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Repurposing Market Drugs to Target Epigenetic Enzymes in Human Diseases

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Abstract

Drug discovery is an exciting yet highly costly endeavor. In the United States, developing a new prescription medicine that gains marketing approval takes near a decade and costs drugmakers for near 3 billion. More challengingly, the success rate of a compound entering phase I trials is just slightly under 10%. Because of these mounting hurdles, repurposing market approved drugs to new clinical indications has been a new trend on the rise. Another merit to this approach is the already confirmed toxicity profiles of the drugs and their possession of drug-like features. Thus, repurposed drugs can reach the market approved stage in a much faster, cheaper, and more efficient way. Notably, epigenetic enzymes play a critical role in the etiology and progression of different diseases. Researchers are now assessing the possibilities of using market approved drugs to target epigenetic enzymes as a novel strategy to curtail disease progression. Thus, in this book chapter, we will provide an outlook on repurposing market drugs to target epigenetic enzymes in various diseases. Consequently, this book chapter will not only provide the readers with current knowledge in this specific field, but also will shed light on the pathway forward for repurposing market drugs to target epigenetic enzymes in human diseases.

Keywords: disease, drug, EMA, epidrug, epigenetic, FDA, repurposing

1. Introduction

1.1 Overview of drug approval agencies

Drug approval agencies are responsible for the oversight and scientific evaluations that ensure the safety and effectiveness of the drugs that reach the market, and eventually, patients. Several agencies regulate drug approval worldwide, with the United States (US) and Europe being the top regulators. Some examples include the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, Japan's Pharmaceutical and Medical Devices Agency (PMDA), Australia's Therapeutic Goods Administration (TGA), and so on [1]. In the last 5 years, the US FDA has approved about 245 drugs, many of which include anti-cancer and neurological disorder drugs [2]. Following drug discovery and preclinical trials, different types of applications can be filed to the FDA to begin a drug's journey to the market. A sponsor can either file the Investigational New Drug (IND) application followed by the New Drug Application (NDA) or the Abbreviated New Drug Application (ANDA). An IND application is submitted if

a drug is deemed safe after preclinical investigations. Then, an NDA can be submitted after the drug is deemed safe from the clinical trial results. At this point, a request can be made to produce and market the drug in the US [3]. On the other hand, ANDA is filed for the approval of generic drugs. Although clinical studies are not needed for this application, sponsors must prove that their drug is similar and bioequivalent to the original approved branded counterpart [4]. In the European Union, sponsors submit a clinical trial application (CTA) followed by a marketing authorization through either a centralized process or a decentralized process [3, 5]. Notably, both the FDA and EMA have similar yet distinct regulatory mechanisms to categorize drug approvals. For example, the FDA may grant drugs a standard approval, fast-track designation, accelerated approval, breakthrough designation, or priority review. Similarly, besides the standard approval, the EMA has accelerated assessment and conditional approval for expedited programs to bring a drug to market faster [5]. Taken together, these drug approval agencies do participate in a global collaborative effort to protect and improve public health by ensuring patients' timely access to safe and effective medicines [6].

1.2 Overview of traditional drug discovery method

The world population is constantly increasing and aging, with a census of close to 8 billion people in 2021 [7]. Additionally, there remains a growing necessity for novel therapeutics to combat the increasing number of cancers, metabolic disorders, infectious diseases, neurodegenerative diseases, and diabetes, as they are a major burden on public health. Despite this necessity, the rate of creation and approval of novel therapeutics is slow by comparison with estimated costs ranging from several hundred million dollars (USD) to several billion per therapeutic with an estimated development time of 12–15 years [8]. The reasons behind these high costs and difficulties with bringing novel therapeutics to market are in some ways straightforward: many projects fail in clinical trials; clinical trials are expensive and time-consuming; therapeutics have failed in the market due to previously unknown public health concerns; research costs are constantly increasing, and the initial investment cost of each therapeutic is high for a pharmaceutical company [9–12]. Traditional drug discovery involves the identification or creation of a new molecular entity (NME). The identification process of an NME usually proceeds as follows: initial basic research generates data supporting inhibition or activation of a protein or pathway that will result in a therapeutic effect in a disease state. Then a lead discovery compound such as a small molecule or biological therapeutic is discovered following some compound screening. The target is validated, and preclinical screening is performed, then the therapeutic can go through clinical trials before filing for drug agencies' approval [11]. The basic steps of this process are illustrated in **Figure 1**. However, at any step of the drug discovery timeline, the therapeutic can fail for a multitude of reasons. Generally, it comes down to two main factors: efficacy and safety [11]. For instance, several therapeutics of AstraZeneca have failed in phase II trials due to toxicological concerns [13]. Other studies stopped clinical trials when the newly developed therapeutics had decreased efficacy compared to existing therapeutics [14]. Furthermore, the time during each of these steps can be lengthy with several years, such as effort needed for compound discovery, clinical development, clinical trials, and FDA or EMA filing (**Figure 1**) [15]. For instance, the overall percent likelihood of approval (LOA) from phase I to approval in all therapeutic fields from 2011 to 2020 was merely about 8% [16]. The LOA differed greatly per therapeutic and per phase (lead compound to phase I, phase I to phase II, etc.). The only step of drug discovery where therapeutics were highly likely to progress was during NDA approval, with a success rate of 80–90% [17]. These

I. Traditional Drug Discovery

II. Repurposing of Market Drug

Figure 1.
Traditional drug discovery process (I) from discovery of target, validation, trials, and FDA/EMA approval with timescale versus repurposing of a market drug (II). This schematic describes the timeline of traditional drug discovery, wherein years of rigorous basic research leads to discovery of a drug, which then undergoes extensive pre-clinical development before going through the clinical trial and market approval phase. With the advent of drug repurposing approach, the timeliness and cost-efficiency of drug discovery significantly improved the driving of a drug for newer indications to the market faster.

are what led to the long development times for therapeutics discovered through traditional drug discovery methods. In summary, the overall takeaway message is that there is a multitude of factors that can stall drug discovery, and an alternative methodology may be a better approach to bring therapeutics to market.

1.3 Overview of basis of drug repurposing

Due to the immense financial costs and timescale associated with traditional drug discovery methods, it is natural to assume alternatives may be preferable, such as repurposing current therapeutics. As shown in **Figure 1**, repurposing known therapeutics follows a similar but truncated development cycle as traditional drug discovery. The timeline includes the discovery of a therapeutic target, usually a new therapeutic indication for a previously approved indication. Then, it is followed by clinical trials. Given that the information on the preclinical, pharmacokinetic, and pharmacodynamic are already known, the clinical trial phase moves faster. Following this step is filing for market approval as usual [18, 19]. This allows for a development time of 5–10 years compared to 12–15 years of development for traditional drug discovery (**Figure 1**). This also drives down the two major factors hampering novel drug development: cost of new therapeutics and time of discovery to market. Therefore, it is not surprising that an increasing number of therapeutics developed by the FDA or EMA are repurposed therapeutics [20]. Interestingly, the discovery of novel indications for therapeutics has been made through a multitude of approaches. Drug repurposing involves integrating data from multiple resources and the use of different approaches to allow for the discovery of novel indications. One major path for novel indications is model-based computation or *in silico* drug repurposing. This can include numerous screens of a therapeutic concerning its drug molecular targets, chemical structure, and signaling pathways to predict unknown targets or biomarkers for disease [18]. Besides computational modeling, high-throughput and/or high-content screening (HTS/HCS) of drug compounds are frequently used to screen known therapeutics for novel targets [21]. Additionally, *in silico* screening of known compounds can be used for molecular docking or binding-based studies [22]. Furthermore, *in silico* screening can also help with the computational prediction of novel metabolic pathways, signaling pathways,

and protein-protein interactions between diseases and known drugs [23]. Other major methods of screening for novel indications of current therapeutics include recently AI-based machine learning, which has been used to some effect to screen large groups of compounds for anti-Sars-Cov-2 inhibition [24]. Further predictive modeling of drug repurposing includes network modeling wherein networks of drugs, genes, and drug products, as well as their interactions and relationships can be modeled, allowing for a greater understanding of structure-guided targeting of therapeutics [25]. Furthermore, large-scale genome-based predictive modeling, such as genome-wide association studies (GWAS) can help predict potential novel therapeutic interactions [26]. Another aspect not commonly studied is the known side effects of therapeutics and how it can be used to identify novel therapeutic targets *via* computational modeling [27]. According to Sahragardjoonegani and colleagues, roughly two-thirds of new therapeutics approved by the FDA within the last 15 years have not been indicated for secondary indications besides their original purpose [28]. This creates a largely untapped field of current therapeutics that have not been studied in the context of other diseases. Overall, drug repurposing for therapy requires less time and cost for development and research than traditional drug discovery. Thus, it is an attractive approach for the discovery of new therapeutics.

2. Role of epigenetic enzymes in human diseases

Epigenetics is the study of mechanisms that results in heritable changes in gene expression without the alteration of the genetic code [29]. The deregulation of epigenetic mechanisms, such as DNA methylation and histone modifications, have been reported to facilitate differential expression of genes, many of which underlie the etiology and/or the progression of human diseases [30].

These epigenetic mechanisms are mediated by their respective epigenetic enzymes. For instance, DNA methyltransferases (DNMTs) coordinate the methylation of DNA by catalyzing the transfer of a methyl group to cytosine (C) from the donor molecule S-adenosylmethionine (SAM) [31]. The methylated DNA is read by methyl-Cp-guanine (G) binding domains (MBD) protein. DNA methylation can be reversed by a group of human demethylase enzymes termed ten-eleven translocation proteins (TET 1/2/3) [31]. DNA methylation is responsible for gene silencing and often occurs in regions rich in C and G nucleotides, also known as CpG islands. The catalysis of DNA methylation is primarily conducted by the following family of DNMTs: DNMT1, DNMT3A, and DNMT3B [32]. These enzymes help maintain the integrity of the human genome, regulate transcriptional processes, and aid cellular development and differentiation [33]. Thus, dysregulation of DNA methyltransferase and demethylases are implicated in several human diseases.

Similarly, the covalent modification of histones is another facet of epigenetics that plays a pivotal role in human diseases. The core histone proteins, H2A, H2B, H3, and H4, form an octameric structure that wraps about 146 base pairs of DNA to form a nucleosome, and the linker histone, H1, connects the repeating nucleosomes that make up the chromatin. Histones' terminal regions project out of the chromatin in a tail-like structure, and these tails are subjected to post-translational modification (PTM) by different histone-modifying enzymes [28, 31]. Some of the most common classes of histone-modifying enzymes include histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs) [34]. HATs and HDACs are writers and erasers of acetylation, respectively, on lysine (K) residues of histones and non-histone proteins. The acetylation of histones results in a relaxed chromatin that promotes gene transcription [35]. HATs are classified into Type A: p300/CBP, general control

non-depressible 5 (GCN5)-related N-acetyltransferase (GNAT), Moz, Ybf2/Sas3, Sas2, Tip60 (MYST), nuclear receptor coactivator- (NCOA-) related HAT, and transcription factor-related HAT; and Type B: HAT1, HAT2, HatB3.1, Rtt109, and HAT4 [36]. While HDACs comprise 18 enzymes: HDAC1-11 and sirtuins (SIRT)1-7 [37]. The BRD and extra terminal domain (BET) proteins are responsible for recognizing K residues that are acetylated [37]. On the other hand, methylation of histones, which occurs on either K or arginine (R) residues of histones, can lead to gene transcription repression or activation. The addition of methyl group(s) to histones is mediated by HMTs while its removal is mediated by HDMs [34]. HMTs are further subdivided into lysine methyltransferases (KMTs) and arginine methyltransferases (PRMTs) [38]. Similarly, HDMs are classified into lysine demethylase 1 (LSD1 or KDM1) and Jumonji C (JmjC) domain-containing histone demethylases [39]. Together, these classes of histone-modifying enzymes regulate the expression of genes vital to many human biological processes.

2.1 Epigenetic enzymes implicated in cancer

The dysregulation of epigenetic enzymes is one of the chief contributors to cancer development and progression. Several cancers are accompanied by significantly altered DNA methylation status, and this has been shown to serve as a diagnostic and prognostic marker [40]. The resulting imbalance in gene expression is mainly caused by hypomethylation of oncogenic genes or hypermethylation of tumor-suppressive genes. Thus, inhibiting DNA methyltransferase and/or DNA demethylase is a promising therapeutic strategy for many of these cancers. For example, in breast cancer models, the inhibition of DNMT exerts reduced cellular proliferation, migration, and anchorage-independent growth activity and potentiates anti-cancer immunity [41, 42]. Similarly, inhibiting DNMT sensitizes non-small cell lung cancer (NSCLC) to ionizing radiation and a potent targeted therapeutic poly (ADP-ribose) polymerase (PARP) inhibitors [43]. The overexpression of DNMT, particularly DNMT3Ab, in gastric cancer facilitates the epithelial to mesenchymal transition (EMT)-related metastasis and correlates with poor prognosis in gastric cancer patients [44]. Aberrant gene silencing or activation caused by deregulated DNMTs and TETs have also been widely reported in renal, colorectal, brain, pancreatic, bladder, prostate, and other hematological cancers [45]. Among the genes that are implicated in DNA methylation dysregulation include but are not limited to retinoblastoma tumor-suppressor gene (Rb), breast cancer susceptibility gene 1 (BRCA1), cyclin-dependent kinase inhibitor 2A (CDKN2A), and microRNAs [46]. Collectively, the atypical expression of some of these genes leads to genomic instability and uncontrolled cell cycle progression.

Likewise, the PTM of histone tails at gene promoters and on specific residues of non-histone proteins promote different cancer hallmarks. HATs and HDACs regulate acetylation patterns on several proteins and serve as co-activators/repressors of transcription factors implicated in cancer [35, 36]. For instance, in prostate cancer tissues, CBP/p300 transcript levels are significantly high. They potentiate the constitutive activation of androgen receptor signaling in castration-resistant prostate cancer, leading to increased tumor growth [47]. Moreover, the overexpression of the human MYST1, a member of HATs, promotes acetylation of Nrf2 at K588, thereby aiding the tolerance of replication stress in NSCLC [48]. The erasure of acetylation marks is also an important driver of cancer progression. HDACs are typically overexpressed and result in the silencing of key tumor suppressor genes. Particularly, in breast cancer, the use of HDAC inhibitors has shown remarkable potential in preventing hormonal-based therapy resistance through the restoration of epigenetic alterations [49]. A separate review has extensively delineated the role of HDACs in altering

gene expression in cancer through chromatin remodeling and transcription factors regulation [50]. Also, the methylation and demethylation of histone and non-histone substrates have a diverse function in carcinogenesis. For example, the high expression of human telomerase reverse transcriptase (hTERT) observed in many cancers is associated with the heavily trimethylated histone H3K4. H3K4 is a known substrate of SMYD3, a KMT that is commonly overexpressed in cancers [51]. Also, different KMTs such as KMT2A and Dot1-like protein (DOT1L) fuse with proto-oncogenes to promote the progression of hematological malignancies [38]. Another overexpressed KMT in cancer, enhancer of zeste homolog 2 (EZH2) catalyzes the methylation of H3K27 and genes like p16, NF- κ B, CDK4, Ras, β -catenin to further different tumors' survival [52]. Similarly, overexpression of KDMs, such as LSD1, LSD2, and KDM5B, cause increased tumor growth and chemoresistance *via* aberrant demethylation of H3K4 in prostate cancer, breast cancer, NSCLC, and hepatocellular carcinoma [53]. A growing number of studies have also documented the widespread role of the known human PRMTs in cancers. The overexpression of PRMTs has been found in breast, prostate, colon, bladder, ovarian, skin, and gastric cancers, including various hematological malignancies [54]. Notably, our group extensively studies PRMT5, and we discovered that its overexpression in pancreatic and colorectal cancer results in increased cell growth, migration, and anchorage-independent growth *via* dimethylation of R30 of NF- κ B subunit, p65 [55, 56]. We also revealed that PRMT5 oncogenic role in colorectal cancer potentiates NF- κ B signaling through dimethylation of R205 of Y-box binding protein 1 (YBX1) [57]. Taken together, the deregulation of epigenetic enzymes has an entrenched and indisputable role in the etiology and progression of many cancers, making them promising therapeutic targets.

2.2 Epigenetic enzymes implicated in neurodegenerative disorders

Recently, genomic profiling studies and molecular investigations have delineated the impact of epigenetic alterations on neurodegeneration. Neurodegenerative diseases encompass the gradual loss of cognitive and/or motor functions in humans. Examples include but are not limited to Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS) [58]. It has been reported that the DNA methylation of AD-associated genes, such as the β -secretase (BACE), amyloid precursor protein (APP), and presenilin 1 (PS1) genes, is dramatically decreased in AD cell models and results in the exacerbation of AD pathology [59]. In a genome-wide study conducted by Huynh and colleagues on MS patients' brains, several differential methylated regions in the DNA were observed. Genes that are critical to oligodendrocyte regulation, such as BCL2L2 and NDRG1, were found to be hypermethylated and showed decreased expression levels [60]. Also, given that HATs like p300/CBP are involved in memory formation, its loss has been shown to lead to different neurological dysfunction, which is characteristic of HD, Rubinstein-Taybi syndrome, and AD [61, 62]. Thus, HDAC inhibitors can be used as a therapeutic strategy to offset the imbalanced role of HATs in the aforementioned neurodegenerative diseases. On the contrary, the downregulation of p300 levels by native α -synuclein (α syn) exerts neuroprotective function in the brain. Thus, it has been suggested that misfolded α syn, a major phenotype of PD, may lead to enhanced p300/CBP activity, thereby causing impaired motor function [63]. In ALS, reduced p300/CBP has been found to cause the hypoacetylation of the cyclin D1 gene, a critical gene for cell cycle progression [64]. Similarly, increased methylation marks on histones have been linked with aging, an important risk factor in neurodegeneration [65]. In ataxia-telangiectasia, the loss of A-T mutated (ATM) increases the tri-methylation of H3K27 *via* EZH2 stabilization, thereby affecting neuronal survival [66]. Also, overexpression of an

H3K9 methyltransferase, ERG-associated protein with SET domain (ESET, also known as SET domain bifurcated 1, SETDB1), is shown to be markedly increased in HD patients, and the inhibition of ESET was reported to restore the normal behavioral and neuronal function in HD mice [67]. Moreover, PRMT1 was reported to play a neuroprotective role in ALS *via* asymmetric dimethylation of H4R3, a methylation mark that aids histone acetylation, and consequently, transcription of survival genes [64]. Collectively, this brief overview shows that chromatin modification *via* epigenetic processes is critical to neuronal function.

2.3 Epigenetic enzymes implicated in cardiovascular diseases

Cardiovascular disease, one of the leading causes of mortality globally, is comprised of a group of diverse disorders known to be influenced by genetic, environmental, and epigenetic mechanisms [68]. For example, GWAS on atherosclerotic aorta versus normal aorta showed the differential methylation of DNA is associated with atherosclerotic plaque stability, vascular remodeling, low-density lipoprotein (LDL) signaling, among other biological processes [69]. This suggests the role of altered DNA methylation in the pathogenesis of atherosclerosis. Similarly, case-control investigations on heart failure patients revealed differential methylation of angiogenic genes known to be involved in endothelial cell migration and capillary tube formation [70]. Also, multiple studies have demonstrated that high levels of HDAC and DNA/histone methylation have been linked to the causation of high blood pressure, a known symptom of hypertension [71]. Similarly, the use of HDAC inhibitors attenuates myocardial infarction in *in vivo* studies [72]. A separate study showed that environmental factors, such as particulate matter in air pollution known to cause impaired cardiac function, increase the methylation of Toll-like receptor 2 (TLR2), causing its gene silencing. TLR2 is known to proffer immunity following environmental challenges [73]. Thus, its hypermethylation has been linked to the cardiac dysfunction caused by air pollution. Also, *de novo* mutations have been found in histone-modifying genes in congenital heart disease, including KMT2D, KDM5A, and KDM5B, thereby suggesting their role in the disruption of cardiac development [74]. The overexpression of PRMT6 has been reported to induce cardiac hypertrophy and its associating increase in asymmetric dimethylation of H3R2 promotes the expression of atrial natriuretic peptide (ANP), a hypertrophic marker [75]. This diverse implication of epigenetic enzymes in various cardiac functions suggests its potential as a treatment approach for cardiovascular diseases.

3. Classes of epigenetic enzymes targeted with repurposed market drugs

As discussed in previous sections, epigenetics is pivotal to the etiology and progression of different human diseases. And multiple studies have shown that targeting epigenetic enzymes has a profound effect on attenuating the severity or progression of diseases [59]. Given that the traditional approach to drug discovery is costly and time-inefficient, it is more valuable to reposition readily available market drugs for new disease indications. In this section, we will discuss the major epigenetic enzymes being targeted with repurposed drugs or preclinical compounds and examples of the repurposed drugs with their old and new indications.

3.1 Repurposed drugs for DNMTs

The alteration of DNA methylation is one of the prominent underlying causes of different diseases. Several market drugs have been shown to lessen disease

progression *via* targeting DNMT, suggesting that those drugs could have newer indications. As summarized in **Table 1**, hydralazine is a hypertensive drug that has been repurposed as both DNMT inhibitor and HDAC inhibitors [76]. In combination with another drug, valproate, hydralazine showed a significant increase in progression-free survival in patients with advanced cervical cancer in a randomized phase II clinical trial [95]. Currently, a phase III clinical trial is underway to examine the effect of hydralazine on AD (NCT04842552). It has been suggested that the stability of polyglutamine repeat expansion, an underlying cause of multiple neurodegenerative diseases, can be caused by hypermethylation of the repeat and the use of hydralazine induces demethylation [96]. This may suggest a mechanism through which hydralazine helps ameliorate AD. Another repurposed drug, procaine, a local anesthetic agent, has been reported to be a potent inhibitor of DNMT activity with an anti-tumor effect in gastric cancer [77]. Procaine has also been shown to exert cardioprotective and neuroprotective effects [78]. Other examples of repurposed drugs that target DNMTs include Procainamide, Mithramycin A, Nanaomycin A, and Disulfiram, etc. [79] (**Table 1**).

Table summarizes the different market approved drugs for other indications known to target epigenetic enzymes in newer indications. The listed drugs are either in preclinical or clinical trial phase for their newer indications.

3.2 Repurposed drugs for HDACs

Among the different classes of epigenetic enzymes, HDAC has the highest number of market-approved inhibitors for diseases, especially in cancer [97]. Vorinostat is the first HDAC inhibitor approved by the FDA for cutaneous T-cell lymphoma (CTCL) treatment [98]. Another HDAC inhibitor, Belinostat, has been granted accelerated approval for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) [99]. Also, repurposed drugs that target HDAC are on the rise. One category of drugs that targets HDAC is statins. Statins are a class of medications developed to inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase for atherosclerosis treatment [100]. Multiple studies have shown that statins exhibit anti-cancer activity and attenuate diabetic nephropathy *via* the inhibition of HDAC [80, 81]. Similarly, the anti-malaria drug artemisinin was reported to exert anti-cancerous effects on breast cancer cells partly *via* the inhibition of HDAC [82]. Through indirect inhibition of HDACs and other epigenetic modifiers, metformin, a type 2 diabetic medication, has been suggested to have a protective effect on cancer, cognitive impairment, and cardiovascular diseases [83]. Carbamazepine, which is approved for the treatment of psychomotor and grand mal seizures, has been reported to inhibit HDAC 3, 6, and 7 and reduce cancer growth in breast, liver, and colon cancer [101]. Currently, trichostatin A (TSA), an approved antifungal drug with HDAC inhibitory activity, is undergoing a phase I clinical trial for relapsed or refractory hematologic malignancies (NCT03838926) (**Table 1**).

3.3 Repurposed drugs for HATs

The normal levels of gene acetylation can also be restored by HAT inhibitors in diseases. This category of inhibitors is particularly explored as anti-cancer agents, given that inhibiting HATs would only exacerbate cardiovascular and neurodegenerative disease progression. Also, the role of HATs in cancer is context-specific as certain HAT family members can act as oncogenes or tumor suppressors in different tumors. For example, the overexpression of p300/CBP, GCN5, and males absent on the first (MOF) has been shown to sustain cancer hallmarks in glioma, colon, lung cancer, mixed-lineage leukemia (MLL), and acute myeloid leukemia (AML). On the other

Drug	Previous indication	New indication	Epigenetic target	Phase of development	Reference(s)
Hydralazine	Hypertension	Advanced cervical cancer	DNMT	Phase II clinical trial	[76]
		Alzheimer's disease	HDAC	Phase III clinical trial	(NCT04842552)
Procaine	Pain relief	Neurodegenerative and cardiovascular diseases	DNMT	Preclinical	[77, 78]
		Gastric cancer			
Mithramycin	Antibiotic	Lung, esophagus, and other chest cancers	DNMT1	Phase II clinical trial	NCT01624090
Nanaomycin A	Antibiotic	Colon, lung, and bone marrow cancers	DNMT3B	Preclinical	[79]
Procainamide	Ventricular arrhythmias, supraventricular arrhythmias, atrial flutter/fibrillation, and Wolf-Parkinson-White syndrome	Colon cancer	DNMT1	Preclinical	[79]
Statins	Atherosclerosis	Lung, colon, and gastric cancer	HDAC	Preclinical	[80, 81]
		Diabetic neuropathy			
Artemisin	Malaria	Breast cancer	HDAC	Preclinical	[82]
Metformin	Type 2 diabetes	Cancers, neurological disorders, and cardiovascular diseases	HDAC	Preclinical	[83]
Carbamazepine	Psychomotor and grand mal seizures	Breast, liver, and colon cancer	HDAC	Preclinical	[79]
Trichostatin A	Fungal disease	Relapsed or refractory hematologic malignancies	HDAC	Phase I clinical trial	(NCT03838926)
Astemizole	Allergies	Lymphoma	EZH2	Preclinical	[84]
Apomorphine hydrochloride	Parkinson's disease	Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and multiple cancers	EZH2	Preclinical	[85]
Hydroxychloroquine	Malaria	Multiple myeloma	EZH2	Preclinical	[86]
Cloperastine	Cough	Cancers	PRMT5	Preclinical	PCT/ US2020/067694 [87, 88]

Drug	Previous indication	New indication	Epigenetic target	Phase of development	Reference(s)
Candesartan	Hypertension	Cancers	PRMT5	Preclinical	PCT/ US2020/067694 [87, 88]
Tranlycypromine	Depression	AD	LSD1	Preclinical	[89, 90]
		Cancer			
Phenelzine	Depression	Prostate cancer	LSD1	Phase II clinical trial	[91]
Pargyline	Hypertension	Breast cancer	LSD1	Preclinical	[92]
Nitroxoline	Antibiotic	Leukemia	BRD4	Preclinical	[93]
Azelastine	Hay fever and allergies	Cancer	BRD4	Preclinical	[94]

Table 1.
Examples of repurposed drugs with epigenetic targets in human diseases.

hand, the deletion of p300/(CREB binding protein) associated factor (pCAF) and Tip60 promotes tumorigenesis in certain cancers [35]. Currently, there have been no investigations into the use of market-approved drugs to target HATs in cancer. Natural compounds targeting HATs, such as anacardic acid, plumbagin, garcinol, and lunasin have been reported to have potent anti-cancer properties [79]. Notably, the progression of HAT inhibitors into clinical trials has been challenging due to the resulting false positive hits gotten from HTS [102]. Thus, more effort is needed to find existing market drugs that not only inhibit HATs activity but also attenuate tumor progression.

3.4 Repurposed drugs for HMTs

Given the diverse roles of the two classes of HMTs, KMTs, and PRMTs, in different diseases, there have been increasing efforts towards developing/repurposing drugs that affect HMTs for the treatment of diseases. Under the class of KMT enzymes, EZH2 is one of the highly pursued targets for epigenetic therapy. For example, Astemizole (**Table 1**), an antihistamine drug used to treat allergies, disrupts the proliferation of lymphoma cells *via* inhibition of EZH2 methyltransferase activity [84]. Also, a pilot HTS identified 4 out of 1600 FDA-approved drugs as putative EZH2 inhibitors, with apomorphine hydrochloride being the most potent inhibitor [103]. Apomorphine hydrochloride, under the brand name Kynmobi, is FDA approved for the treatment of PD Off episodes [104]. A separate review has suggested the repurposing of apomorphine hydrochloride in AD, ALS, HD, and multiple cancers considering the mounting evidence that demonstrates its neuroprotective and anti-cancer effects [85]. However, whether this drug exerts its protective properties *via* EZH2 remains to be investigated. The anti-malaria drug, hydroxychloroquine, inhibits EZH2 and has been reported to be effective for the treatment of multiple myeloma (MM) [86]. Furthermore, there are about 10 clinical trial studies investigating PRMT inhibitors for both solid and hematological malignancies on clinicaltrials.gov. Given the lack of investigation on market approved drugs for targeting PRMTs in diseases, our lab has taken considerable efforts to address this important gap. Currently, we have a provisional patent on repurposing the FDA-approved drugs for cough (Cloperastine) and for hypertension (Candesartan) to target PRMT5 in tumors (PCT/US2020/067694) [87, 88].

3.5 Repurposed drugs for KDMs

One of the types of KDMs, LSD1, is a member of the amine oxidase family. Consequently, it shares sequence similarity with monoamine oxidase (MAO), an important enzyme involved in the clearance of neurotransmitters from the brain [105]. As a result, approved monoamine inhibitors, such as the antidepressant tranylcypromine, can also inhibit LSD1 [89]. Notably, tranylcypromine has been reported to suppress amyloid β -induced proinflammatory responses in AD mouse models [89]. Tranylcypromine also reduces tumor growth and metastasis. Hence, its derivatives were developed to optimize the inhibition of LSD1 [90]. One of these derivatives, ORY-1001, is in phase II clinical trial for AML, relapsed, phase I clinical trial for extended-stage disease small cell lung cancer (ED SCLC), and phase I clinical trial for refractory or relapsed acute leukemia (AL). Also, other classes of MAO inhibitors, such as pargyline (anti-hypertensive drug) and phenelzine (antidepressant), inhibit LSD1 with anti-cancer effects in breast and prostate cancer, respectively [91, 92]. On the other hand, the second class of KDM, the JmJc KDM, is yet to be investigated for market drug repurposing. Nonetheless, a couple of pharmaceutical companies are taking strides to develop inhibitors against this class of KDM in hematological and solid cancers [32].

3.6 Repurposed drugs for BETs

BET protein family, including BRD2, BRD3, BRD4, and BRDT, are readers of acetylated K residues on histones and non-histone proteins. BET inhibition is effective against kidney diseases, tumor development, cardiovascular disease, and other inflammatory diseases [106]. Some drugs have been repurposed to target BET proteins in diseases. For example, nitroxoline (**Table 1**) is an FDA-approved antibiotic and also a potent inhibitor of most BET family members. A study reported that nitroxoline significantly reduced the proliferation of leukemia cells *via* induction of apoptosis and cell cycle arrest. The anti-cancer action of nitroxoline is partly through BET inhibition and its downstream targets [93]. Another class of BET inhibitors, for example, molibresib, is a derivative of benzodiazepines, a psychoactive class of drugs used to treat neurological-related conditions. Molibresib is currently in phase I clinical trial for the treatment of multiple cancers [107]. Additionally, azelastine, an antihistamine used to treat hay fever and allergies, was ranked as one of the top drugs for having the best binding affinity to BRD4 [94]. Collectively, the aforementioned approved and putative repurposed drugs could serve as an effective BET inhibition-based therapy in different diseases.

4. Recent advances in drug repurposing for epigenetic-based therapy

Repurposing drugs for epigenetic-based therapy is a newly emerging field with significant potential for the development of drugs for diseases with high incidences, such as cancer and cardiovascular diseases. Notably, epigenetic enzymes play a critical role in the molecular pathology of the diseases discussed in this chapter. Thus, it is important to increase the development of drugs targeting epigenetic enzymes in a timely and cost-efficient manner. Due to the increased development of HTS methods, availability of comprehensive omics data, and advances in computational tools, the use of drug repurposing as a therapeutic strategy is highly promising. Through literature database search, researchers can often extrapolate the potential efficacy of a market-approved drug in a new indication based on the drug's molecular effect and cellular impact in an older indication. Such information opens a window of opportunity to examine the use of market-approved drugs in a new indication. For example, researchers observed that artemisinin, an approved malaria drug derived from the wormwood plant, forms free radicals with iron. Considering that increased iron levels are a well-established risk factor for breast cancer development, an investigation was launched into the anti-cancer effects of artemisinin [82]. Moreover, recent studies in epigenetic-based therapy have also adopted molecular docking tools to identify valuable drug candidates that can be repurposed for new indications [94, 108]. The study of the target structure and ligand interaction significantly scales down the evaluation of drugs that are unlikely to bind to the epigenetic targets that fuel a disease progression. This approach also leverages structural similarities of a market-approved drug's target to discover potential newer indications. Notably, our group developed an AlphaLISA-based high-throughput screen (HTS) that aided the identification of promising market-approved drug candidates which targets PRMT5. This unique HTS method allowed us to preclinically investigate the efficacy of candesartan and cloperastine, a hypertensive and cold medicine, respectively, in several solid cancers [87, 88]. As with other drug discovery approaches, the exciting advances in targeting epigenetic enzymes with market-approved drugs can be improved with additional extensive research on various aspects of the drug's molecular mechanisms. In some cases, although a

repurposed drug is known to have an epigenetic effect, its primary molecular target is not always clear. This gap creates an avenue for the possibility of off-target effects that may be adverse in newer indications. Similarly, the challenges with false-positive results in HTS can be surmounted by incorporating the dose-response factor as a critical variable for understanding a market-approved drugs' efficacy against an epigenetic target. Also, considering that the function of a market-approved drug can be context-dependent, it is critical to pursue new indications known to be highly driven by an epigenetic target of interest. Collectively, addressing the gaps in molecular mechanisms that drive disease pathology and improving existing screening methods will significantly advance the field of epigenetic-based therapy using market-approved drugs.

5. Future perspectives

Given that the *de novo* drug discovery approach for epigenetic targets is time-consuming, costly, and has a high failure rate in clinical trials, researchers may consider increasing their efforts into repurposing drugs with known epigenetic effects for newer disease indications. One of the merits of drug repurposing is that it alleviate patients' treatment costs and provide hope to those with rare conditions. Recognizing this approach as a great benefit to patients, governmental agencies and philanthropic organizations should increase the establishment of funding programs for drug repurposing endeavors [109]. More importantly, the paradigm for drug discovery is moving from a single target to a multitarget approach and drug repurposing is a suitable strategy to meet this evolving paradigm in pharmacology [110]. Thus, considering the slow pace and millions to billions of dollars spent on bringing a single drug to market, it is worthwhile to steer efforts and resources towards drug repurposing for epigenetic-based therapy in human diseases.

6. Executive summary

- Drug repurposing is a creative approach to drug discovery that comprises finding new indications for approved drugs in the market or drugs that have been recalled/inefficacious in a previous indication.
- The advent of computer-aided drug discovery and the HTS methods have significantly accelerated the drug repurposing process.
- The extensive role of molecular targets such as DNMTs, HDACs, HMTs, KDMs, and BETs in several human diseases necessitates the development of drugs to alleviate the progression of diseases driven by the aforementioned epigenetic enzymes.
- Thus, epidrugs (drugs that target epigenetic marks) have been widely incorporated in the management of diseases such as cancer, cardiovascular diseases, kidney disease, and neurological disorders.
- Recent advances in the drug repurposing approach increased the use of market-approved drugs to target epigenetic enzyme-driven diseases.
- Currently, several market-approved drugs have shown significant pre-clinical efficacy in diseases and/or are undergoing clinical trials for new indications.

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Conflict of interest

The authors declare no potential conflicts of interest.

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