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DRUG REPURPOSING: OLDER DRUGS NEW TRICKS

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ABSTRACT

Despite the massive investment in science, technology, clinical trials, pharmaceutical product development still costs at least 10 to 15 years and more than $500 million and 42 billion. Moreover, the quantity of chemical, biological entities that have been approved by the U.S.FDA has been decreasing since the late 1990s. So, to overcome this loss of productivity and economy, drug repurposing plays a major role. Drug repurposing can also be named as drug repositioning, retasking or reprofiling. It means that those drugs that have been abandoned or not being used can be identified and used for new disease or ailment. Novel uses of existing drug cost much less to develop compared to new drug discovery and development. Recycling of old drug and re-Profiling the existing drug for novel results could deliver the increased productivity that the industry needs while shifting the locus of production to biotechnological companies. The companies are increasingly using existing pharmacopoeia for repositioning candidate and thus there is success in it.

Keywords: *drug repositioning, drug discovery, FDA, pharmacotherapies, recycling.*

I. INTRODUCTION

The biopharmaceutical industry has a problem output has not kept pace with the enormous increases in pharma R&D spending [1].This gap in productivity exists even though pharma companies have invested prodigious amounts in novel discovery technologies, such as structure-based drug design, combinatorial chemistry, high-throughput screening (HTS) and genomics[2], which were sold on the promise of improving productivity. For example, many in the industry invested heavily in the idea that HTS technology would bring 20-fold improvements in throughput. Well over US $100 million has been invested to date in this technology [3];The past decade has witnessed the unprecedented transition of drug discovery projects frommajor pharmaceutical houses to academic [4], non-profit and small business research units,with particular focus on orphan and neglected diseases [5]. This transition was facilitated byseveral factors: *i)* the increased innovation gap observed

in pharmaceutical companies; *ii)* anumber of mega-mergers among pharmaceutical companies, against the backdrop of aglobal economic downturn – which has resulted in a mass migration of skilledpharmaceutical labor towards other research units, notably academia; *iii)* the launch of twomajor initiatives in the US, Clinical and Translational Science Award, CTSA [6],

II. HOW DRUG REPURPOSING WORKS

Drug repurposing works in two distinct phases: candidate drug identification and drug effect testing [7]. Candidate drug identification is the identification of potential drugs for repurposing, achieved through simple trial and error, advanced text mining approaches, or the analysis of gene expression patterns. Historically, trial and error have been the main driving force behind drug repurposing. In 1964, for example, Israeli physician Dr.Jacob Sheskin discovered a novel treatment for leprosy when he prescribed to a patient a drug typically regarded as a sedative [8]. Instead of simply putting the patient to sleep, the drug actually mitigated many of the leprosy symptoms experienced by the individual. This serendipitous case is the most primitive example of drug repurposing but demonstrates the potential it holds as a therapeutic strategy. Today, researchers focus on more targeted ways to look for drug candidates to repurpose based on knowledge of disease pathology and drug mechanisms [7]. Modern screening technology, in conjunction with the wealth of data available with the rise of Big Data, has paved the way for the development of a systematic way to repurposing drugs. Text mining, for example, has allowed bioinformaticians to search published scientific literature for similarities and links between diseases and drugs [9].

TABLE 1- CLASSIFICATION OF DRUG RE PURPOSING STUDIES ACCORDING TO THE DRUG RE-POSITIONING EVIDENCE LEVEL (DREL)

DREL Level	Quality of scientific evidence	References
0	No evidence; includes *in silico* predictions without confirmation.	[10,11,12,13]
1	*In vitro* studies with limited value for predicting *invivo*- human situations.	[14,15]
2	Animal studies with hypothetical revelance in man.	[16]
3	Incomplete studies in man at the appropriate dose, e.g., prrof of concept; very few cases or inference from medical records; some clinical efforts observed.	[17]
4	Well documented clinical end points observed for the repurposed drug at doses within safety limits.	[18]

III. MERITS OF DRUG REPURPOSING [19]

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.

IV. DE-MERITS OF DRUG REPURPOSING [19]

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 favourable. 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.

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FIG. 1-REPURPOSING STRATEGIES [20]

TABLE 2-EXAMPLES OF REPURPOSED DRUGS, THEIR TARGETS AND INDICATIONS: [21]

Drug name	Original target	**Original indication**	New target	**New indication**
Successful repositionings from approved drugs:				
Duloxetine	Serotonin and nor epinephrine reuptake	depression	Serotonine and norepinephrine reuptake	Stress, urinary incontinence, fibromyalgia, chronic musculoskeletal pain
Everolimus	mTOR	Immunosuppressant	Unchanged	Pancreatic neuroendocrine tumors
Imatinib	BCR-ABL	CML	KIT, PDGFRA	GIST
Minoxidil	Unknown	Hypertension	Unknown	Hair loss
Nelfinavir	HIV-1 protease	AIDS	Inhibits AKT pathway	In clinical trials for multiple cancers

Sildenafil	PDE5	Angina	Unchanged	Erectile dysfunction, pulmonary arterial hypertension
Sunitinib	Multiple kinases	GIST, renal cell carcinoma	Unchanged	Pancreatic neuroendocrine tumors
Trastuzumab	HER2	HER2-positive breast cancer	Unchanged HER2-	HER2-positive metastatic gastric cancer
Successful repositionings from investigational drugs:				
Crizotinib	MET kinase	Clinical trials for anaplastic large-cell lymphoma	*EML4-ALK* oncogene	NSCLC
Thalidomide	Unknown	Morning sickness (withdrawn)	Inhibits tumor necrosis factor α production	Leprosy
Thalidomide	Unknown	Morning sickness (withdrawn)	Inhibits angiogenesis	Multiple myeloma
Zidovudine	Reverse transcriptase	Failed clinical trials for cancer	Reverse transcriptase	AIDS

V. WHY DRUG REPURPOSING? [7,22,23]

R&D is arguably not the form of innovation currently most needed in today's cash-strapped healthcare systems. So, Cost-effective and efficient, drug repurposing presents a promising means of finding treatments for the thousands of untreatable rare diseases that persist in the modern healthcare system today. Rare genetic conditions are a target of great potential for drug repurposing. Of the 7,000 different rare diseases in existence worldwide, only 400 currently have licensed treatments. This means that there is a large treatment gap for millions ofpeople with little hope for disease-altering clinical support. With the development of genomic sequencing, however, the repurposing of drugs has become a promising area of exploration. Genomic sequencing has enabled scientists to quickly match existing drugs to the impaired biochemical pathways

associated with various diseases. In doing so, researchers can save millions of dollars on the R&D that would go into the development of a novel drug.

VI. UNSUCCESSFUL ATTEMPTS IN DRUG REPOSITIONING

Drug repositioning has not always been successful. There are some examples where drug repurposing failed. For example, bevacizumab- a kinase inhibitor failed to show efficacy in a phase III trial for gastric cancer despite having already been repositioned to many other cancers [24]. Similarly, the multi-kinase inhibitor sunitinib has also failed in clinical trials for breast cancer, colorectal cancer, lung cancer and prostate cancer, but was approved for the treatment of Gastric and intestinal tumors, pancreatic neuroendocrine tumors and renal cell carcinomas. [24]

TABLE 3- LATEST ADVANCEMENTS AND ONGOING RESEARCH IN DRUG REPURPOSING[25,26,27,28]

DRUG:	REPURPOSED USE:	REPORTED BY:	DESCRIPTION:
HYDROXYUREA	GLIOBLASTOMA (GBM)	Teng J *et al*	Over the last two decades, the major improvement in the treatment for GBM has been the addition of the chemotherapeutic agent temozolomide (TMZ) to the standard of care (surgery and radiation), however, despite this aggressive therapy, over 90% of patients die within five years after diagnosis. Combining FDA-approved drug hydroxyurea with TMZ for the treatment of GBM could be highly beneficial for these patients, which could increase the survival rate of those patients.
SIMVASTATIN	REDUCES THE RISK OF PROSTATE CANCER MORTALITY IN PATIENTS WITH	Yu-An Chen *et al*	This population-based cohort study demonstrated that statin use significantly decreased the mortality of Prostate cancer patients, and that this risk was inversely associated with the cumulative defined

	HYPERLIPIDEMIA		daily dose of simvastatin therapy. The results of this study revealed that statins may be used for drug repositioning and in the development of a feasible approach to prevent death from Prostate cancer.
PROBENECID	HEART FAILURE	Nathan Robbins *et al*	A new study found that probenecid — which is a drug commonly used to treat gout — improved heart function in a small number of individuals with heart failure. First study author Nathan Robbins from the University of Cincinnati College of Medicine in Ohio — and colleagues recently reported their findings in the Journal of the American Heart Association.
PRANLUKAST	TUBERCULOSIS	Archita Mishra *et al*	The Indian researchers, through extensive studies, have found that the drug, Pranlukast, destroys a specific metabolic pathway in Mycobacterium tuberculosis (Mtb), the causative agent of TB, which is crucial for its survival in human cells. It does so without causing any damage to host cells. The pathway was till now not known as a drug target for TB.
ANTI-LEUKEMIC DRUGS	PREVENTION OF MELANOMA METASTASIS.	Rakshamani Tripathi*et al*	Published in Science Signaling, the study showed new evidence linking the activation of ABL kinases – cancer-promoting genes – to the secretion of pro-metastatic cathepsins in melanoma. Cathepsins are enzymes that degrade proteins and are highly expressed in cancer cells, resulting in their release into the environment between the cells. These enzymes "chew up" the fibrous matrix

			around tumors, which allows them to get into the blood stream and lymphatic system and spread around the body. Their work showed that ABL kinases induce cathepsin expression and secretion by increasing the activity of key transcription factors that upregulate numerous proteins involved in metastasis. Transcription factors bind to the regulatory part of genes and induce their expression. This study is the first to demonstrate that ABL kinases not only increase the abundance of the transcription factors, but also regulate the ability of these transcription factors to bind to the promoters and induce gene expression. Lastly, the researchers found that ABL kinases inhibitors already approved by the Food & Drug Administration for treating leukemia also prevented metastasis induced by secreted cathepsins in animal models of metastatic melanoma.
VORINOSTAT	ANTI-CRYPTOSPORIDIAL ACTIVITY		Recently published study exhibited anti-cryptosporidial activity of histone deacetylase (HDAC) inhibitor vorinostat at nanomolar level in vitro. The study also demonstrated irreversible killing of the parasite by vorinostat by inhibiting the parasite at different developmental stages via targeting parasite's HDAC enzymes. These data suggest the potential for repurposing of vorinostat to treat cryptosporidiosis.

VII. CONCLUSION:

One of the greatest advantages of drug repurposing is its ability to bypass many of the costly and time-consuming steps of the drug development process including research and design, preclinical trials, and clinical trials. Removing such steps in the drug development pathway helps reduce the time drugs take to reach the clinic. Drug repurposing is a field of drug development that is rapidly expanding because of its relatively small financial burden, high success rate, and recent developments in its associated technologies. Apart from pharmaceutical companies, biotechnicians, academics, and clinicians are all able to play a significant role in pushing this innovation. Recently, patient groups and healthcare startups (https://healx.io/) have also begun to take note of this field and are actively raising funds to drive this promising area of research.

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IX. COMPETING INTERESTS:

Authors have declared that no competing interests exist.

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