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Drug Repurposing from an Academic Perspective

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Abstract

Academia and small business research units are poised to play an increasing role in drug discovery, with drug repurposing as one of the major areas of activity. Here we summarize project status for a number of drugs or classes of drugs: raltegravir, cyclobenzaprine, benzbromarone, mometasone furoate, astemizole, R-naproxen, ketorolac, tolfenamic acid, phenothiazines, methylergonovine maleate and beta-adrenergic receptor drugs, respectively. Based on this multi-year, multi-project experience we discuss strengths and weaknesses of academic-based drug repurposing research. Translational, target and disease foci are strategic advantages fostered by close proximity and frequent interactions between basic and clinical scientists, which often result in discovering new modes of action for approved drugs. On the other hand, lack of integration with pharmaceutical sciences and toxicology, lack of appropriate intellectual coverage and issues related to dosing and safety may lead to significant drawbacks. The development of a more streamlined regulatory process world-wide, and the development of pre-competitive knowledge transfer systems such as a global healthcare database focused on regulatory and scientific information for drugs world-wide, are among the ideas proposed to improve the process of academic drug discovery and repurposing, and to overcome the “valley of death” by bridging basic to clinical sciences.

Introduction

The past decade has witnessed the unprecedented transition of drug discovery projects from major pharmaceutical houses to academic [1], non-profit and small business research units, with particular focus on orphan and neglected diseases [2]. This transition was facilitated by several factors: *i)* the increased innovation gap observed in pharmaceutical companies; *ii)* a number of mega-mergers among pharmaceutical companies, against the backdrop of a global economic downturn – which has resulted in a mass migration of skilled pharmaceutical labor towards other research units, notably academia; *iii)* the launch of two major initiatives in the US, Clinical and Translational Science Award, CTSA ([3], http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/), which supports clinical and translational research, and the Molecular Libraries Program ([4], http://mli.nih.gov/mli/) which supports primarily research in chemical probe development; as well as a complementary initiative in Europe, the Innovative Medicines Initiative, IMI ([5],) – which fosters joint projects between academic and pharmaceutical research units; and *iv)* last but not least the increasing amount of public and open source data, knowledge and software that can be utilized for drug discovery projects.

Enabled by favorable legislative changes in the Food, Drug and Cosmetic Act (FDCA), such as the Hatch-Waxman Amendments (discussed in [6]) and by the gradual public opinion shift that the pursuit of pharmaceutically-related projects is acceptable in academia, an increased interest has emerged in drug repurposing (or repositioning). Under the 505(b)(2) section of the FDCA (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc es/ucm079345.pdf), such efforts can offer temporary protection for: *i)* new molecular entities, NMEs; *ii)* new dosage forms; *iii)* new administration routes; *iv)* new indications; and *v)* new NME combinations. From a scientific standpoint, the most rewarding research objective is to discover novel therapies for unmet clinical needs, a

process that seems more attainable via drug repurposing [7], as opposed to *de novo* drug discovery. The rationale behind this is that *de novo* drug discovery is a lengthy and costly process, whereas already approved drugs are more likely to be repurposed for another indication. Although the number of clinical studies required when repurposing drugs appears smaller, the petitioner must nevertheless conduct clinical trials with respect to efficacy (e.g., for the novel indication), and sometimes for safety as well (e.g., when doses higher than the approved ones are needed). The financial burden placed on the petitioner, whether an academic unit or any other (non-profit) organization, exceeds the million dollar range. Although a number of private organizations such as the Gates Foundation (http://www.gatesfoundation.org/Pages/home.aspx), as well as the US Congress via the Cures Acceleration Network, CAN (http://www.govtrack.us/congress/bill.xpd?bill=s111-914) may provide such funding, there currently exists no general mechanism to derive funding for such research. This can effectively block the repurposing process, in particular in budget-conscious institutions.

The Changing Landscape of Academic Drug Discovery

The increased focus on translational research in academia is rebalancing the goals of discovery across the traditional areas of academic success: research, education, and service. For physicians in medical schools, service typically includes patient care, while for both MD and PhD faculty, this is likely to include broader service to the community such as benefits to human health via research, which in turn may have commercial value. These factors have combined to yield increasingly more significant programs in drug discovery and development. For example, as clinical trials themselves have become an important endpoint in academic medicine, the interest in drug repurposing seeks to balance both profit and the service drive, where profit is not only measured by financial gain, but also by publications, grants, and faculty promotion and tenure decisions.

These changes have been accelerated by NIH programs that support drug discovery and development, as well as clinical trials such as the National Cancer Institute's Experimental Therapeutics Program (NExT http://next.cancer.gov/default.htm) and the NIH Rapid Access to Therapeutic Development Program (RAID to be re-launched as BRIDGS http://nctt.nih.gov/bridgs/). These forces have led several institutions to collect, use, and report on approved drugs, such as those from Johns Hopkins University ([8], http://htc.wustl.edu/library/JHCCL.html), the NCGC Pharmaceutical Collection ([9], http://tripod.nih.gov/npc/) and have also led NIH to make available collections of molecules that have been previously used in clinical trials (NIH Clinical Collections, http://nctt.nih.gov/now).

The drive to move research to clinical trials has been embedded in the NCI Cancer Centers Program and more recently in the Clinical and Translational Science Awards (CTSA). In both cases, trials based on investigator-initiated efforts rather than by pharmaceutical companies are valued. The CTSA consortium is facilitating drug repurposing through the Pharmaceutical Assets Portal ([10],http://www.ctsapharmaportal.org/), whereas NIH held a repurposing summit on April 21, 2011 with pharmaceutical industry leadership to discuss the availability of molecules that have proven safe in clinical trials but not necessarily efficacious for the intended target [11], and considers using approved and abandoned drugs to boost translational research [12]. The Director of NIH, Francis Collins, has proposed the co-localization of The CTSA Network, the NCTT, the Therapeutics for Rare and Neglected Diseases (http://trnd.nih.gov/), and Regulatory Science, as well as Molecular Libraries and its potential successor the Cures Acceleration Network, within a new center to be called National Center for Advancing Translational Science, NCATS (http://www.nih.gov/about/director/07062011_translationalscience.htm).

Drug Repurposing at UNM

At UNM, unique opportunities have presented themselves with respect to the integration of basic research, conducted at the UNM Center for Molecular Discovery (PI: Larry Sklar; http://screening.health.unm.edu/), and the clinical research that is conducted at the UNM Clinical and Translational Science Center (PI: Richard Larson; http://hsc.unm.edu/research/ctsc/) as well as the UNM Cancer Center, UNMCC (PI: Cheryl Willman; http://cancer.unm.edu/). Each of these centers has supported repurposing: UNMCMD through pilot screens of approved drug collections; UNMCC through support of core resources and grant support for pilot screens as well as early phase animal studies; and UNM CTSC through requests for applications linking clinical trials to repurposing screens [13].

The UNMCMD specializes in discovery using high throughput flow cytometry [14] integrated with virtual screening [15], as well as knowledge mining and drug informatics [16]. Taken together the center has conducted more than a dozen repurposing projects, using unique technologies that allow for simultaneous screening of multiple molecular and cellular targets [17]. Flow cytometric approaches allow for the homogeneous discrimination of fluorescence associated with cells, while also distinguishing particles from the fluorescence signal from those in the surrounding volume [18].

These capabilities provide important discovery opportunities in blood cancer therapeutics – in partnership with UNMCC; in infectious diseases and immunology – in partnership with UNM's CTSC and the UNM Center for Infectious Diseases and Immunology; and in other molecular interactions. The licensing arm of UNM, the UNM Science and Technology Corporation (http://stc.unm.edu/) supports and enables deployment of UNMCMD technologies for repurposing screens, as well as for investigator-initiated discoveries related to drug repurposing. The UNMCMD suspension cell technology is uniquely positioned for studies with white blood cells, infectious agents and pathogens, and host-pathogen interactions. To better qualify our statements regarding drug repurposing in the academia, we briefly discuss a number of drug repurposing projects at UNM, and their current status (as of August 2011). These projects are summarized in Table 1. Several reviews [19,20] and techniques [21,22,23] related to drug repurposing are available.

Computational Projects

Raltegravir

An HIV-1 integrase inhibitor approved by the FDA in 2006, raltegravir is marketed by Merck & Co. under the trade name Isentress™, and is indicated primarily for the treatment of HIV infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy, in combination with other drugs. Led by Rob Hromas, MD (UNMCC), a team of basic and clinical scientists at UNM identified the DNA repair enzyme metnase [24] as a potential target for adjuvant therapy in cancer [25]. Identified via structure-based virtual screening [26] studies conducted by Andrei Leitão and Tudor Oprea (unpublished), Raltegravir was in fact confirmed as a metnase inhibitor, at doses that are roughly 10 times higher than the currently approved maximum dose for Isentress™. A pilot, serial biopsy study in patients with head and neck squamous cell carcinoma, evaluating the potentiation of cisplatin chemotherapy by raltegravir, is ongoing under the leadership of Julie Bauman, MD (UNMCC; http://stc.unm.edu/technologies/featured/Novel-Inhibitors-and-Bi-functional-Compounds-for-Cancer-Treatment.php).

Cyclobenzaprine

A skeletal muscle relaxant approved by the FDA in 1977, the precise mechanism of action of cyclobenzaprine has not been elucidated. This drug is marketed by McNeill Consumer Healthcare and Alza under the trade name Flexeril™, for the temporary relief of skeletal muscle spasms of local origin. While not a repurposing project per se, we present this as an example of effective basic and clinical pharmacological research. Whether cyclobenzaprine can cause the serotonin syndrome (SS) is subject to debate [27, 28]. A limited number of case reports are available, whereas the pharmacological profile of cyclobenzaprine has not, until now, been publicly available. In collaboration with Jordi Mestres, PhD (Hospital del Mar, Barcelona) and Steve Seifert, MD (UNM Poison Control Center), we provided evidence [29] that cyclobenzaprine blocks, with moderate to high potency, the serotonin and norepinephrine transporters as well as five serotonin receptor subtypes at therapeutically relevant concentrations. We further suggest that the serotonin syndrome should be considered when indicative signs occur in the context of cyclobenzaprine exposure [29]. No clinical trials are planned based on these drug-target associations. However, this example is illustrative for i) the type of research needed to associate drugs to targets (drug informatics and virtual screening; medical informatics and clinical expertise; toxicology); ii) the difficulties encountered when trying to associate clinical outcomes (e.g., symptoms that may or may not be associated with the serotonin syndrome) with therapeutic (causative) agents. Taken together, these are the type of studies that could advance drug repurposing efforts.

Screening Projects

Benzbromarone

is a highly effective uricosuric agent, widely used in the treatment of gout since 1969, but was withdrawn by Sanofi in 2003 after reports of serious hepatotoxicity [30]. It is not FDA approved, but continues to be available in several countries including Japan and Spain as Urinorm™. Screening of the Prestwick Chemical Library(http://www.prestwickchemical.com/index.php?pa=26) identified it to also be an inhibitor of *Staphylococcus Aureus* quorum sensing [31], which is a cell-to-cell communication system that coordinates bacterial behavior on the basis of cell density and mediates the switch to a virulence-associated phenotype [32]. Benzbromarone inhibits production of quorum sensing signaling pathway (RNAIII) transcripts (IC_{50} = 150 nM) and of the virulence factors α-hemolysin and lipase that are elicited in the presence of autoinducing protein (AIP), but does not affect bacterial viability [31]. Recent unpublished studies have shown it has activity *in vivo* in a dermonecrosis murine skin infection model as well. However, because its activity was limited to only a subset of *S.aureus* strains of clinical significance, further studies were abandoned in favor of a structurally different compound identified in later screens and determined to be more broadly active *in vivo*.

Mometasone furoate

An anti-inflammatory corticosteroid approved by the FDA in 1987, mometasone furoate is a very potent glucocorticoid receptor agonist marketed by Schering (now part of Merck & Co.) under the trade name Nasonex™, which is indicated primarily for the treatment of seasonal allergic rhinitis. Led by Richard Larson, MD and Stuart Winter, MD (both UNMCC), a team of basic and clinical scientists at UNM have focused on the hypothesis that blocking multi-drug resistance protein 1 (MDR-1, also known as P-glycoprotein or ABCB1) could serve as adjuvant therapy in cancer, by enhancing the effectiveness of anti-cancer therapy. High-throughput flow cytometry screens conducted at UNMCMD identified mometasone furoate as one of the low-micromolar MDR-1 inhibitors [33] via flow-cytometric multiplex assays [34]. However, the dose required to achieve MDR-1 inhibition is almost 1000 times higher than the currently approved dose for allergic rhinitis. Well

designed clinical studies [35] for Zosuquidar, a potent MDR-1 inhibitor, have shown that MDR-1 is not an effective target in anti-cancer therapy [36]. Therefore, no clinical trials will be conducted based on this drug-target association.

Astemizole

This potent second generation antihistamine (histamine H-1 receptor antagonist) was launched in 1983 as Hismanal™ by Janssen Pharmaceutica (now Johnsson and Johnsson). Although it lacks sedative effects under normal dosage, it was withdrawn from the U.S. market in 1999 after it was determined that Hismanal™ 10 mg tablets are directly linked to cardiac toxicity [37]. Using the HyperCyt flow cytometry system to detect intracellular granularity induction [38], we screened the Prestwick Library, with subsequent validation to identify astemizole as a potent inducer of cellular autophagy and death in prostate cancer cells. The screen was based on the analysis of cell light scatter as a reflection of granule or autophagosome content. We have found that astemizole acts synergistically with radiation to augment prostate cancer cell killing, which may occur through an autophagic facilitated mechanism. Our current studies are directed toward both the identification of specific molecular targets through which astemizole induces autophagic processes in prostate cancer cells as well as toward preclinical *in vivo* studies to support astemizole's repurposing as a novel intervention for the treatment of prostate cancer.

NSAIDs for ovarian cancer

The R-enantiomers of naproxen and ketorolac, two non-steroidal anti-inflammatory drugs (NSAIDs), have demonstrated specificity for inhibiting Rho family GTPases, in particular Rac and Cdc42. The S-isomer of naproxen has been FDA approved for pain relief as Aleve™ since the 1970s and as generic drug since 1994. Ketorolac, also used for pain relief, has been approved since 1989 (as racemic mixture) under the tradenames Toradol™ and Acular™, as well as a generic drug. These two drugs are potential candidates as adjuvant therapy following debulking surgery to prevent ovarian tumor growth and dissemination during post-surgical recovery prior to administration of chemotherapy. Led by Angela Wandinger-Ness (PI) and Zurab Surviladze, flow cytometric screening of the Prestwick Library identified Naproxen in a multiplex assay. Six individual low molecular weight GTPases, constructed as Glutathione Sulfo-Transferase (GST) fusion proteins were captured on 6 populations of microspheres displaying glutathione (GSH) and labeled with different intensities of red fluorescence that could be distinguished by flow cytometric analysis [39]. The assay detected small molecules that blocked the binding of a green fluorescent guanine nucleotide analogue. R-naproxen and the follow-up hit ketorolac (identified via virtual screening by Tudor Oprea) block Rac and Cdc42 GTPase activation in response to growth factor stimulus and downstream cellular responses that depend on these activated GTPases including cell proliferation, migration, adhesion and tumor growth in xenograft models [Hudson et al., manuscript in preparation]. Having completed cell-based and preclinical animal studies, current work is focused on performing a pilot clinical trial of ketorolac to determine its distribution in the peritoneal compartment (Carolyn Muller, MD).

Tolfenamic acid

launched in 1976 as Clotam™, is an NSAID related to mefenamic acid, which is not FDA approved. It's typical serum concentration, around 20 micromoles/L in plasma [40], has demonstrated long-term cell viability at 100 μM [41]. We have recently identified Tolfenamic acid as a competitive inhibitor ($K_i \approx 26$ μM) of the binding of pathogenic hantavirus to decay accelerating factor (DAF/CD55). Led by Tione Buranda and Brian Hjelle, this project was made possible by UV-irradiation of the Sin Nombre virus for BSL-2 handling, labeling with a fluorescent probe, and detection of the cell-virus binding. Together, these approaches allowed screening of cell-virus interactions without a wash step

by flow cytometry. DAF is a ubiquitous glycosylphosphatidylinositol anchored protein expressed on the surface of polarized epithelium, and is a known mediator of cellular entry by viruses and other pathogens [42]. Its properties make this drug a suitable target for treating infections by a wide range of pathogens. However, tolfenamic acid induces *in vitro* paracellular permeability in renal cortical tubular epithelial cells (our data), and is a positive allosteric modulator of the androgen receptor [43] in addition to being an inhibitor of cyclooxygenases with preference for the COX-2 subtype. These problems could be resolved via medicinal chemistry while conserving the ability to interfere with binding to DAF. The mechanism of NSAID-induced permeability has been described elsewhere [44]. Thus, such information could be used in SAR optimization.

Phenothiazines

are a class of "privileged structures" [45] with versatile binding properties that exhibits a number of desirable drug-like characteristics. Phenothiazine derivatives have been used as antimalarials (late 19th century), antihelminthics (mid-20th century), antihistaminics (1940s), sedatives, and antipsychotics (1950s). Current literature suggests the possibility for using phenothiazines and their derivatives for the treatment of Parkinson's and Alzheimer's diseases, and as antibacterial and antifungal compounds [46]. A high-throughput flow cytometry-based screen of the Prestwick Library was used to seek allosteric antagonists of the α4β1-integrin VLA-4 (Very Late Antigen 4, [47]). The assay was based upon conformational flexibility of the integrins, and the ability of integrin ligands to induce epitopes termed Ligand-Induced Binding Sites (LIBS) that are exposed as a result of the conformational change [48, 49]. Using anti-LIBS mAbs and the homogeneous detection capability of high throughput flow cytometry, we identified several phenothiazines and structurally related compounds that: 1) prevented exposure of the LIBS epitope after the addition of VLA-4-specific ligand; 2) decreased VLA-4-specific ligand binding affinity; and 3) blocked VLA-4-dependent cell adhesion. In mice the compounds mobilized hematopoietic progenitors into the peripheral blood, as has been previously reported for other unrelated VLA-4 antagonists [47]. VLA-4 is a cell adhesion molecule that is expressed on all major leukocyte subsets. It plays a major role in the regulation of immune cell recruitment to inflamed endothelia and sites of inflammation. It participates in antigen presenting cell-lymphocyte interactions, retention and mobilization of immature progenitors in the bone marrow, and cancer cell trafficking, metastasis. Integrins represent an attractive target for treatment of inflammatory diseases, anti-angiogenic therapy, anti-thrombotic therapy, and cancer. Integrin ligands can also be used as imaging tools, as well as probes for studies of integrin functional activity and molecular conformation. At present we are in the process of testing VLA-4 antagonists in hematological malignancies related applications.

Methylergonovine maleate

(also known as methylergometrine maleate) is an amine ergot alkaloid that directly stimulates contractions of uterine smooth muscle (oxytocic), and has been marketed since 1946 as Methergine™ (Novartis) for the prevention and treatment of postpartum hemorrhage caused by uterine atony. Methylergonovine was identified in a high throughput flow cytometric multiplex screen of the Bcl-2 family [50] using Bcl-XL, Bcl-W, Bcl-B, Bfl-1, and Mcl-1 and Bcl-2 (the eponymous member of the Bcl-2 family). This multiplexed screen evaluated the perturbation of protein interactions between the fluorochrome-conjugated BH3 peptide of Bim [51], which is green fluorescent, and the six Bcl-2 proteins, as perturbed by small molecules. For high throughput flow cytometry, six individual Bcl-2 family members, constructed as GST fusion proteins were captured on 6 populations of microspheres displaying GSH and labeled with different intensities of red fluorescence that could be distinguished by flow cytometric analysis [52, 53]. Bcl-2 family members regulate apoptosis in part by their balance of anti-apoptotic and pro-apoptotic activities. In humans,

six genes have been identified that encode anti-apoptotic proteins characterized by the presence of conserved motifs designated as four Bcl-2 homology (BH) regions, BH1, BH2, BH3, and BH4 [54]. The fold of anti-apoptotic Bcl-2 family protein forms a hydrophobic cleft that serves as a receptor that binds peptide ligands (BH3 peptides) displayed by pro-apoptotic Bcl-2 family members. This BH3 domain displayed by pro-apoptotic family members forms an amphipathic helix, where the helix binds in the cleft of the anti-apoptotic proteins. The screen thus identified compounds that displace BH3 peptides from binding to anti-apoptotic Bcl-2 family proteins, either by competitive or allosteric mechanisms. The apparent affinity (IC_{50} for BH3 peptide displacement) of Methylergonovine for the Bcl-2 family targets is not dissimilar to other compounds that have been taken into the clinic (through Phase II) for development as chemosensitizers for cancer (e.g., Obatoclax; Gossypol) [51].

Beta-adrenergic receptor drugs

We (Yang Wu and JW Jarvik) developed an innovative high-throughput platform integrating fluorogen activating protein technology with high-throughput flow cytometry to detect real-time protein trafficking to and from the plasma membrane. The technology is based on tagging proteins with single chain antibodies that confer fluorescence on intercalating dyes (fluorogens) [55, 56]. We envision that the approach is applicable to identifying canonical and non-canonical ligands for GPCR, and orphan GPCR as well as other receptor classes. This technology has been validated using the β_2 adrenergic receptor (β_2AR) system and extended to screening against the Prestwick Library targeting β_2AR, CCR5, CXCR4, and the orphan receptor GPR32. A total of 34 known β_2AR ligands (both agonists and antagonists) were found in the library, including a prodrug that requires hydrolysis in blood serum and monooxygenase-catalyzed oxidation in tissues. No known ligand for the other receptors is presented in the Prestwick library. The pilot screens not only successfully identified 33 of the 34 known ligands of β_2AR (with the exception of the prodrug), but also yielded several new hits that induce or prevent receptor internalization. These hit molecules are currently under investigation to determine the mechanism of action. Molecules that regulate receptor internalization pathway via a non-canonical manner may lead to immediate drug repurposing or novel drug designs for old receptor classes.

Lessons Learned from our Repurposing Efforts

Our multi-year, multi-project experience in drug repurposing offers unique insights in the strengths and weaknesses of performing drug repurposing research in an academic setting. While these may not be generally applicable, we hope that these observations will be used to help improve the situation, i.e., for seeing these promising studies through to fruition, as well as with respect to logistics and funding.

Advantages

Translational focus—Aligned with, and benefiting from academic freedom, translational research in academia offers incentives by fostering novel collaborations and pairing up basic scientists with clinicians across multiple disciplines. Immediate access to hospitals and health care practitioners is a tremendous advantage, one that often short-cuts the communication gap between two (otherwise separate) cultures.

Disease focus—Activities specific to clinical education and clinical research affords in-depth expertise in particular disease areas, removing “activation barriers” and enabling projects to rapidly advance past the early (basic science) stages. Conversely, clinical observations can lead to immediate pathway links and studies at the cellular and molecular

level. In this manner, diseases that lack effective therapies can rapidly be subjected to drug repurposing efforts.

Target focus—Those targets that are nodal points in general mechanisms such as cell division, autophagy, apoptosis and metabolism can be subjected to therapeutic manipulation for various, sometimes clinically different endpoints. The complete understanding of pathway inter-dependencies and shunts, and the clinical consequences of modulated therapeutic perturbations for such targets can only be accomplished by close, effective communication between basic scientists, clinicians and pharmaceutical scientists.

Disadvantages

Dosing and Safety—Since drugs are approved only after intense scrutiny, which observes clear therapeutic benefits within well-defined safety margins, the clinical utility of finding novel drug-target interactions is often hampered by issues related to dosage (i.e., approved dose range) and delivery capability (i.e., the ability to deliver the drug to particular targets at the disease focal region). Dosing and delivery encompass safety aspects as well, as sufficient exposure of the target to the drug (or its active metabolites) needs to be accomplished for a minimal length of time. Novel drug-target interactions are frequently disclosed in peer-review or patent literature, in particular for those older drugs that have not been comprehensively profiled prior to approval. Quite often, these reports show micromolar-level potency. The burden of proof and therapeutic relevance, however, falls on the discovery team, which has to establish that, at dosage within the approved margin, such effects can be observed in the clinic. In our experience, so far, it has been rare to find novel drug-target interactions within the constraints of the approved therapeutic window. If the anticipated potency falls outside that range, the discovery team has to begin with Phase I clinical trials, which effectively blurs the distinction between de novo drug discovery and repurposing.

Lack of integration with pharmaceutical sciences and toxicology—Dosing and safety aside, it is conceivable that the drug in question can be repurposed if appropriate delivery devices or formulations could be implemented to provide drug exposure to the targeted tissue, while limiting exposure to other tissues. As noted earlier, finding novel formulations or delivery mechanisms for existing drugs is a viable repurposing strategy. In our experience, it is unusual for the discovery team to include scientists from pharmaceutical and toxicological sciences in the translational efforts.

Appropriate intellectual property coverage—For off-patent drugs, the number of options with respect to intellectual property (IP) protection is more limited. The situation is quite delicate for those cases where clinical practice leads to off-label prescriptions for the drug in question, for precisely that indication. Even if truly novel mechanisms are fully explained, this rarely leads to protected marketing rights from regulatory agencies. More lucrative scenarios can be envisioned when the newly found drug-target-disease triplet is unique; such scenarios can lead to use and possibly to formulation/delivery patents, if the IP landscape is favorable. One specific limitation is the lack of experts in the legal issues related to drug repurposing, since in itself this is quite a novel field for academia. Another limiting factor, often noted by the industry, is the disclosure of novel drug-target-disease associations via PubChem or other on-line databases, or via publications (which range from peer-reviewed literature to blogs). Such disclosures effectively hamper IP protection efforts, often to the point of not seeking patent protection.

Overcoming the Valley of Death: Room for Improvement

Often referred to as the "valley of death", the gap between basic and clinical sciences, with respect to drug discovery and repurposing, could perhaps be avoided if more streamlined workflows and measures are designed.

- Success in drug repurposing is compounded by the fact that not only multiple basic and clinical disciplines have to converge, but legal, economic and regulatory aspects are to be weighed in as well. In particular for academic units not benefiting from high-level federal and private funding, it would be beneficial to develop an "Experimental Drug Network" (EDN) comprised of legal, economic and regulatory experts that provide sound advice in a non-competitive manner. This could perhaps be built into the CTSA network. One possible alternative is to take advantage of the highly-experienced work-force now being mobilized from the pharmaceutical industry.
- The European Medicines Agency (EMA), regulatory agencies from the US, Japan, Canada, South Africa and Australia, as well as from other countries that comply with existing standards, and the World Health Organization, are currently deprived of access to a single source for data, information and knowledge related to drugs that are marketed, withdrawn or submitted for approval. By developing a Global Healthcare Database (GHD) that captures all the pharmaceutically relevant aspects, we anticipate that costs related to research, clinical trials and regulatory aspects will be streamlined. In its current form, separate clinical trials need to be conducted if approval is sought in each country. Developing a unique "drug approval strategy" supported by a unique GHD resource would benefit citizens world-wide, particularly in the current economic climate, since major pharmaceutical houses are severely cutting down costs and reducing the workforce, thus stifling innovation.
- For orphan and neglected diseases, the network of academic and small-to-medium enterprises (SMEs) should be encouraged to develop such a "global" system, one that could include an open-access database, as well as an agreed-upon strategies (e.g., with respect to clinical trials, IP protection and manufacturing).
- Extend the "investigational new drug" (IND) system to other experimental therapeutic protocols. The US Centers for Disease Control (CDC) can distribute a number of products (e.g., artesunate, melarsoprol, nifurtimox, suramin and spiramycin) to qualifying licensed physicians that are registered with the FDA as Clinical Investigators. This mechanism could perhaps be extended to non-life threatening diseases, for example to orphan and neglected diseases and other diseases lacking therapies, for INDs that are deemed to be safe, and promising, by the CTSA or by "EDN" advisors.
- Expand the scientific role of the FDA and the EMA (as well as other regulatory agencies in the context of a global strategy) to conduct research in "regulatory science", in particular related to drug safety and toxicology. This area of expertise should be regarded as "precompetitive knowledge" by the drug discovery community, both in academia and the industrial sector. As such, the expertise collectively gathered by regulatory agencies impact the success rate of both new and repurposed drug applications.

Conclusion

The emerging sector of academic drug discovery is gradually replacing its early period enthusiasm with the informed realism of clinically meaningful therapeutics practice. There

are significant advantages of conducting research in an integrated environment. Risks also exist, pertaining to lack of experience with, for example, dosage and IP, which hamper the output of such projects. Perhaps more ambitious changes could assist with the development of global strategies for drug approval, as well as databases and systems that enable the transfer of precompetitive knowledge to reduce the risk of failure.

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Table 1
Summary of drug repurposing projects at UNM

Durg Name	Existing Target/Disease	New Target/Disease	Indentification	Repurposing Project Status
Raltegravir	HIV-1 integrase; antiviral for treatment of HIV-infected patients	metnase; adjuvant therapy in cancer	virtual screening supported by experiments	pilot clinical trial for head and neck squamos cell carcinoma is on-going
Cyclobenzaprine	not described; skeletal muscle relaxant	mono-amine transporters and serotonin receptors; may cause serotonin syndrome	virtual screening supported by experiments	N/A
Benzbromarone	xanthine oxidase; uricosuric for treatment of gout	quorum sensing signaling pathway; antibacterial	target-based screening of the Prestwick Chemical Library	abandoned because it lacks patent in vivo activity
Mometasone Furoate	glucocorticoid receptors; for treatment of seasonal allergy	P-glycoprotein; adjuvant therapy in cancer	target-based screening of the Prestwick Chemical Library	abandoned because the target (P-gp) was proved to lack effectiveness in clinical trials for Zosuiquidar
Astemizole	histamine H1 receptors; antihistamine for treatment of seasonal allergy	inducer of autophagy; as adjuvant therapy in prostate cancer	phenotypic screening of the Prestwick Chemical Library	in vivo studies for prostate cancer are on-going
R-Naproxen	cyclooxygenases; non-steroidal anti-inflammatory drug for short-term treatment of pain	RAC and CDC42 GTPases; as adjuvant therapy in cancer	target-based screening of the Prestwick Chemical Library	abandoned in favor of ketorolac
Ketorolac	cyclooxygenases; non-steroidal anti-inflammatory drug for short-term treatment of pain	RAC and CDC42 GTPases; as adjuvant therapy in cancer	virtual screening based on Naproxen	pilot clinical trial for ovarian cancer, to evaluate peritoneal distribution
Tolfenamic acid	cyclooxygenases; non-steroidal anti-inflammatory drug for short-term treatment of pain	inhibitor of hantavirus/DAF binding; antiviral against Sin Nombre virus	phenotypic screening	medicinal chemistry optimization under consideration
Phenothiazines	prototype for neuroleptic drugs; antipsychotics for the management of schizophrenia	VLA-4; anti-adhesion inhibitors against inflammation and cancer	target-based screening of the Prestwick Chemical Library	in vivo studies for hematologic malignancies are on-going
Methylergonovine maleate	oxytocic; for treatment of post-partum uterine hemmorhage	Bcl-2 family proteins; anti-apoptotic as adjuvant therapy in cancer	target-based screening of the Prestwick Chemical Library	abandoned because it has other potent in vivo activity
Beta-adrenergic receptor drugs	beta-2 adrenergic receptor agonists are used for the therapeutic management of asthma	non-cannonical G-protein coupled receptor ligands	target-based screening of the Prestwick Chemical Library	in vitro biological tests are on-going