molecular weight and AlogP than orphan-designated products with at least one marketing approval for a common disease indication or one marketing approval for a rare disease from the FDA's rare disease research database. Capturing these *in vitro* data on old drugs for new uses will be important for potential reuse and analysis by others to repurpose or reposition these or other existing drugs. We have created databases which can be searched by the public and envisage that these can be updated as more studies are published.

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INTRODUCTION

As productivity of the pharmaceutical industry continues to stagnate, we call attention to the merits of reconsidering new potential applications of drugs that are already approved, whether they be old or new (1). This is commonly termed "drug repositioning," "drug repurposing," or "finding new uses for old drugs," and has been reviewed extensively in the context of finding uses for drugs applied to major diseases (2) but is also of value for orphan or rare diseases. The benefits of repositioning include the availability of chemical materials and previously generated data that can be used and presented to regulatory authorities and, as a result, the potential for a significantly more time- and cost-effective research and development effort than typically experienced when bringing a new drug to market.

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To date, multiple academic groups have screened 1,000–2,000 drugs against different targets or cell types relevant to rare, neglected and common diseases, and this information has not been thoroughly compared or captured in a database for analysis until now (Supplemental Material Table I). We have identified 34 such studies published in the last six years which have identified one or more drug molecule active in either whole cell or target-based assays. Several of these studies attempt to find new molecules active against diseases like malaria and tuberculosis for which there are several approved drugs, yet there is still a need to find molecules with a better side effect profile or as a replacement for drugs for which resistance has been shown. These issues alone justify the continued search for drugs perhaps with novel mechanisms of action.

Several libraries of FDA-approved or foreign-approved drugs have been screened, but there is currently not one definitive source of all these molecules that researchers could access at cost for themselves. For example, the John Hopkins Clinical Compound Library (JHCCL) consists of plated compounds available for screening at a relatively small charge and has been examined by more than 20 groups with more than a half dozen publications to date (3–6). A number of new uses for FDA-approved drugs have been identified by screening these or other commercially available libraries of drugs or off-patent molecules, *e.g.* the NINDS/Microsource US drug collection and Prestwick Chemical library (see Supplemental Material Table I). In total, a conservative estimate indicates at least 109 previously approved drugs have shown activity *in vitro* against additional diseases different than those for which the drugs were originally approved. For these molecules to have any impact on their respective diseases, they will obviously have to show *in vivo* efficacy. Upon manual curation of this dataset we were able to create a database of validated structures, which is now publically available (www.collaborativedrug.com). In addition, we were able to generate molecular properties for these molecules. We invite others to speculate as to which may show *in vivo* relevant activity. We have performed several analyses of the dataset to understand how they compare to drugs already repurposed for rare diseases.

PROMISCUOUS *IN VITRO* REPURPOSED DRUGS

Thirteen of these 109 drugs (Fig. 1) showed activity against more than one additional disease, thereby suggesting a degree of promiscuity which we believe has not been widely acknowledged elsewhere. We found through our meta-analysis that the class III antiarrhythmic amiodarone was active in neurodegeneration assays and could also selectively remove embryonic stem cells. The antidepressants amitriptyline and clomipramine suppressed glial fibrially acidic protein (7) and inhibited mitochondrial permeability transition (8). The anti-psychotic chlorprothixene showed antimalarial activity (9) and suppressed glial fibrially acidic protein (7). The anti-cancer drug daunorubicin was active against neuroblastoma (10) and was an NF-kB inhibitor (11). The cardiac glycoside digoxin was active against retinoblastoma (12) and an inhibitor of hypoxia inducible factor (13). The progestrogen hydroxyprogesterone has antimalarial (9) and glucocorticoid receptor modulator activity. The antineoplastic mitoxantrone was active against neuroblastoma and was a glucocorticoid receptor modulator (14). The cardiac glycoside ouabain was an inhibitor of hypoxia inducible factor (13) and NF-kB (11). The antipsychotic prochlorperazine was an inhibitor of mitochondrial permeability transition (8) and myosin-II associated S100A4 (15). The antihelmintic Pyrvinium pamoate has antituberculosis activity (6) and antiprotozoal activity against *C. parvum* (16) and *T. Brucei* (17). The anti-psychotic thioridazine had antimalarial activity (9) and was an inhibitor of mitochondrial permeability transition (8). Finally, the anti-psychotic trifluoperazine was active in neurodegeneration assays (18), an inhibitor of mitochondrial permeability transition (8) and myosin-II associated S100A4 (15).

Interestingly, the mean predicted molecular properties of these 'promiscuous compounds' are AlogP 3.6 ± 2.7 and molecular weight (MW) 442.8 ± 150.0 (Table I). These values are not statistically significantly different when compared to the whole dataset of 109 molecules (mean AlogP of 3.1 ± 2.6 and molecular weight of 428.4 ± 202.8) and are closest to the "natural product lead-like rules" (MW <460, Log P<4.2) described elsewhere (19). This is suggestive that the 109 molecules are generally quite large compared to drugs in general, as, for example, Vieth *et al.*, who showed 1,193 oral drugs to have a mean MW of 343.7 and CLOGP of 2.3 (20). Another group has screened 3,138 compounds against 79 assays, primarily GPCR, and showed that approximately 20–30% of the compounds were promiscuous compounds and had a mean MW (493) and AlogP (4.4) that was higher than for selective compounds (MW 436 and AlogP 3.3) (21). However, no statistical testing was presented to show whether this was significant or not. It is possible that our set of promiscuous compounds is too small to discern any meaningful difference in these properties. A more recent study on polypharmacology identified promiscuous chemotypes as carbon skeletons in drugs and bioactive compounds (22). All 13 promiscuous compounds in our analysis possessed carbon skeletons identified previously as promiscuous by this group.

PREVENTING REDISCOVERY

From our analysis (see Supplemental Material Table I) there are several examples in which independent groups have

screened drug libraries in whole cell assays or used different assays to discover compounds with similar activity such as glial fibrially acidic protein and mitochondrial permeability transition for neurodegeneration, and hypoxia inducible factor and NF-kB for cancer. Additionally, several groups have screened FDA-approved drugs against malaria (9,23). How do researchers now avoid repeating the same discoveries that others have made? One way would be to capture all of the published uses of these drugs *in vitro* and combine with information on uses that have already been identified in the laboratory or clinic. This has not been done to date. The FDA has recently provided a resource, the rare disease research database (RDRD), which lists orphan-designated products (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/Howtoapply forOrphanProductDesignation/ucm216147.htm) with at least one marketing approval for a common disease indication for a rare disease indication or for both common and rare disease indications. In the last category, there are less than 50 molecules (including large biopharmaceutical drugs). These tables from the FDA do not capture the high throughput screening (HTS) data generated to date from diverse laboratories involved in screening libraries of drugs (Supplemental Material Table I).

We have curated the molecular structures for these FDA datasets and generated their physicochemical properties. The mean predicted molecular properties of these compounds in the RDRD databases with at least one marketing approval for a common disease indication include AlogP 1.4 ± 3.0 and molecular weight 353.2 ± 218.8 (Table I), while those with at least one marketing approval for a rare disease indication have AlogP 0.9 ± 3.3 and molecular weight 344.4 ± 233.5. Although these values have large standard deviations, the means are close to the published "lead-like" rules (MW <350, LogP <3, Affinity ~0.1 μM) (24,25) and closer to the properties of 'oral drugs' highlighted by Vieth *et al.* (20). When these two FDA datasets are compared with the 109 previously approved drugs shown to have activity *in vitro* against additional diseases (Table I), the differences in AlogP and MWT are statistically significant. Also, the number of rings and aromatic rings are higher in the *in vitro* dataset. It should be noted that these datasets are relatively small with several showing skewed property distributions, hence the use of non-parametric testing. Some of the properties like ALogP and MW correlate weakly ($r^2 = 0.07$), while other properties such as the number of rings and MW more strongly ($r^2 = 0.61$). Such correlations between physicochemical proper-

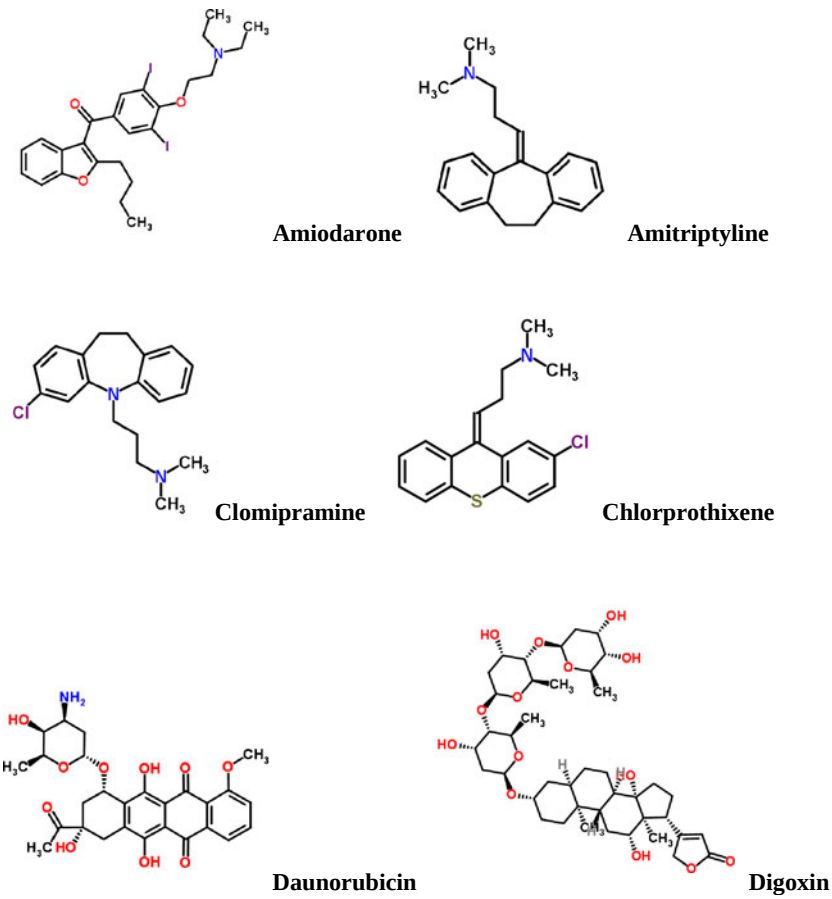
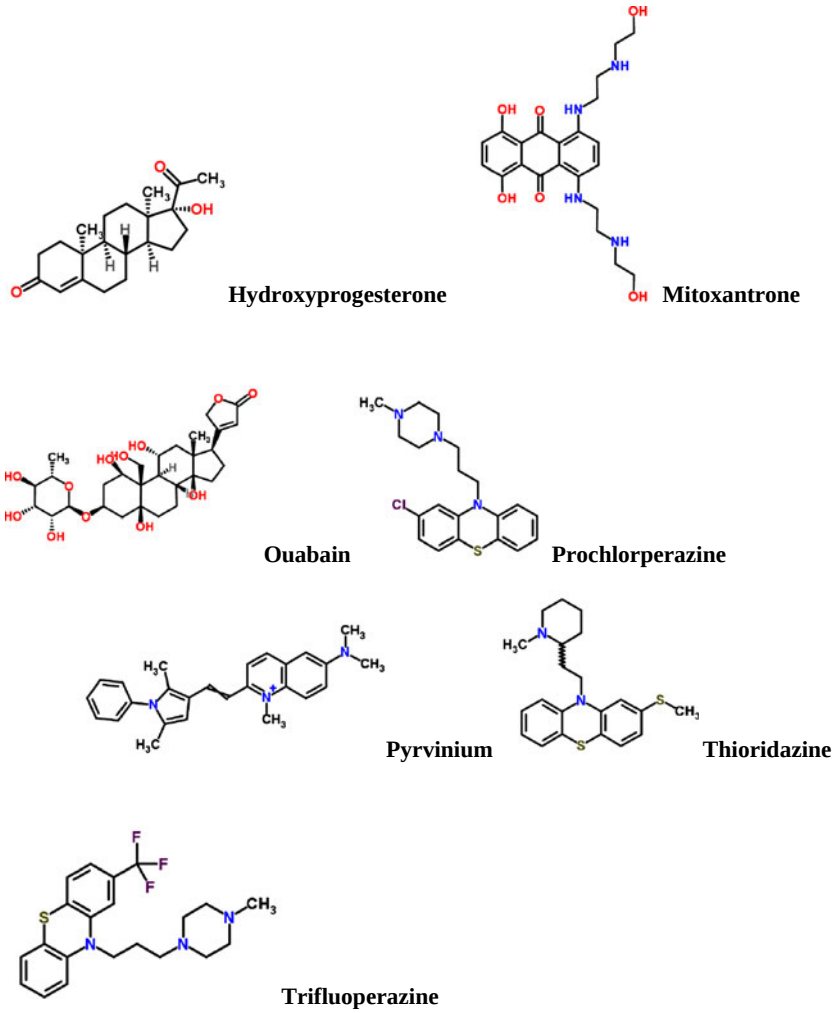


Fig. 1 Structures of FDA-approved drugs found to have multiple activities beyond what they were approved for when screened *in vitro*. Structures downloaded from www.chemspider.com.

Fig. 1 (continued)



ties in large sets of FDA-approved drugs have been indicated previously by others (20). However, our analysis may suggest for the first time that compounds with activity and approved for rare and common diseases have different ALogP and MW to those compounds that have been shown to have *in vitro* activity for various diseases (including rare, neglected and common diseases).

The excel files provided by the FDA at their RDRD website are not structure searchable or connected to data in other NIH databases that may be of utility for assisting researchers. There are other useful resources that are less well known. The Collaborative Drug Discovery (CDD) database (26) has focused on collecting data for neglected diseases (27–29). Dr. Chris Lipinski (Melior Discovery) provided a database of 1,055 FDA-approved drugs with designated orphan indications, sponsor name and chemical structures. In addition, CDD has collated and provided a database of 2,815 FDA-approved drugs from a list of all approved drugs since 1938 (23). These data can enable cheminformatics analysis of the physicochemical properties of compounds (28,30,31) and are available for free access and searchable by substructure, similarity or Boolean searches upon registration (*e.g.*, see http://www.collaborativedrug.com/register). We have therefore made the datasets from this study, and those curated based on the content in RDRD, publically accessible in the CDD database.

The curation of datasets of available drugs or orphan drugs with their uses could be used for searching with pharmacophore models (32) or other machine-learning methods to find new compounds for testing *in vitro* and to accelerate the repositioning process or focusing of *in vitro* screening on select compounds (33,34). A study using similarity ensemble analysis, applying Bayesian models to predict off-target effects of 3,665 FDA-approved drugs and investigational compounds (35), showed the promiscuity of many compounds. While the *in vitro* validation of the computational predictions focused on GPCRs, some of the collated data from the current study could also provide a useful method for further validation of this or other future *in silico* repositioning methods (36).

Table I Calculated Mean Molecular Properties (±SD) of Orphan-Designated Products and Compounds Identified with Additional Potential Therapeutic Uses Through *In Vitro* High Throughput Screening of Approved Drug Libraries

Dataset	ALogP	Molecular Weight	Number of Rotatable Bonds	Number of Rings	Number of Aromatic Rings	Number of Hydrogen bond Acceptors	Number of Hydrogen bond Donors	Molecular Polar Surface Area
Compounds identified *in vitro* with new activities ($N=109$)[a]	3.1 ± 2.6 (−4.3–13.93)	428.4 ± 202.8 (167–2–1255.42)	5.4 ± 3.8 (0–20)	3.8 ± 1.9 (0–12)	2.0 ± 1.4 (0–12)	5.6 ± 4.2 (1–27)	2.0 ± 1.9 (0–9)	89.6 ± 69.3 (3.2–379.6)
Compounds identified *in vitro* with multiple new activities ($N=13$)	3.6 ± 2.7 (−2.2–7.2)	442.8 ± 150.0 (277.4–780.9)	5.1 ± 3.1 (1–12)	4.2 ± 1.5 (3–8)	1.8 ± 1.2 (0–4)	5.5 ± 4.6 (1–14)	2.2 ± 3.3 (0–8)	79.5 ± 78.8 (3.2–206.6)
Orphan-designated products with at least one marketing approval for a common disease indication ($N=79$)[b]	1.4 ± 3.0** (−12.6–6.4)	353.2 ± 218.8* (78.1–1462.71)	5.3 ± 6.4 (0–37)	2.8 ± 1.7* (0–8)	1.2 ± 1.3** (0–6)	5.3 ± 6.0 (1–51)	2.5 ± 3.0 (0–18)	99.2 ± 110.7 (12.5–839.2)
Orphan-designated products with at least one marketing approval for a rare disease indication ($N=52$)[b]	0.9 ± 3.3** (−13.1–8.3)	344.4 ± 233.5* (30.0–1394.6)	5.3 ± 5.3 (0–34)	2.4 ± 1.9** (0–10)	1.3 ± 1.4** (0–6)	6.2 ± 4.2 (2–25)	2.7 ± 2.8 (0–17)	114.2 ± 85.3* (37.3–544.8)

[a] disulfiram excluded from this analysis

[b] Compounds from the FDA rare disease research database (RDRD), which lists Orphan-designated products (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm)

Properties calculated using Discovery Studio 2.5.5 (Accelrys, San Diego, CA). The datasets of approved drugs repositioned for common or rare diseases from the FDA's rare disease research database were compared with the *in vitro* dataset ($N=109$) curated in this study using a Non-parametric Wilcoxon/Kruskal-Wallis 2 sample test, *$p<0.05$, **$p<0.0001$. Comparison of the mean molecular properties for the subset of thirteen *in vitro* inhibitors with the larger dataset ($n=109$) did not show a statistically significant difference. Range is in parenthesis. All datasets are available at www.collaborativedrug.com.

MAKING REPOSITIONING ROUTINE

As the availability, at a reasonable cost, of FDA-approved drugs in a format for HTS is now relatively commonplace, what remains necessary so that the burgeoning numbers of academic screening centers or other groups can accelerate repositioning? An exhaustive database that cross references the molecules, papers, and activities would certainly be a valuable starting point, and capturing the hit rates of such libraries *versus* other compound library screening, preclinical and clinical data would be valuable. It is not yet obvious whether a drug has progressed straight from these *in vitro* screens to orphan drug status, but the screening of drug libraries may certainly accelerate this. Evidence of migration from *in vitro* screens to orphan status would obviously be immensely valuable. Clearly, very old drugs like the tricyclic antidepressants, anti-psychotics and cardiac glycosides appear to be promiscuous, having been found to possess many activities against additional diseases *in vitro*. Whether these 'new uses for old promiscuous drugs' will translate into the clinic remains in question. The follow-up of compounds from *in vitro* screening to appearance in the clinic is limited, as in the case of Ara-C (cytarabine) for Ewing's sarcoma, which went to a Phase II clinical study and showed toxicity and minimal activity (37). To our knowledge, in most cases, clinical studies have not been described in over six years in which this high throughput screening work has appeared. Perhaps focusing on screening just these few classes of promiscuous compounds against any disease of interest would yield additional activities and test this hypothesis.

In performing our analysis of the literature, it appears that many groups have taken the 'new uses for old drugs' approach (38). At the same time, it has not been recognized that there appears to be a subset of 'promiscuous' old drugs (approximately 12% of the compounds identified to date *in vitro*). We cannot, however, distinguish these molecules as different from the complete dataset based on the simple molecular descriptors used in this study. The 109 molecules identified by screening *in vitro* appear to be statistically more hydrophobic and with a higher MW and AlogP than orphan-designated products with at least one marketing approval for a common disease indication or one marketing approval for a rare disease from the FDA RDRD. These may be useful insights, suggesting that some compounds that may have different molecular properties to those already orphan-designated may have many potential repositioning activities and could be the focus of more aggressive screening against many more diseases. It will also be important to rule out *in vitro* false positives due to aggregation (39) or other causes. Capturing these *in vitro* data on promiscuous old drugs for new uses in a format that is readily mined and comprehensive will be important for reuse and analysis by others, and we welcome suggestions as to who should be responsible for funding, developing, and maintaining it.

Since this perspective was originally submitted for publication and passed through the peer review process, it

has come to our attention that the NIH Chemical Genomics Center has released a database described as "a comprehensive resource of clinically approved drugs to enable repurposing and chemical genomics" (40). This will be used along with the NCGC screening resources as a component of the NIH therapeutics for rare and neglected diseases (TRND) program. The database has undergone a preliminary evaluation by us and may indeed be a useful future resource for the community. However, we urge significant caution due to a large number of errors identified in the molecular structure representations in the database (41); hence, this database will need further manual curation and correction before the structures can be used for other applications such as virtual screening. We believe there is scope for several efforts to provide databases of validated compounds and data that may be useful for repurposing.

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