

REVIEW

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Multi-omics based and AI-driven drug repositioning for epigenetic therapy in female malignancies

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Abstract

Histone post-translational modifications (PTMs) have long been recognized as critical regulators of chromatin dynamics and gene expression, with aberrations in these processes driving tumorigenesis, immune escape, metastasis, and therapy resistance. While multi-omics technologies are generating ever more detailed maps of the histone landscape, translating these insights into clinical practice remains challenging. The ongoing convergence of high-throughput omics technologies and Artificial Intelligence (AI) is revolutionizing drug repositioning strategies, offering new precision tools to identify histone-targeted therapies for solid tumors. In this review, we explore how AI-driven multi-omics integration is currently reshaping therapeutic opportunities by uncovering novel drug–target–patient associations with unprecedented accuracy. Special focus is given to gynecologic and breast cancers, where chromatin remodeling dysregulation is particularly widespread, conventional therapeutic approaches have demonstrated substantial limitations and drug resistance represents a major clinical obstacle. These aggressive and lethal cancers exemplify areas where AI-powered repurposing of epi-drugs is making tangible clinical advances, enhancing tumor sensitivity to treatments like immunotherapy, but also offering new avenues to overcome challenging phenomena such as drug resistance and cancer relapse. We critically discuss these challenges and the effectiveness of a combination strategy approaches based on AI-driven patient stratification and biomarker-guided therapy optimization to maximize clinical benefits. In an era where precision oncology demands both specific drugs and the application of smarter strategies, the integration of AI, multi-omics, and targeting of chromatin remodelers may herald a transformative shift in the management of solid tumors, bridging the gap between biological insights and therapeutic innovation.

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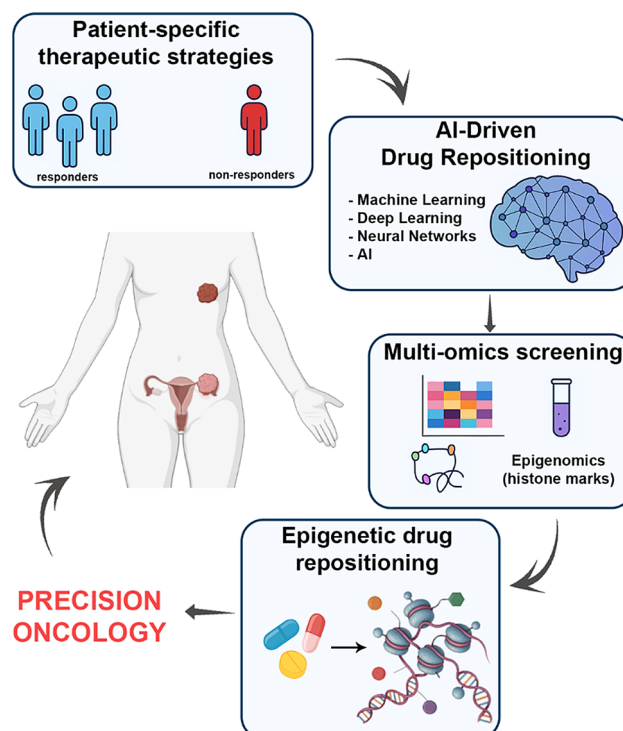
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Graphical Abstract

Keywords Response and resistance to therapy, Epigenetic targeted therapies, Multi-omics integration, AI-driven drug repurposing, Precision oncology

Background

In eukaryotic cells, DNA is packed together with nuclear proteins, predominantly histone proteins, to form a complex macromolecular structure termed chromatin. The generally accepted concept of chromatin involves its condensed folding into chromosomes which must be decondensed to allow several genomic processes such as transcription, recombination and replication in response to specific stimuli [1]. The nucleosome, the basic repeating unit of chromatin, consists of an octamer made up of four core histones (H3, H4, H2A, and H2B) [1] which are subject to diverse PTMs that influence chromatin structure and functions. These modifications are mediated by specific enzymes in both the histone core domains and tails, ensuring a balance essential for proper gene expression and biological functions [2]. The imbalance of this regulatory network can perturb cellular homeostasis and is associated with multiple human malignancies [3]. Understanding the molecular mechanisms governing histone-modifying enzymes is therefore key for developing therapies able to restore a functional equilibrium within the cell. In recent years, epigenetic enzymes have been described as promising drug targets mainly for their structure, reversibility of elicited modifications and

key role in gene expression regulation. This opened the path for drug repurposing, which seeks novel therapeutic applications for existing FDA-approved drugs or preclinical compounds. Instead of developing new drugs from scratch, repurposing leverages known safety profiles and pharmacology, thus accelerating the discovery of treatments for different diseases. This approach can involve experimental testing or computational (in silico) methods to identify promising candidates. In this review, we explored cutting-edge and innovative strategies for targeting epigenetic modulators responsible for key histone modifications and highlighted the therapeutic potential of drug repositioning in solid tumors, with a focus on female malignancies. Finally, we discussed emerging approaches for predicting candidate repositionable drugs for cancer treatment, leveraging artificial intelligence technologies.

Epigenetic regulation of chromatin: functional domains of chromatin modifiers as druggable targets

Histone proteins are subject to diverse PTMs that regulate chromatin structure and gene expression. Imbalances and abnormal PTMs are described to affect several

cancer hallmarks, such as tumor growth, invasion or apoptosis. Each of these marks is added by a specialized set of enzymes also named ‘writers,’ interpreted by effector ‘reader’ proteins, and removed by ‘eraser’ enzymes, thus creating a dynamic multifaceted and regulatory system [4]. These main features and the most biologically meaningful histone marks are summarized in Table 1.

In recent years, many studies have highlighted the potential of epigenetic enzymes as highly druggable targets due to their well-defined catalytic domains, the reversibility of their modifications, and their pivotal role in regulating gene expression [33]. These structural and functional characteristics make them particularly amenable to selective inhibition by small molecules, thereby facilitating the rational design of next-generation epigenetic drugs (epi-drugs) with improved specificity and efficacy. This approach is further bolstered by the rapid advancement of epigenetic therapies, with over 75 epi-drugs identified as potential therapeutic agents as of 2022, including many approved for clinical use and others at various stages of clinical development [34].

Targeting epigenetic writers

Epigenetic writers are categorized into several families based on their function, molecular structure, key domains and allosteric regulation residues. These features represent potential targets to inhibit their enzymatic outcome through the development of selective drugs. The catalytic domains of histone acetyltransferases (HATs), methyltransferases and kinases are considered druggable, with different classes of small molecules either

directly interfering with enzymatic activity or influencing their association with essential cofactors. HATs typically contain a catalytic domain that transfers acetyl groups from acetyl-CoA to lysine residues on histones and a lysine-binding pocket that directly recognizes the target for acetylation [34]. Designed inhibitors can affect both functional sites. Furthermore, research on HAT inhibitors is progressing with the development of proteolysis-targeting chimeras (PROTACs), specific degraders equipped with E3 ubiquitin ligase enabling targeted degradation through a ubiquitin-dependent mechanism [34, 35]. Histone Methyl transferases (HMTs) own a SET domain that transfers a methyl group from S-adenosyl-L-methionine (SAM) to lysine or arginine residues, with potentially druggable residues around SAM binding pocket [34, 36]. For example, Tazemetostat (EPZ-6438) inhibits EZH2 activity in a competitive mechanism [37]. Histone kinases own a kinase domain that phosphorylates specific residues on histones, using ATP molecules as phosphate donors. Residues surrounding the ATP-binding pocket can be targeted to inhibit its enzymatic activity or can be used to develop specific competitive inhibitors [38]. Other epigenetic writers, such as DOT1L and PRMT5, are under clinical investigation. The first-in-class DOT1L inhibitor, Pinometostat (EPZ-5676), competitively blocks SAM binding, thereby reducing H3K79 methylation and gene expression of several oncogenic targets [39, 40]. A Phase I study in pediatric patients with relapsed/refractory MLL-rearranged acute leukemia demonstrated a reduction in leukemic blasts in approximately 40% of patients, highlighting the limited clinical

Table 1 Main features of the most biologically meaningful histone marks

Histone Modification	Process	Writers	Erasers	Biological Effects	Cancer Associations	References
Methylation	Addition of methyl groups to lysine (K) and arginine (R) residues from S-adenosyl methionine (SAM) of H3 or H4 tails	histone methyltransferases HMTs (KMTs, PRMTs)	histone demethylases (KDMs)	Can activate (e.g., H3K4me) or repress (e.g., H3K27me, H3K9me) transcription	Altered H3K27, H3K4, H3K9, H4K20, H4R3 methylation is documented in multiple cancers (prostate, lung, kidney, breast, pancreatic, gastric and ovarian cancer)	(5–14)
Acetylation	Addition of acetyl group the ϵ -amino group of lysine (K) residues	histone acetyltransferases (HATs)	histone deacetylases (HDACs)	Chromatin relaxation and gene activation	Dysregulated H3K27ac, H4K8ac linked to breast and colorectal cancer; HDAC overactivity in gastric, prostate, lung, liver cancers	(15–23)
Phosphorylation	Addition of phosphate groups to serine (S), threonine (T), tyrosine (Y)	Kinases (e.g., Aurora kinases)	phosphatases (e.g., PP1)	Chromatin remodeling, DNA damage response and cell cycle control	Abnormal H3S10ph associated with breast, gastric, skin cancers, glioblastoma. PKM2-mediated H3T11ph in brain tumors	(24–29)
Ubiquitination	Addition of ubiquitin to histones	E1, E2, E3 ligases (e.g., CRL4B)	deubiquitinatin g enzymes (DUBs)	Regulates transcription and genome stability	CRL4B-mediated H2AK119Ub promotes tumorigenesis with PRC2. Loss of UBR7 (H2BK120Ub) drives triple-negative breast cancer	(30–32)

efficacy of pinometostat as monotherapy and supporting further investigation in combination regimens [41, 42]. In this context of drug combination strategies, several pre-clinical studies continue to provide compelling evidence for pinometostat repositioning in female malignancies, particularly when combined with existing clinically approved therapies [43–46]. Early-phase clinical trials have evaluated PRMT5 inhibitors such as PF-06939999 in solid tumors. In a phase I trial, PF-06939999 demonstrated a favourable safety profile, dose-dependent pharmacokinetics, and robust pharmacodynamic activity, with plasma SDMA inhibition reaching approximately 80% at the recommended phase 2 dose (RP2D). Importantly, early-phase studies have also included patients with cervical and endometrial cancers, suggesting potential efficacy in female malignancies [47].

Targeting epigenetic readers

Epigenetic readers can recognize and decipher the histones epigenetic code *via* specific functional domains such as bromo-, chromo-, tudor-, PHD fingers, ubiquitin binding, and 14-3-3 domains [48]. Thus, epigenetic readers act as “sensors” able to decode histone marks to modulate gene expression in a context-dependent manner. Particularly, they can modulate chromatin structure by recruiting chromatin-remodeling complexes [49] or, alternatively, they can also serve as scaffolds for transcriptional factors repositioning and activity [48]. Like writers, readers are classified based on their functional domains, structure, and molecular tasks. For instance, enzymes with chromodomains (e.g. CHD, HP1) [50], PHD fingers (e.g. TFIID) [51] and Tudor domains (e.g. PHF19) [52] selectively recognize histone methylation marks. Those with bromodomains (e.g. BRD2, BRD4, BRPF1) [52] and PHD fingers (e.g. KMT2D) [53] read acetylated histone tails. Meanwhile, proteins containing UBD (e.g. 53BP1) [54] recognize ubiquitinated histones, and those with 14-3-3 domains (e.g. XRCC1) [54] bind to phosphorylated histones. Their intrinsic properties are currently being leveraged to develop specific inhibitors. An increasing amount of preclinical evidence highlights their pivotal role in key oncogenic processes of female malignancies, including hormone receptor signaling, immune evasion, and chromatin accessibility. For instance, BRD4 has been shown to sustain estrogen receptor (ER) signaling in breast cancer and to promote MYC-driven transcriptional programs in high-grade serous ovarian carcinoma, making it a promising therapeutic target for BET inhibitors [55]. Likewise, PHF19, a PHD finger protein, has been implicated in the regulation of PRC2-mediated repression and tumor progression in endometrial cancer, further supporting the translational interest in reader-targeted therapies [56]. Moreover, preclinical studies have linked BRPF1 overexpression to

enhanced proliferation and poor prognosis in hormone-responsive cancers, including breast and ovarian tumors, suggesting its potential as a therapeutic target for epigenetic intervention [57]. These have focused a clinical interest on first-generation BET inhibitors (BETis), such as RO6870810, that have advanced into clinical trials for both solid tumors and hematologic malignancies [58]. These compounds function as acetyl-lysine mimetics, competitively binding to the bromodomain pocket and displacing BET proteins from chromatin. RO6870810 retains the core thienodiazepine scaffold that confers high affinity for the acetyl-lysine recognition pockets of BRD2, BRD3, BRD4, and BRDT, with reduced off-target interactions and improved solubility and metabolic stability. In a phase I clinical trial involving patients with solid tumors, including independent cohorts of NUT carcinoma (NC) and diffuse large B-cell lymphoma (DLBCL) harboring MYC abnormalities, RO6870810 demonstrated a favorable safety profile, predictable pharmacokinetics, on-target pharmacodynamic modulation, and preliminary single-agent antitumor activity. These results establish proof-of-principle for BET inhibition in MYC-driven cancers and support the continued development of RO6870810 both as monotherapy and in combination regimens [59, 60]. Also in this case, PROTACs-based degraders opened an alternative route to target these epigenetic mediators [34].

Targeting epigenetic erasers

Histone demethylases, deacetylases and ubiquitin-specific proteases (USPs) are involved in chromatin dynamics and architecture by ‘erasing’ several histone marks promoting gene transcription or repression. In recent years, abnormal expressions and function of these enzymes have been linked with the development and progression of multiple neoplasms [61, 62]. Histone demethylases are divided in two different subfamilies: the lysine specific demethylases LSD (KDM1A/1B) are responsible for mono- and di- demethylation and they carry out their enzymatic activity using a C-terminal amine oxidase domain (AOD) through FAD-dependent mechanism [4], while Jumonji C (JmjC) family is involved in all type of methylation removal and its catalytic activity is dependent on two cofactors, 2-oxoglutarate (also known as α -ketoglutarate) and Fe^{2+} [63]. Exploiting the structural and functional features of these enzymes, several inhibitors have been created to suppress their catalytic activity and their oncogenic effects through various mechanisms, such as blocking of cofactors binding or histone substrate competitive inhibition [34]. For example, Kruidenier et al. underlined that GSK-J1/J4, the specific inhibitor of the H3K27me3/me2-demethylases JMJD3/KDM6B and UTX/KDM6A, interferes with the enzymatic activity acting as a competitor for the two

cofactors needed by the enzyme, α -ketoglutarate and Fe^{2+} , but not for the substrate [63]. HDACs catalyze the hydrolyses of acetyl-lysine to yield lysine and acetate [64] and, to counteract their aberrant activity, specific inhibitors have been developed based on their spatial structure, characterized by highly conserved and homologous domains, with a catalytic channel, a zinc cation (Zn^{2+}) and secondary pockets [34]. HDACs inhibitor design is also based on direct targeting the active enzymatic domains or suppressing the cofactors binding [64]. Vorinostat, Belinostat and Panobinostat, for example, are HDAC inhibitors containing hydroxamic acid moieties that chelate Zn^{2+} , directly interfering with their catalytic domain [64], while, disrupting the essential nicotinamide adenine dinucleotide (NAD^+) binding, represent an important strategy to suppress the NAD^+ -dependent HDACs (sirtuins) activity [34]. Drug development targeting histone epigenetic modifiers has traditionally focused on catalytic pocket inhibition and cofactors competitive suppression. However, due to the conserved and complex nature of catalytic pockets, allosteric sites have emerged as promising alternatives [65]. Therefore, enzymes like KDM5A, p300, Gcn5, and PRMT3, containing both catalytic and non-catalytic domains linked by different residues that are distant from the active site, can be exploited for allosteric inhibition [65]. Advances in structural analysis and chemical tools are now enabling the exploration of these sites, offering new therapeutic opportunities. (Fig. 1). USPs represent the major subclass of deubiquitinating enzymes (DUBs), playing a crucial role by removing ubiquitin from target proteins. These influence

epigenetics at multiple levels, for example, USP7 and USP11 regulate Polycomb Repressive Complex 1 (PRC1) activity by modulating ubiquitination of its catalytic subunits, thus influencing gene silencing and chromatin remodeling [66]; USP12 and USP26 modulate androgen receptor (AR) ubiquitination by altering its stability and transcriptional activity, which is critical in prostate cancer progression. Similarly, OTUB1 targets estrogen receptor alpha, affecting its chromatin binding and gene regulation [67]. Recent advances have led to the development of specific inhibitors targeting USPs and other DUBs, which hold therapeutic promise, especially in cancer [68, 69]. These inhibitors aim to disrupt aberrant USP activity by offering a novel strategy for targeted therapy.

Advancements and classification of epi-drugs

To date, three generations of epi-drugs have been developed, with third-generation compounds designed to better account for protein complex interactions, leading to enhanced target specificity. Depending on the target of interest, the best known epi-drugs are classified in: DNA methyltransferase inhibitors (DNMTi) that block DNA methylation performed by DNA methyltransferase enzymes [70, 71], histone deacetylase inhibitors (HDACi) that block histone deacetylation [70], bromodomain and Extra-Terminal protein inhibitors (BETi) [72], histone methyltransferase inhibitors (HMTi) [72, 73] and histone demethylase inhibitors (KDMi) [71, 72]. The PROTAC strategy has recently emerged as a leading innovation in epigenetic therapy, leveraging targeted protein degradation to selectively eliminate pathogenic epigenetic

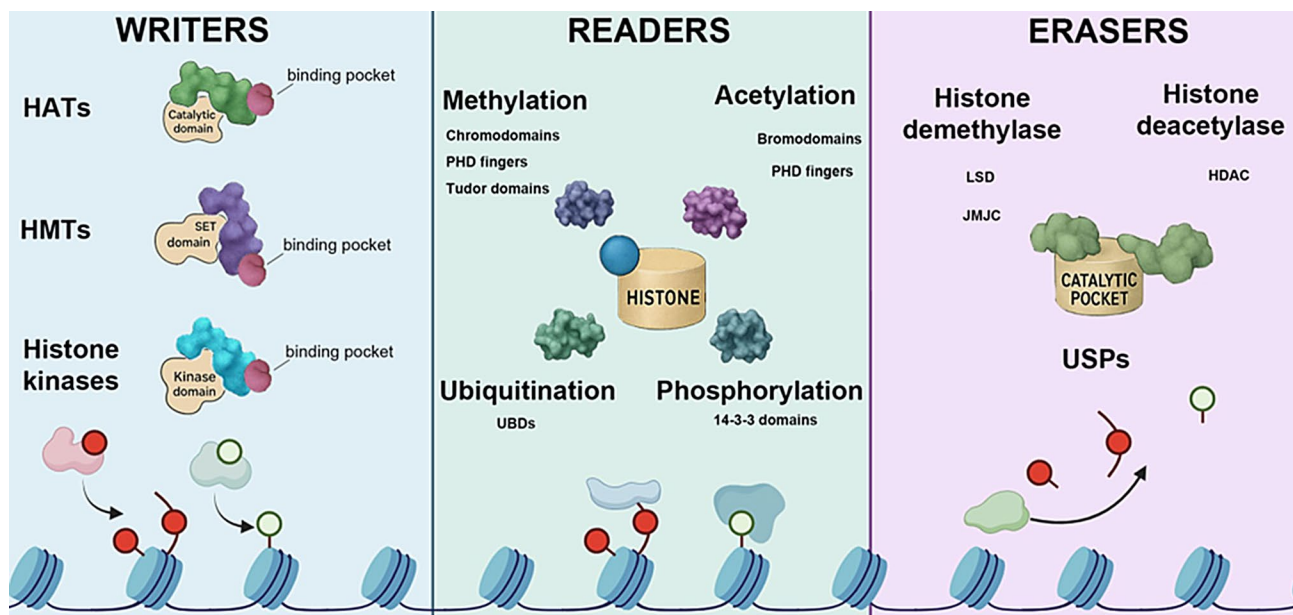


Fig. 1 Targeting epigenetic writers, readers and erasers. The upper part of the panel indicates the targetable domains of each molecule, while the lower part displays the mechanisms of action for each class of molecules

regulators through recruitment of ubiquitin-proteasome system [74], and thus representing a promising therapeutic modality because it does not merely inhibit the activity of a protein but induces its complete degradation in rapid time [75]. The fact that it works by recruiting an E3 ubiquitin ligase to the target protein, leading to ubiquitination and subsequent proteasomal degradation can overcome some limitations such as those related to resistance caused by mutations [76]. In addition to PROTAC, molecular glues represent another class of targeted protein degraders, particularly these are heterobifunctional molecules that link a target protein with the E3 ligase promoting its degradation without requiring a linker [77]. Since PROTACs eliminate the entire target protein rather than just blocking its activity, they may cause side effects from full protein loss, which can disrupt multiple cellular functions. Moreover, PROTAC work catalytically, meaning that one molecule can degrade many target proteins enabling high potency at low doses [78]. Concurrently, multi-target epigenetic drugs are gaining traction by simultaneously modulating interconnected pathways, enabling synergistic combination therapies that address complex disease mechanisms [34]. Recent developments in CRISPR-based epigenome editing technologies offer a novel approach to regulate gene expression without modifying the underlying DNA sequence [79, 80]. Notably, the dCas9-KRAB and dCas9-TET systems have demonstrated promising potential in preclinical models of solid tumors. These systems utilize a catalytically dead Cas9 (dCas9) protein fused to effector domains to modulate gene expression without introducing double-strand DNA breaks. Guided by specific RNAs, the dCas9 complex can localize to targeted genomic regions, where the attached effector domains either activate or repress transcription. The dCas9-KRAB system combines the dCas9's targeting ability with the Krüppel-associated box (KRAB) domain, a strong transcriptional repressor. In contrast, the dCas9-TET system fuses dCas9 with the catalytic domain of ten-eleven translocation (TET) enzymes, promoting DNA demethylation. Both systems have been successfully applied across various cancer models [81, 82]. Their ability to provide spatial and temporal control of gene expression is especially valuable in cancer therapy, where distinguishing malignant from healthy cells is critical.

The therapeutic potential of epigenetic drug repositioning in cancer treatment

The structural and functional deliverability of epigenetic enzymes has provided a strong foundation for epigenetic drug repurposing (DR) strategies. DR, also known as drug repositioning, is the process of finding novel therapeutic applications for existing FDA-approved drugs or compounds in an advanced preclinical setting beyond their original medical indications, relying on either

experimental screening (*in vitro* / *in vivo*) or integrated *in silico* approaches [83].

DR offers a faster and cheaper route to new therapies by exploiting existing drugs with established safety profiles. This approach, particularly for cancer and precision medicine, reduces the costs for development and research [84]. Repurposed drugs can often skip early trials for new uses since their pharmacodynamics, pharmacokinetics, and toxicity assessments are already known, reducing the risk of failure [85]. Consequently, the DR approach represents a valuable strategy for making anti-cancerous drugs readily available to patients at an affordable cost. Potential candidates include non-cancer drugs or drugs approved for other tumor types [86]. Notably, several of these drugs exert a potent anti-cancer activity in hematologic and solid tumors by targeting epigenetic-modifying enzymes, pointing to the clinical potential of epi-drug repurposing in oncology [84, 87]. This approach is currently emerging as a promising strategy to enhance cancer therapy by addressing key clinical therapeutic obstacles, such as tumor progression, immune evasion, and treatment resistance, which are widely known to be also driven by epigenetic imbalance [88]. One of the main drivers of cancer progression is the ability of malignant cells to escape immune surveillance [89]. Epigenetic aberrations contribute to this process by regulating the expression of antigen-presenting major histocompatibility complex (MHC) molecules and immune checkpoint regulators [90]. Repurposed epi-drugs targeting these modifications can stimulate anti-tumor immunity and restore the efficacy of immunotherapies. For example, the DNMTi decitabine, initially approved to reverse abnormal DNA methylation of silenced genes related to cell proliferation and differentiation in acute myeloid leukemia [91], has been involved in upregulation of immune-related genes, including programmed death ligand 1 (PD-L1), in colorectal cancer, thereby enhancing the tumor's susceptibility to PD-1 (programmed cell death protein 1)/PD-L1 blockade therapies [92–94]. The tumor microenvironment (TME), composed of stromal cells, immune cells, and extracellular matrix components, also plays a key role in tumor immune response by regulating the cellular crosstalk [95]. Since epigenetic modifications can modulate the phenotype of cells such as cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs) [96], repurposed epi-drugs can also boost antitumor immunity by targeting them. An example of this is the BETi JQ1. Initially studied in leukaemia for downregulating the expression of the oncogene *c-MYC* [97] and in inflammatory diseases for suppressing inflammatory cytokine expression [98], JQ1 has also demonstrated efficacy in several cancers included ovarian cancer [99], non-small cell lung cancer (NSCLC)

[100] and colorectal cancer [101], by attenuating the suppressive function of Tregs within the TME. An immunosuppressive TME is also supported by tumor metabolic reprogramming, which alters glucose, amino acid, and lipid metabolism to sustain rapid proliferation and survival [102]. This metabolic shift leads to the accumulation of oncometabolites, which act as substrates or cofactors of epigenetic-modifying enzymes and are thereby increasingly recognized as inducers of epigenetic modifications [103]. Notably, although research is still limited, a repurposed role for metformin, an FDA-approved drug for managing type 2 diabetes [104], has been suggested in this context. Specifically, metformin has been shown to suppress the proliferation of breast cancer cells by reducing levels of the oncometabolite 2-hydroxyglutarate (2HG) and the histone methylation related to it [105].

In addition, metabolic reprogramming combined with tumor-induced immune modulation sustains the dissemination of malignant cells [106], another key feature of cancer aggressiveness closely linked to epigenetic alterations [107]. Remarkably, the HDACi vorinostat, approved for regulating genes involved in the progression of cutaneous T-cell lymphoma [108], has been shown to suppress lung metastasis in breast cancer, both in vitro and in vivo [109]. Interestingly, vorinostat has also been found to have a potential role in targeting tumor stemness. Cancer stem cells (CSCs) are a small subpopulation of tumor cells that, due to their high DNA repair capability and the expression of multidrug resistance transporters, contribute to cancer relapse and chemoresistance by driving the differentiation of cancer cells into heterogeneous lineages in response to chemotherapeutics [110, 111]. In this context, it has been reported that vorinostat can reverse cisplatin resistance by decreasing the head and neck CSCs population through the downregulation of *Nanog*, a key transcription factor driving their pluripotency [112]. Beyond re-sensitization to chemotherapy, another useful application of epi-drugs has been reported in overcoming tumor resistance to radiotherapy (RT). The HDACi valproic acid, an FDA-approved drug that treats various neurological and psychiatric disorders, has demonstrated radio-sensitization effects in glioma [113]. Particularly, its mechanism of action has been hypothesized to involve hyperacetylation, which enhances RT-induced DNA double-strand breaks and inhibits DNA damage repair mechanisms, thereby promoting cell cycle arrest and cell death [114]. Altogether, the above-mentioned evidence highlights how epi-drugs repurposing represents a powerful strategy within precision oncology to target key cancer-driving processes by rewiring the cancer epigenome. (Fig. 2).

Treatment landscape and drug resistance in female cancers

Female malignancies comprise various cancers affecting women. Particularly, the most common include gynecologic cancers originating in reproductive organ (cervix, ovaries, uterus, vagina, vulva) and breast cancer, being the most prevalent neoplasm in women. Generally, the main treatment strategies for female malignancies include:

- Surgery, often the first line treatment and usually combined with other therapies.
- Chemotherapy, used to eradicate cancer cells and may be administered before (neoadjuvant) or after (adjuvant) surgery. For breast cancer patients this is commonly used especially for higher-stage or more aggressive subtypes [115]. For ovarian cancer patients, platinum-based chemotherapy is the standard gold treatment, but resistance phenomena occur in about 20% of cases significantly impacting survival [116].
- Radiation, used either as a primary treatment or after surgery to reduce recurrence risk.
- Hormone therapy, employed for hormone receptor-positive breast and endometrial cancers. Drugs like tamoxifen or aromatase inhibitors are used to block hormone-driven tumor growth [115].
- Targeted therapy, an example are PARP inhibitors, used for ovarian cancer treatment especially in patients with BRCA mutations or homologous recombination deficiency, or the use of trastuzumab for HER2-positive breast cancers [117].
- Immunotherapy, now part of frontline treatment for advanced endometrial, cervical, and triple-negative breast cancers, including immune checkpoint inhibitors and, in clinical trials, CAR-T and TIL therapies for breast cancer [117].

The effectiveness of therapeutic response varies by cancer type, stage at diagnosis, and individual patient factors. Of course, early-stage cancers often have high cure rates with surgery and/or radiation. In contrast, advanced or metastatic diseases carry significantly lower survival rates. These kind of cancers are characterized by complex and multifactorial processes that severely limit the effectiveness of current therapies. Furthermore, resistance can be intrinsic (pre-existing) or acquired (developed during treatment), and arises from a dynamic interplay of genetic mutations, tumor heterogeneity, microenvironmental factors, metabolic adaptation, and regulatory RNA networks. For this reason, ongoing researches continue to refine therapeutic strategies, particularly for resistant or recurrent disease [118]. Epigenetic drugs offer a novel avenue to modulate gene expression and

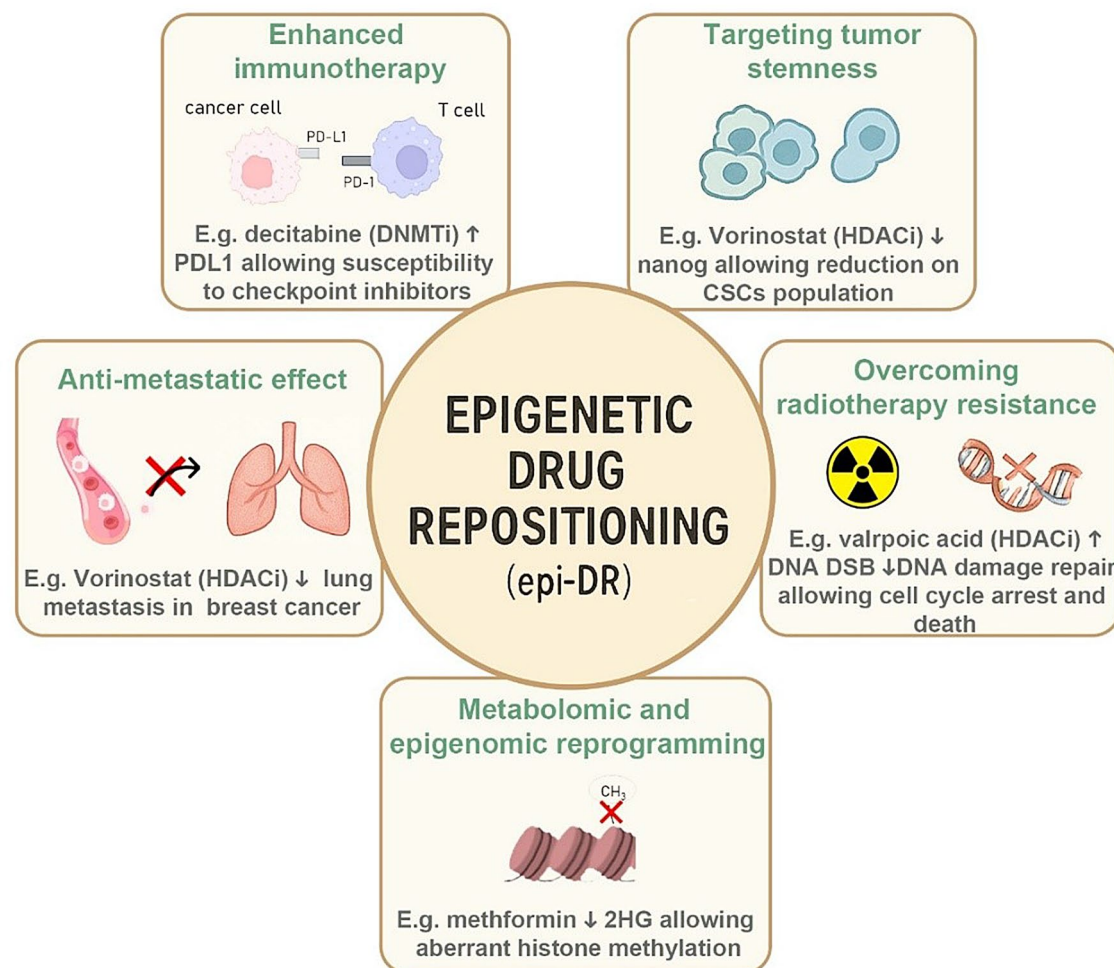


Fig. 2 Therapeutic potential of repositioned epigenetic drug. Main examples of mechanisms of action observed following epi-drugs repurposing

overcome drug resistance in female malignancies by targeting reversible epigenetic changes. While still largely investigational, they hold potential to enhance the effectiveness of existing treatments, particularly in recurrent or resistant ovarian, endometrial, cervical, and breast cancers.

Clinical applications and repositioning of epi-drugs in female malignancies

Epi-drugs have expanded the therapeutic landscape and the clinical outcomes for various cancer patients and particularly in those suffering with gynecological and breast malignancies. For this reason, some have been repositioned for other definite treatments. As of now, the FDA has approved specific epi-drugs to target cancer (Table 2):

DNMT inhibitors (DNMTi), such as azacitidine and decitabine. Azacitidine is a pyrimidine nucleoside analog of cytidine that, when incorporated into the DNA of cancer cells, decreases DNA methylation and subsequently alters the expression of tumor suppressor genes.

As of now, this compound is FDA-approved for treating myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia [34]. Particularly, this is used in adult patients who are unable to complete intensive chemotherapy cycles [119, 120]. Decitabine is a deoxycytidine analog that can be incorporated into DNA and inhibits DNMT activity, reducing methylation and promoting the expression of silenced tumor suppressor genes [120]. This drug has a dual mechanism of action: at low doses, it can promote the expression of tumor suppressor silenced genes, while at high doses has a cytotoxicity effect [121]. This dual activity has sparked interest in investigating hypomethylating agents as antineoplastic drugs also in other kinds of cancer [122]. For this reason, these were repositioned and now are in clinical trial for the management of other kinds of neoplasms. Decitabine and azacitidine are also in clinical trial for the management of cervical and epithelial ovarian cancers, often in combination with immune checkpoint inhibitors [123, 145]. In breast cancer (BC), it was examined whether this class of compounds can reverse gene silencing,

Table 2 FDA-approved epi-drugs to target cancer

Class	Drug(s)	Mechanism of Action	FDA-approved uses	Repositioning in ongoing trials	Treatments	References	
DNMT Inhibitors (DNMTi)	Azacitidine	Inhibit DNMTs by incorporating into DNA, leading to hypomethylation and reactivation of silenced tumor suppressor genes	Myelodysplastic Syndrome	ER+ BC	azacitidine + Tamoxifen	(34,119–125)	
	Decitabine			TNBC	decitabine + PD-L1 inhibitors		
			AML	Cervical and OC	Azacitidine/ decitabine + immune-checkpoint inhibitors		
			CMML	HR+/TNBC	azacitidine + entinostat		
HDAC Inhibitors (HDACi)	Vorinostat	Block the zinc ion in the catalytic site of HDACs preventing substrate access and enzymatic activity	CTCL (Vorinostat, Romidepsin)	BC	Vorinostat + tamoxifen	(124,126–139)	
	Romidepsin				Entinostat + exemestane		
	Belinostat				Panobinostat + doxorubicin		
	Panobinostat		PTCL (Belinostat)	Endometrial/ OC	Panobinostat		
	Valproic Acid			Cervical and OC	Valproic Acid		
	Ricolinostat		MM (Panobinostat)	Platinum-resistant OC	Ricolinostat		
	Entinostat						
HMT Inhibitors (HMTi)	Tazemetostat	Inhibits EZH2 blocking H3K27me3, reactivating silenced genes	Epithelioid Sarcoma	Endometrial and OC	Tazemetostat	(140–144)	
			Follicular Lymphoma				

particularly, the combination of azacitidine and tamoxifen was investigated for overcoming the occurrence of endocrine therapy (ET) resistance [124]. Furthermore, these molecules were investigated also in triple negative breast cancer for the improvement of immune checkpoint therapy response; in a specific phase II clinical trial, decitabine has been tested in combination with PD-L1 inhibitors (pembrolizumab). The combined treatment may enhance breast cancer sensitivity to standard neo-adjuvant chemotherapy by promoting tumor-infiltrating lymphocytes recruitment to tumor tissue [125]. Another DNMTi is hydralazine, a well-known antihypertensive drug. This has emerged as a promising candidate for repurposing in female malignancies due to its epigenetic modulation properties; in fact, this can inhibit DNMTs and synergize with HDACi, reactivating tumor suppressor genes silenced by hypermethylation such as CDKN2A and APC, which are critical in breast and cervical cancers [146, 147]. In a Phase II clinical trial, the combination of hydralazine and magnesium valproate with chemotherapy (doxorubicin and cyclophosphamide) in patients with stage IIb–IIIA breast cancer resulted in both partial and complete responses, showing low toxicity levels [148].

HDAC inhibitors (HDACi). These drugs act by blocking zinc-dependent HDAC enzymes, causing histone hyperacetylation. This relaxes chromatin by weakening the histone-DNA interaction, making accessible certain genomic regions and allowing their transcription [126]. The acetylation has a dual effect: it can activate certain

genes, such as pro-apoptotic or tumor suppressor genes, while simultaneously repressing others, including oncogenes [139]. Among others, vorinostat and romidepsin were approved for the treatment of cutaneous T-cell lymphoma, belinostat was used for peripheral T-cell lymphoma and panobinostat for multiple myeloma [135–138]. Concerning repositioning, the panobinostat is currently studied in ovarian and endometrial cancers, also in combination with chemotherapy [133, 134]. In a clinical trial for ovarian and cervical cancer treatment, the efficiency of valproic acid was tested, often in combination with chemo- or immunotherapy [132], while the ricolinostat, a selective HDAC6 inhibitor, is currently studied in ovarian cancer, particularly for platinum-resistant cases [131]. Vorinostat was described to reactivate Estrogen Receptor alpha (ER α) in MDA-MB-231 cell lines, restoring sensitivity to ligands like tamoxifen or aromatase inhibitors [130]. In a phase II trial, vorinostat was combined with tamoxifen showing clinical benefit in metastatic ER α positive breast cancer [129, 130]. A phase III trial proposed to investigate the effect of the combination of entinostat (not yet approved by FDA) with exemestane in patients with locally advanced or metastatic breast cancer who have experienced disease progression after non-steroidal aromatase inhibitors. This study aimed to confirm preclinical and clinical evidence supporting the use of HDAC inhibitors to overcome resistance to endocrine therapy in breast cancer, to enhance outcomes of patients with advanced disease

[128]. Furthermore, the combination between panobinostat and doxorubicin was investigated in triple negative breast cancer with aggressive tumor biology [127, 130]. In another phase II clinical trial, it was tested the combination of the DNMTi 5-azacitidine and the HDACi entinostat in women with advanced hormone-resistant or triple negative breast cancer. Partial responses were observed only in the hormone-resistant cohort. Tumor analysis pre- and post-treatment showed estrogen receptor modulation in about 50% of post-treatment biopsies from hormone-resistant patients, suggesting that a subset of women may benefit from this epigenetic therapy alone or in combination [124].

HMT inhibitors (HMTi). They are a class of epigenetic drugs that act by inhibiting methyltransferase enzymes that add methyl groups to histone proteins, thus modulating chromatin structure and gene expression. An example of this class of compounds is the HMTi able to block enzymes like EZH1/2 (components of PRC2

complex), which catalyze H3K27me₃, a mark linked to transcriptional silencing [140, 144]. Among these, tazemetostat, that specifically targets EZH2, was FDA-approved for the treatment of epithelioid sarcoma and follicular lymphoma [142, 143]. In female malignancies, its efficiency in treating endometrial and ovarian cancer patients has been tested [141] (Fig. 3).

Bridging molecular insights with technological advances: the role of high throughput epigenomics and computational approaches

Significant progress has been made in elucidating the role of histone PTMs and their potential as therapeutic targets, but the full exploitation of these findings in clinical practice has required a robust and progressive convergence of bench-based technologies and bioinformatics approaches toward clinical translation. The development of omics-based “wet” approaches for profiling histone modifications has led to the emergence of two

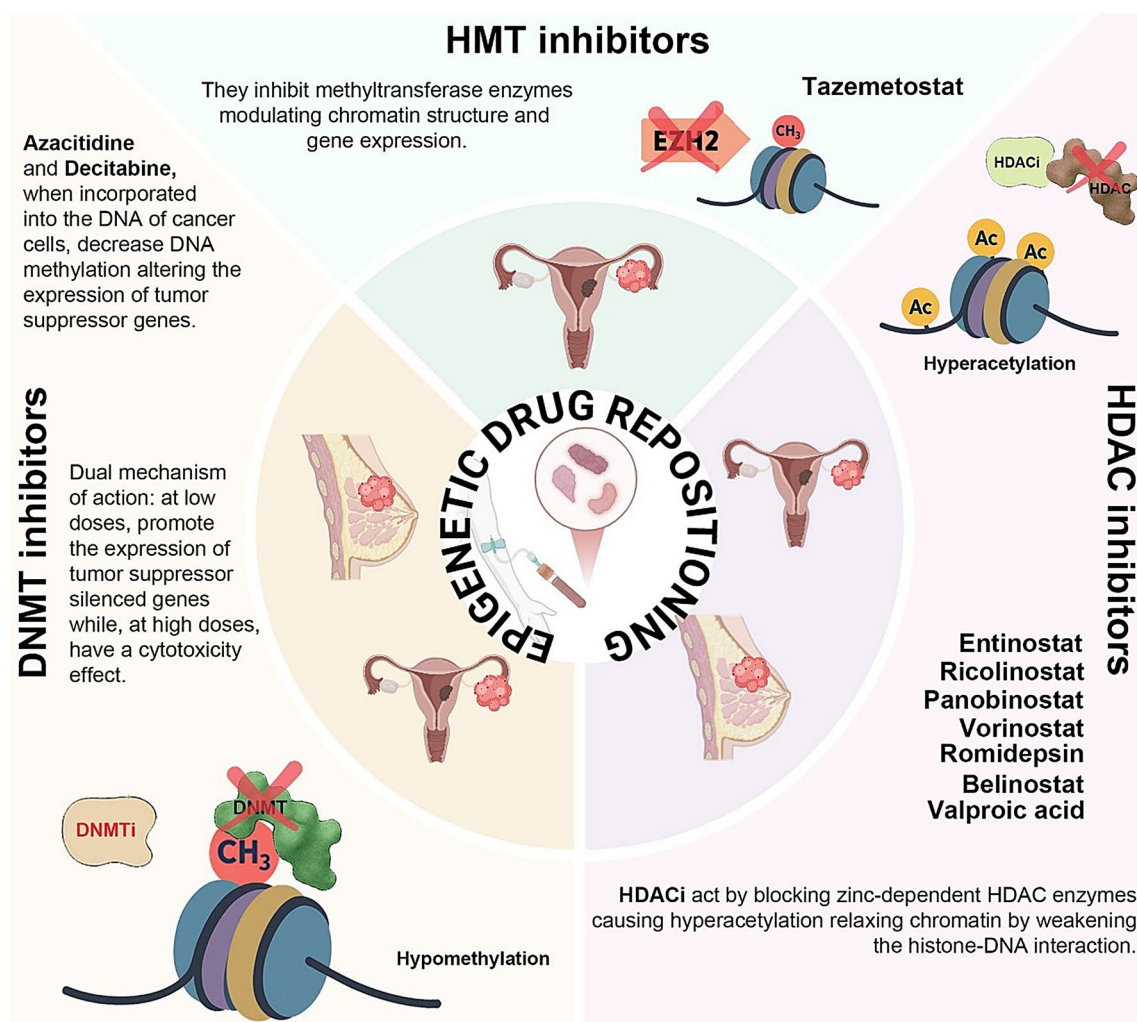


Fig. 3 Clinical application of FDA-approved repositioned epi-drugs. The figure highlights key examples of FDA-approved drug classes, including HMT, DNMT, and HDAC inhibitors. For each class, the mechanism of action is described and illustrated, together with the main representative compounds

major methodological frameworks: population-averaged profiling techniques, collectively referred to as bulk approaches, and high-resolution cell-specific platforms known as single-cell strategies, each with distinct advantages and limitations [149, 150]. Bulk approaches, such as chromatin immunoprecipitation sequencing (ChIP-seq), provide high-resolution maps but require large cell numbers and extensive optimization. Newer techniques like Cleavage Under Targets & Release Using Nuclease (CUT&RUN) and Cleavage Under Targets and Tagmentation (CUT&Tag) reduce background noise and enable profiling from low-input or single-cell samples [151–153]. In single-cell contexts, scCUT&Tag has emerged as a promising tool to profile histone marks with spatial and cell-type specificity, although technical challenges such as sparsity and batch effects still persist [154]. The integration of single-cell histone modification data with transcriptomics, methylomics, and chromatin accessibility data (e.g., via single-cell ATAC-seq) enables the construction of multi-dimensional regulatory maps that clarify the relationship between epigenetic states and cellular phenotypes [155]. These integrative approaches are increasingly being used to identify epigenetic signatures associated with cancer cell plasticity, therapy resistance, and metastatic potential. Collectively, these methods form the basis for linking chromatin states to gene regulation, therapeutic targets, and clinical phenotypes in cancer epigenomics. A comparative summary is provided in Table 3.

Databases The advent of large-scale bioinformatics resources has substantially advanced the study of histone modifications in cancer, providing critical links between basic chromatin biology and translational applications. Several publicly available bioinformatics resources facilitate the analysis of histone modifications, epigenetic alterations, and their clinical implications. The ENCODE repository provides comprehensive, genome-wide maps of regulatory elements, including histone marks [163, 164]. The Cancer Genome Atlas (TCGA) integrates multi-omics data across major tumor types, often coupled with epigenetic profiles [165]. MethSurv and MEXPRESS enable the visualization of DNA methylation and gene expression correlations in cancer cohorts, while cBioPortal and GSCALite offer user-friendly platforms for exploring genomic, epigenetic, and clinical associations [166–168]. A comparative overview is provided in Table 4. Importantly, the availability of these curated, multi-dimensional datasets offers an important source of data as well as a training ground for the application of artificial intelligence (AI) and machine learning (ML) models in epigenetic oncology [171, 172]. By providing high-quality, annotated inputs, including histone modification profiles, enhancer maps, and chromatin state segmentations,

these databases facilitate the training of predictive models for patient stratification, therapeutic response prediction, and drug repositioning strategies as indispensable pillars of the next generation of AI-driven precision medicine initiatives.

The evolving role of multi-omics tools in translational and clinical research

In recent decades, the emergence and progressive maturation of multi-omics technologies have radically transformed the landscape of biomedical research, promoting the systematic integration of data derived from the genome, epigenome, transcriptome, and proteome. This methodological revolution has led to the development of several bioinformatics platforms dedicated to the integrated analysis of these informational layers. These tools have proven fundamental in preclinical research for defining molecular subtypes, identifying biomarkers, and understanding complex pathological mechanisms, particularly in oncology. Within the important Bioconductor project, which aims to develop and share open-source software for precise and reproducible analysis of biological data, many powerful tools for data analysis are available. Among them are iCluster/iClusterPlus, which integrate genomics, transcriptomics, and epigenomics data through sophisticated statistical modeling implemented in the R language to reveal distinct biological subgroups and identify biomarkers with potential clinical significance [173]. Likewise, Similarity Network Fusion (SNF) employs network-based methods to merge various omics layers, including mutations, gene expression, and DNA methylation, into unified similarity networks, enhancing the identification of biologically and clinically relevant patient subgroups [174]. There are also multivariate analysis tools such as mixOmics and STATegra, which offer structured pipelines capable of exploring correlations across multiple omics datasets. In particular, MixOmics facilitates multivariate exploratory analyses such as Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression, whereas STATegra offers a stepwise integration approach combining component analysis with non-parametric statistical techniques, promoting reproducible and comprehensive data integration [175, 176]. Furthermore, recent years have seen the development of emerging platforms that incorporate ML and DL approaches, leveraging complex multi-omics profiles to predict drug targets and patient-specific drug responses. Among these are StarGazer that offers an interactive web interface, and DeepDRA that is currently available as a source-code tool requiring programming expertise [177, 178]. Parallely, several platforms specifically tailored for clinical and translational research have emerged, providing user-friendly environments for investigating relationships between molecular profiles

Table 3 High-throughput methods in cancer epigenomics

Technique	Advantages	Limitations	Bulk/Single-cell	Reference
ChIP-seq	High genome-wide coverage; well-established	Requires high input; low resolution; poor for heterogeneous samples	Bulk	156
CUT&RUN	Low background; works with few cells	Requires fresh/frozen samples; some antibody constraints	Both	152
CUT&Tag	Very low input; high resolution; compatible with single cell	Sensitive to transposase bias; relies on antibody quality	Both	153
CUTAC	High signal in accessible chromatin	Limited to open regions	Bulk/Low input	157
FabLEM	Live-cell compatible; dynamic tracking	Qualitative; not genome-wide	Single-cell	158
Fiber-seq	Multi-layer info (PTMs, methylation, nucleosomes)	Requires specialized equipment; complex data	Single-molecule	159
HiChIP/PLAC-seq	Maps 3D enhancer-promoter interactions	Lower resolution in some contexts; bulk-based	Bulk	160
CUT&Tag2for1	Simultaneous profiling of two marks	Limited to validated combinations	Single-cell	161
CUT&RUN-LoV-U	Enhanced efficiency in low-input and difficult samples	Requires optimization for different contexts	Bulk/Low input	162

and clinical outcomes, including patient survival and therapeutic responses. One widely used example is cBioPortal which integrates and visualizes extensive genomics, transcriptomics, and epigenomics datasets from large patient cohorts, enabling clinicians and researchers to analyze genetic alterations, explore co-occurrences, and assess their prognostic implications [167]. There are also platforms like MethSurv and MEXPRESS that focus on DNA methylation analysis within prognostic contexts, offering rapid and intuitive tools for correlating epigenetic changes with patient survival and other clinical parameters across numerous cancer types [169, 170]. Meanwhile, specialized tools such as PROGmiRV2, OncoLnc, and TANRIC emphasize non-coding RNA analyses, integrating microRNA and long non-coding RNA (lncRNA) expression data with survival outcomes. TANRIC notably provides additional modules to explore differential lncRNA expression between cancerous and normal tissues, the effects of driver mutations, and the broader implications for tumor-related pathways [179–181]. Some platforms focused on proteomics, such as The Cancer Proteome Atlas (TCPA) and its related tool TRGAted integrate protein expression data from Reverse Phase Protein Arrays (RPPA) with genomic and clinical

Table 4 Publicly available bioinformatics database resources

Database/ Tool	Focus	Key Features	Reference
ENCODE	Functional genomics	Histon marks, enhancer, TF binding	164
TCGA	Cancer genomics	Multi-omics (DNA, RNA,epigenetics, clinical)	165
cBioPortal	Cancer genomics visualization	Genomics, mutations, copy number, clinical data	167
MethSurv	DNA methylation	Survival analysis based on methylation profiles	169
MEXPRESS	Expression and methylation	Visualization of methylation-expression correlations	170
GSCALite	Genomics and pathway analysis	Mutation, expression, methylation across cancers	168

information, facilitating comprehensive pan-cancer prognostic analyses through interactive and intuitive web interfaces [182, 183]. Lastly, comprehensive multi-omics integration tools like GSCALite offer detailed gene set analyses across multiple cancer types, dynamically linking gene expression, genomic alterations (SNV, CNV), methylation status, and pathway-level information to survival and therapeutic response predictions [168] (Table 5).

The usefulness and ease of use of these integrated multi-omics tools vary significantly depending on the research context. While algorithmically sophisticated platforms such as iCluster and SNF are primarily applied in preclinical research settings due to their requirement for advanced bioinformatics skills, translational and clinical platforms like cBioPortal, MethSurv, and GSCALite are increasingly becoming integral to clinical practice and research, marking a pivotal convergence between multi-omics big data analytics and practical medical applications.

Predictive modelling of epigenetic drug sensitivity/ repositioning through artificial intelligence and multi-omics platforms

Translational bioinformatics plays a crucial role in linking clinical and molecular data to identify novel uses for existing drugs. The use of computational models and AI enables the analysis of large databases of drugs and biomarkers to identify new therapeutic indications. In particular, off-target analyses, which reveal secondary drug interactions, can uncover unanticipated anticancer properties [184]. AI approaches, including ML and deep learning (DL), have facilitated the integration of multi-omics data including genomics, transcriptomics, epigenomics, and proteomics by significantly improving DR, particularly in the context of epigenetic therapies [185, 186]. Although many of these models remain

investigational and are not yet implemented in routine clinical settings, their capacity to extract predictive features from complex biological data renders them highly valuable for early-phase translational studies and rational therapeutic hypothesis generation [187–189]. Platforms such as PubChem, DrugBank, ChEMBL, and the Drug Repurposing Hub are commonly integrated into ML pipelines for identifying drug–target interactions, often supported by molecular docking and quantitative structure–activity relationship (QSAR) models [190]. A recent example is CHANCE, a supervised ML model using gradient-boosted trees to predict anticancer potential of non-oncological drugs by integrating coding/non-coding mutations into protein–protein interaction networks. The model holds potential for personalized therapy as it incorporates increasingly complex genomic and pharmacological datasets [184]. Nevertheless, multi-omics pipelines face critical data-quality challenges, such as batch effects and data lack, which can compromise downstream reproducibility [191]. To reinforce the clinical reliability of AI/ML/DL predictions, interpretability frameworks are essential. Among them, SHAP (SHapley Additive exPlanations) has emerged as a gold-standard method to validate model behaviour by quantifying the contribution of each input feature to a given prediction [192]. SHAP not only improves model transparency but also allows researchers to verify whether predictions are biologically plausible (e.g., driven by known histone marks), enhancing clinical confidence in model outputs. A compelling example is provided by Ocelot, a framework that models histone modification patterns across tissues using XGBoost and SHAP. This approach revealed asymmetric dependencies between histone marks; for instance, H3K27me3 showed stronger predictive power than H3K27ac in certain repressive contexts, highlighting the biological interpretability of model outputs [193]. Ultimately, incorporating SHAP-based validation into

Table 5 Multi-omics tools in translational and clinical cancer research

Tool	Primary Function	Setting	Ease of Use
iCluster/iClusterPlus	Multi-omic clustering and biomarker identification	Preclinical	Moderate (R knowledge)
SNF	Network-based fusion for multi-omic subgroup identification	Preclinical	Moderate (R knowledge)
mixOmics	Multivariate analysis and prediction modeling (PCA, PLS)	Preclinical	Moderate (well-documented R package)
STATegra	Stepwise pipeline for comprehensive multi-omic integration	Preclinical	Moderate (Bioconductor package)
StarGazer	Drug target prioritization and repositioning analysis	Preclinical	High (interactive web interface)
DeepDRA	Deep learning-driven drug response prediction across datasets	Preclinical	Moderate (Python knowledge)
cBioPortal	Interactive exploration of cancer genomic and clinical data	Clinical/Translational	High (intuitive, clinician-friendly web platform)
MEXPRESS	DNA methylation-gene expression correlation and survival analysis	Clinical/Translational	High (user-friendly visualization tools)
MethSurv	Prognostic survival analysis based on DNA methylation data	Clinical/Translational	High (easy-to-use web platform)
PROGmiRV2	Pan-cancer prognostic analysis of microRNAs using TCGA/GEO data	Clinical/Translational	High (accessible web-based analysis)
OncoLnc	Survival analysis and prognostic insights from lncRNA expression data	Clinical/Translational	High (simple, interactive web interface)
TANRIC	Comprehensive multidimensional analysis of lncRNAs	Clinical/Translational	High (interactive, user-friendly modules)
TCPA/TRGated	Integrated proteomic, genomic, and clinical prognostic analysis	Clinical/Translational	High (interactive, web-based queries)
GSCALite	Comprehensive gene set analysis across multiple cancer datasets	Clinical/Translational	High (dynamic, interactive visualization tools)

epigenetic ML pipelines bridges the gap between prediction accuracy and biological credibility, a crucial step for clinical translation. In oncological pharmacogenomics, traditional ML algorithms are used to analyze high throughput data and support treatment selection. Algorithms such as support vector machines (SVMs), random forests (RFs), logistic regression, k-nearest neighbors (k-NN), and gradient boosting are commonly used to classify tumor subtypes, predict patient response, and identify repositionable epigenetic drugs [186, 187]. In gynecologic tumors like ovarian cancer, ML classifiers trained on TCGA methylation and expression profiles successfully identified patients responsive to HDAC inhibitors such as vorinostat and entinostat [185]. Furthermore, ML-derived signatures have been employed to

reposition drugs for rare tumors like clear cell ovarian carcinoma and uterine carcinosarcoma by integrating data from ReDO_DB and PDX Finder [194, 195]. Instead, DL approach, a subfield of ML, has emerged as a transformative tool in biomedical research due to its ability to automatically extract multi-level features from large-scale, heterogeneous datasets [196]. Unlike conventional ML approaches, which require manual feature engineering and predefined input structures, DL models can process raw data directly, identifying complex non-linear associations across multiple biological layers such as genomics, transcriptomics, and epigenomics [196, 197]. DL models, particularly convolutional and recurrent neural networks, have demonstrated superior performance in tasks involving unstructured data such as images,

genomics sequences, and multi-omics profiles. Their ability to integrate and model complex relationships across various biological layers makes them particularly suited for epigenetic research and drug repositioning efforts [198, 199]. One of the most comprehensive approaches is DeepDRK, a deep learning framework specifically designed to predict anticancer drug response combining genomic mutations, gene expression, and drug structural features using a kernel-based similarity approach [200]. These representations are used to train a deep neural network (DNN) to classify cancer cell lines (CCL)-drug pairs into sensitive, resistant, or unclear based on binarized experimental drug response data. Importantly, when applied to TCGA patients, DeepDRK identified breast cancer patients likely to respond to repositioned agents such as vorinostat based on their epigenetic similarity to sensitive cancer cell lines. Moreover, in uterine corpus endometrial carcinoma, the same drug showed poor predictive response, likely due to higher intratumoral heterogeneity and insufficient representation in the training dataset [189]. Other models like DeepChrome, a convolutional neural network (CNN)-based framework designed to predict gene expression levels from ChIP-seq profiles of five core histone marks (H3K4me3, H3K4me1, H3K36me3, H3K9me3, H3K27me3) profiled across 56 cell types in the REMC (Roadmap Epigenomics Mapping Consortium) database [201, 202]. The input matrix is constructed by binning signal intensities in a 10,000 bp window around the transcription start site (TSS), capturing both local and long-range regulatory patterns [201]. Notably, DeepChrome includes an optimization-based visualization module to identify which combinations of marks (e.g., H3K4me3+H3K36me3) are most predictive of high expression, and which repressive combinations (e.g., H3K27me3+H3K9me3) contribute to gene silencing [201, 203]. Although developed using cancer cell line data, these chromatin patterns are consistent with epigenomic features observed in primary tumors from TCGA [204], supporting the translational relevance of histone-based predictive models for drug response. Particularly, genes in breast cancer with active chromatin (H3K4me3/H3K36me3) may respond to HDACi like vorinostat, targeting acetylation-enriched transcriptional landscapes [201, 204, 205]. In another study, a multi-task neural network was trained on data from the Cancer Cell Line Encyclopedia (CCLE) and GDSC databases. This model integrated copy number variations, mutations, expression data, and methylation profiles, achieving an $R^2=0.90$, that is, the model was able to explain 90% of the variability in the prediction of drug response, and identified candidate repositioned drugs with epigenetic modes of action, such as vorinostat and entinostat, in various solid tumors [188]. The Dr.VAE model (Drug

response Variational Autoencoder) introduced a semi-supervised approach using transcriptomic data before and after drug perturbation. Although it initially focused on gene expression, the framework could be extended to integrate histone acetylation or methylation marks, particularly valuable in predicting response to epigenetic modifiers in resistant tumors [206]. More recently, graph-based DL approaches such as GraphDRP and GraOmicDRP have emerged. These models combine protein-protein interactions, mutation profiles, and chromatin accessibility data to predict the effect of existing drugs in new indications. When applied to HDACi and DNMTi, these methods revealed differential sensitivities across tumor types with distinct histone modification profiles [207]. Finally, novel strategies leveraging large language models (LLMs) such as GPT-4 have been proposed to annotate and stratify clinical trial outcomes, improving the quality of datasets for drug repositioning [208]. By systematically classifying therapies as “positive” or “negative” based on real-world efficacy and toxicity, these AI-driven approaches could refine drug repurposing pipelines across oncology and other diseases. These methods are still primarily applied in preclinical settings, but their ability to generate biologically interpretable predictions makes them valuable tools for guiding experimental validation and drug prioritization in early-phase epigenetic research, as they are capable of decoding epigenetic complexity associated with therapeutic repurposing.

AI-driven platforms and practical successes in epigenetic drug repositioning

Beyond theoretical frameworks, several AI and ML platforms have already demonstrated real-world utility in drug repositioning, offering scalable solutions that bridge preclinical insights with clinical translation [209]. These technologies range from enterprise-level systems to open-source toolkits, all designed to support the discovery and prioritization of repurposable epigenetic therapies. *PandaOmics*, the multimodal AI platform developed by Insilico Medicine, integrates transcriptomics, genomics and text features to rank disease drivers and suitable compounds; its workflow has already uncovered 28 repurposable ALS targets and progressed the *de novo*-designed TNIK inhibitor ISM001-055, derived from a repositioning hypothesis for idiopathic pulmonary fibrosis, into a phase II trial, providing a real-world proof-of-concept for end-to-end AI acceleration [210, 211]. Graph-based reasoning at a population scale is exemplified by the BenevolentAI Knowledge Graph, which linked the JAK inhibitor baricitinib to viral endocytosis pathways and correctly predicted its clinical utility against COVID-19, a result later confirmed in the ACTT-2/COV-BARRIER trials [212]. Earlier natural-language

and semantic-network solutions such as IBM Watson for Drug Discovery have likewise demonstrated value, identifying previously unknown ALS genes that now serve as anchors for repurposing screens [213]. For laboratories that need deployable code rather than full SaaS ecosystems, the open-source DeepPurpose toolkit offers pretrained deep-learning models for drug-target interaction prediction that can be fine-tuned on histone-modifying enzymes with only a few lines of Python [214]. Polypharmacology-oriented platforms such as Cyclica's Ligand Express exploit inverse docking combined with deep learning to expose proteome-wide off-target profiles; this capability is particularly relevant to epi-drugs, whose promiscuous binding often underlies new therapeutic effects and safety liabilities [215]. Finally, heterogeneous-network engines like Project Rephetio/Hetionet, which integrates more than two million curated biomedical relationships, provide disease-agnostic scoring of 755 approved drugs and can be interrogated to prioritise histone-deacetylase or DNA-methyltransferase inhibitors for novel indications based on network-proximity metrics [216]. Collectively, these AI/ML platforms provide a scalable toolbox, from cloud-based enterprise suites to open libraries, that can systematically uncover, rank and mechanistically rationalise repositioning opportunities for the expanding arsenal of epigenetic therapeutics.

Future challenges in integrating epigenetic targeting into clinical treatment of solid tumors

The integration of drug repurposing with epigenetic therapies offers promising new avenues for cancer treatment, particularly for solid tumors [88]. However, several challenges remain before these approaches can be fully implemented in clinical practice. Key obstacles include the heterogeneity of epigenetic markers across cancers, which complicates the design of targeted therapies. This diversity requires the development of personalized treatments tailored to each patient's unique genetic profile [217]. Fine-tuning repurposed drugs to target specific epigenetic alterations in tumors is essential to improving treatment efficacy. Another challenge is the integration of multi-omics data with AI-driven models. While omics technologies can reveal novel therapeutic targets, the heterogeneity of these datasets complicates their integration, limiting the accuracy of AI predictions. Standardizing data formats and refining computational models will be crucial for making AI-driven models more effective in predicting therapeutic outcomes [218]. The validation of repurposed drugs in new cancer settings is also a significant hurdle. Although repurposed drugs can leverage existing safety data, they still require thorough evaluation to prove their efficacy and safety for new indications. Regulatory bodies may mandate further clinical trials or real-world evidence to back their approval, which can

increase both the time and cost of development [219]. The lack of substantial funding from the private sector, combined with long regulatory approval timelines, places a heavy burden on universities and non-profit organizations [220]. Increased investment is needed to facilitate large-scale trials and validate these drugs for regulatory approval.

Ethical considerations are paramount as AI continues to play a role in drug repurposing. EHR systems within the European Health Data Space (EHDS) enable secure and cross-border exchange of health data, while ensuring patient ethical protection through informed consent, control over personal data, data security, and compliance with GDPR (General Data Protection Regulation) privacy regulations (DOI: [https://doi.org/10.1016/S2589-7500\(23\)00156-5](https://doi.org/10.1016/S2589-7500(23)00156-5)). Ensuring transparency and interpretability of AI models is key to maintain trust in these tools for clinical decision-making [217].

Conclusions

Among epigenetic mechanisms, histone modifications are emerging as particularly attractive targets for therapeutic intervention. Histone marks, such as acetylation, methylation, phosphorylation, and ubiquitination are dynamically regulated and frequently dysregulated in female malignancies, contributing to key oncogenic processes including proliferation, immune evasion, metastasis, and drug resistance [221–224]. Targeting histone modifications with epigenetic drugs, such as histone deacetylase inhibitors (HDACis) and bromodomain inhibitors (BET inhibitors), offers several clinical advantages: these agents are generally versatile, since they can be easily combined with chemotherapy, immunotherapy, or targeted therapies [225–227]. Furthermore, the repositioning of epi-drugs targeting histone regulators may offer a strategic advantage in overcoming therapy resistance, a major limitation in the management of the above-mentioned tumors. In fact, aberrant chromatin remodeling is increasingly recognized as a driver of both intrinsic and acquired resistance to conventional therapies, including hormone therapies, tyrosine kinase inhibitors, and immune checkpoint blockade [228, 229]. Finally, recent advances in spatial and single-cell transcriptomics offer new opportunities to resolve inter-tumoral heterogeneity and better capture epigenetic reprogramming events associated with drug resistance [230–232]. Notably, AI nowadays represents the “ace up the sleeve” of translational research, accelerating the integration of multi-omics analyses, biomarker discovery, and drug development pipelines across both preclinical and clinical phases. AI-powered drug repositioning strategies have led to tangible clinical successes. For instance, recent analyses highlight that AI-discovered or AI-repurposed molecules show an 80–90% success rate in Phase

I trials, demonstrating how AI-driven approaches can enhance early clinical development productivity [233]. Moreover, frameworks combining real-world data, multi-omics profiling, and drug-target affinity prediction are accelerating hypothesis generation and trial design for repositioned drugs [234]. Despite these advancements are exciting, the translation of repositioned epigenetic drugs into clinical settings requires careful attention to safety profiles. Many epi-drugs exhibit class-specific toxicities: DNMT inhibitors are associated with myelosuppression [235], BET inhibitors with thrombocytopenia and gastrointestinal effects [236], and HDAC inhibitors with cardiac toxicity [237]. Emerging strategies such as biomarker-guided patient selection (e.g., H3K27me3 loss, EZH2 mutations), dose de-escalation protocols, and pharmacodynamic monitoring of on-target effects (e.g., global histone acetylation levels) represent key approaches to improve the therapeutic index of these compounds [238]. Future repositioning efforts must incorporate these toxicity management strategies early in preclinical and translational stages, to ensure that epigenetic therapies not only maximize efficacy but also maintain acceptable safety profiles in solid tumor settings. Moreover, the clinical potential of epi-drugs to bypass toxicity effects resides also in their pharmacological flexibility. Their versatile pharmacokinetics, oral bioavailability, and capability to be administered at adjustable dosing schedules make them ideal candidates for combination strategies [84]. This therapeutic adaptability is particularly valuable in the context of female malignancies, where therapeutic efficacy increasingly relies on strategies capable of addressing their inter- and intra-patient variability, including genomic instability and dynamic epigenetic reprogramming, often limiting the efficiency of monotherapies [239]. Additionally, the adoption of advanced preclinical models, such as patient-derived xenografts (PDX) and patient derived organoids (PDO), will be essential for more accurately evaluating drug efficacy and epigenetic dependencies. Nevertheless, these models present limitations, including incomplete immune system recapitulation and epigenetic drift during culture [240]. Historically, the clinical translation of repositioned agents has been limited by modest single-agent efficacy and lack of industry investment; however, the integration of AI and big omics data is now overcoming these hurdles by enabling scenario-specific drug matching in real-world settings [234]. Looking forward, integrating AI-powered multi-omics analysis with explainable ML frameworks and spatial/single-cell epigenomics will be vital to unravel tumor-specific vulnerabilities and predict therapeutic responses [194]. Moreover, AI may not only accelerate drug discovery timelines but also nearly double overall R&D productivity soon [233], offering unprecedented opportunities

for clinical innovation. In conclusion, while challenges remain, the convergence of AI, multi-omics profiling, and epigenetic drug repositioning holds the transformative potential to redefine precision oncology by enabling faster, safer, and more effective therapeutic treatments of highly complex and heterogeneous solid tumors, as gynaecological and breast ones.

Abbreviations

2HG	2-hydroxyglutarate
53BP1	Tumor suppressor p53-binding protein 1
AI	Artificial Intelligence
ALS	Amyotrophic Lateral Sclerosis
AOD	Amine Oxidase Domain
APC	Adenomatous Polyposis Coli protein
ATAC	Assay for Transposase-Accessible Chromatin
ATP	Adenosine Triphosphate
BC	Breast Cancer
BET	Bromodomain and Extra-Terminal motif
BETi	BET inhibitor
BRD2	Bromodomain-containing protein 2
BRD3	Bromodomain-containing protein 3
BRD4	Bromodomain-containing protein 4
BRDT	Bromodomain Testis-specific protein
BRPF1	Bromodomain and PHD Finger Containing 1
CAFs	Cancer-Associated Fibroblasts
CCL	Cancer Cell Lines
CCLC	Cancer Cell Line Encyclopedia
CDKN2A	Cyclin-Dependent Kinase Inhibitor 2 A
CHD	Chromodomain Helicase DNA-binding protein
CHIP	Chromatin Immunoprecipitation
CNN	Convolutional Neural Network
CNV	Copy Number Variation
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CSCs	Cancer stem cells
CUT&RUN	Cleavage Under Targets & Release Using Nuclease
CUT&Tag	Cleavage Under Targets and Tagmentation
dCas9-KRAB	Deactivated Cas9 fused to KRAB
dCas9-TET	Deactivated Cas9 fused to TET
DL	Deep Learning
DLBCL	Diffuse Large B-Cell Lymphoma
DNMTi	DNA Methyltransferase Inhibitor
DNN	Deep Neural Network
DOT1L	Disruptor of Telomeric Silencing 1-Like
DR	Drug Repurposing
Dr.VAE	Drug response Variational Autoencoder
ER	Estrogen Receptor
ERα	Estrogen Receptor alpha
ET	Endocrine Therapy
EZH1/2	Enhancer of Zeste Homolog 1/2
FAD	Flavin Adenine Dinucleotide
FDA	U.S. Food and Drug Administration
Gcn5	General Control Non-repressed Protein 5
GDSC	Genomics of Drug Sensitivity in Cancer
HAT	Histone Acetyltransferase
HDAC	Histone Deacetylase
HDAC6	Histone Deacetylase 6
HDACi	Histone Deacetylase Inhibitor
HMT	Histone Methyl transferase
HMTi	Histone Methyltransferase Inhibitor
HP1	Heterochromatin Protein 1
JAK	Janus Kinase
JmjC	Jumonji C Domain-containing protein
JMJD3	Jumonji Domain-containing 3
JQ1	BET Bromodomain Inhibitor
KDM1A/1B	Lysine Demethylase 1 A/1B
KDM5A	Lysine Demethylase 5 A
KDM6B	Lysine Demethylase 6B (aka JMJD3)
KDMI	Lysine Demethylase Inhibitor

KMT2D	Lysine Methyltransferase 2D
k-NN	k-Nearest Neighbors
LLM	Large Language Models
lncRNA	long non-coding RNA
LSD	Lysine-Specific Demethylase
MDSC	Myeloid-Derived Suppressor Cells
MHC	Major Histocompatibility Complex
ML	Machine Learning
MLL	Mixed Lineage Leukemia
MYC	Proto-oncogene c-Myc
NAD	Nicotinamide Adenine Dinucleotide
NC	NUT carcinoma
NSCLC	Non-Small Cell Lung Cancer
p300	Histone Acetyltransferase p300
PCA	Principal Component Analysis
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death Ligand 1
PDO	Patient Derived Organoids
PDX	Patient-Derived Xenografts
PHF19	PHD Finger Protein 19
PLS	Partial Least Squares
PRC2	Polycomb Repressive Complex 2
PRMT3	Protein Arginine Methyltransferase 3
PRMT5	Protein Arginine Methyltransferase 5
PROTACs	Proteolysis-Targeting Chimeras
PTM	Post-Translational Modification
QSAR	Quantitative Structure–Activity Relationship
REMC	Roadmap Epigenomics Mapping Consortium
RFs	Random Forests
RP2D	Recommended Phase II Dose
RPPA	Reverse Phase Protein Arrays
RT	Radiotherapy
SAM	S-adenosyl-L-methionine
scCUT&Tag	single-cell CUT&Tag
SDMA	Symmetric Dimethylarginine
SET	Su(var)3–9, Enhancer-of-zeste and Trithorax domain
SNF	Similarity Network Fusion
SNV	Single Nucleotide Variant
SVMs	Support Vector Machines
TAM	Tumor-Associated Macrophages
TCGA	The Cancer Genome Atlas
TCPA	The Cancer Proteome Atlas
TET	Ten-Eleven Translocation
TFIID	Transcription Factor IID
TME	Tumor Microenvironment
Tregs	Regulatory T cells
TSS	Transcription Start Site
UBD	Ubiquitin Binding Domain
USPs	Ubiquitin-Specific Proteases
UTX/KDM6A	Ubiquitously Transcribed Tetratricopeptide Repeat on chromosome X
XRCC1	X-ray Repair Cross Complementing protein 1

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Author contributions

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References

1. Millán-Zambrano G, Burton A, Bannister AJ, Schneider R. Histone post-translational modifications - cause and consequence of genome function. *Nat Rev Genet.* 2022;23(9):563–80.
2. Turner BM. Decoding the nucleosome. *Cell.* 1993;75(1):5–8.
3. Piunti A, Shilatifard A. Epigenetic balance of gene expression by polycomb and COMPASS families. *Science.* 2016;352(6290):aad9780.
4. Biswas S, Rao CM. Epigenetic tools (The writers, the readers and the Erasers) and their implications in cancer therapy. *Eur J Pharmacol.* 2018;837:8–24.
5. Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, et al. Global histone modification patterns predict risk of prostate cancer recurrence. *Nature.* 2005;435(7046):1262–6.
6. Barlési F, Giaccone G, Gallegos-Ruiz MI, Loundou A, Span SW, Lefesvre P, et al. Global histone modifications predict prognosis of resected Non small-cell lung cancer. *J Clin Oncol.* 2007;25(28):4358–64.
7. Seligson DB, Horvath S, McBrien MA, Mah V, Yu H, Tze S, et al. Global levels of histone modifications predict prognosis in different cancers. *Am J Pathol.* 2009;174(5):1619–28.
8. Wei Y, Xia W, Zhang Z, Liu J, Wang H, Adsay NV, et al. Loss of trimethylation at lysine 27 of histone H3 is a predictor of poor outcome in breast, ovarian, and pancreatic cancers. *Mol Carcinog.* 2008;47(9):701–6.
9. Park YS, Jin MY, Kim YJ, Yook JH, Kim BS, Jang SJ. The global histone modification pattern correlates with cancer recurrence and overall survival in gastric adenocarcinoma. *Ann Surg Oncol.* 2008;15(7):1968–76.
10. Simon JA, Lange CA. Roles of the EZH2 histone methyltransferase in cancer epigenetics. *Mutat Res.* 2008;647(1–2):21–9.
11. Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature.* 2002;419(6907):624–9.
12. Bracken AP, Pasini D, Capra M, Prosperini E, Colli E, Helin K. EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.* 2003;22(20):5323–35.
13. Croonquist PA, Van Ness B. The polycomb group protein enhancer of Zeste homolog 2 (EZH 2) is an oncogene that influences myeloma cell growth and the mutant Ras phenotype. *Oncogene.* 2005;24(41):6269–80.
14. Marsolier J, Prompsy P, Durand A, Lyne A-M, Landragin C, Trousset A, et al. H3K27me3 conditions chemotolerance in triple-negative breast cancer. *Nat Genet.* 2022;54(4):459–68.

15. Karczmarski J, Rubel T, Paziewska A, Mikula M, Bujko M, Kober P, et al. Histone H3 lysine 27 acetylation is altered in colon cancer. *Clin Proteom*. 2014;11(1):24.
16. Li Q-L, Wang D-Y, Ju L-G, Yao J, Gao C, Lei P-J, et al. The hyper-activation of transcriptional enhancers in breast cancer. *Clin Epigenetics*. 2019;11(1):48.
17. Cohen I, Poręba E, Kamieniarz K, Schneider R. Histone modifiers in cancer: friends or foes? *Genes Cancer*. 2011;2(6):631–47.
18. Weichert W, Röske A, Gekeler V, Beckers T, Ebert MPA, Pross M, et al. Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: a retrospective analysis. *Lancet Oncol*. 2008;9(2):139–48.
19. Weichert W, Röske A, Niesporek S, Noske A, Buckendahl A-C, Dietel M, et al. Class I histone deacetylase expression has independent prognostic impact in human colorectal cancer: specific role of class I histone deacetylases in vitro and in vivo. *Clin Cancer Res*. 2008;14(6):1669–77.
20. Weichert W, Röske A, Gekeler V, Beckers T, Stephan C, Jung K, et al. Histone deacetylases 1, 2 and 3 are highly expressed in prostate cancer and HDAC2 expression is associated with shorter PSA relapse time after radical prostatectomy. *Br J Cancer*. 2008;98(3):604–10.
21. Minamiya Y, Ono T, Saito H, Takahashi N, Ito M, Mitsui M, et al. Expression of histone deacetylase 1 correlates with a poor prognosis in patients with adenocarcinoma of the lung. *Lung Cancer*. 2011;74(2):300–4.
22. Rikimaru T, Taketomi A, Yamashita Y, Shirabe K, Hamatsu T, Shimada M, et al. Clinical significance of histone deacetylase 1 expression in patients with hepatocellular carcinoma. *Oncology*. 2007;72(1–2):69–74.
23. Krusche CA, Wülfing P, Kersting C, Vloet A, Böcker W, Kiesel L, et al. Histone deacetylase-1 and -3 protein expression in human breast cancer: a tissue microarray analysis. *Breast Cancer Res Treat*. 2005;90(1):15–23.
24. Komar D, Juszczynski P. Rebelled epigenome: histone H3S10 phosphorylation and H3S10 kinases in cancer biology and therapy. *Clin Epigenetics*. 2020;12(1):147.
25. Skaland I, Janssen EAM, Gudlaugsson E, Klos J, Kjelleevold KH, Søliland H, et al. Phosphohistone H3 expression has much stronger prognostic value than classical prognosticators in invasive lymph node-negative breast cancer patients less than 55 years of age. *Mod Pathol*. 2007;20(12):1307–15.
26. Takahashi H, Murai Y, Tsuneyama K, Nomoto K, Okada E, Fujita H, et al. Over-expression of phosphorylated histone H3 is an indicator of poor prognosis in gastric adenocarcinoma patients. *Appl Immunohistochem Mol Morphol*. 2006;14(3):296–302.
27. Nielsen PS, Riber-Hansen R, Jensen TO, Schmidt H, Steiniche T. Proliferation indices of phosphohistone H3 and Ki67: strong prognostic markers in a consecutive cohort with stage I/II melanoma. *Mod Pathol*. 2013;26(3):404–13.
28. Pacaud R, Cheray M, Nadaradjane A, Vallette FM, Cartron P-F. Histone H3 phosphorylation in GBM: a new rationale to guide the use of kinase inhibitors in anti-GBM therapy. *Theranostics*. 2015;5(1):12–22.
29. Yang W, Xia Y, Hawke D, Li X, Liang J, Xing D, et al. PKM2 phosphorylates histone H3 and promotes gene transcription and tumorigenesis. *Cell*. 2012;150(4):685–96.
30. Liu F, Chen J, Li K, Li H, Zhu Y, Zhai Y, et al. Ubiquitination and deubiquitination in cancer: from mechanisms to novel therapeutic approaches. *Mol Cancer*. 2024;23(1):148.
31. Hu H, Yang Y, Ji Q, Zhao W, Jiang B, Liu R, et al. CRL4B catalyzes H2AK119 monoubiquitination and coordinates with PRC2 to promote tumorigenesis. *Cancer Cell*. 2012;22(6):781–95.
32. Adhikary S, Chakravarti D, Terranova C, Sengupta I, Maitiuheti M, Dasgupta A, et al. Atypical plant homeodomain of UBR7 functions as an H2BK120Ub ligase and breast tumor suppressor. *Nat Commun*. 2019;10(1):1398.
33. Chen B, Li P, Liu M, Liu K, Zou M, Geng Y, et al. A genetic map of the chromatin regulators to drug response in cancer cells. *J Transl Med*. 2022;20(1):438.
34. Dai W, Qiao X, Fang Y, Guo R, Bai P, Liu S, et al. Epigenetics-targeted drugs: current paradigms and future challenges. *Signal Transduct Target Ther*. 2024;9(1):332.
35. Li X, Song Y. Proteolysis-targeting chimera (PROTAC) for targeted protein degradation and cancer therapy. *J Hematol Oncol*. 2020;13(1):50.
36. Husmann D, Gozani O. Histone lysine methyltransferases in biology and disease. *Nat Struct Mol Biol*. 2019;26(10):880–9.
37. Julia E, Salles G. EZH2 Inhibition by tazemetostat: mechanisms of action, safety and efficacy in relapsed/refractory follicular lymphoma. *Future Oncol*. 2021;17(17):2127–40.
38. Luan Y, Li J, Bernatchez JA, Li R. Kinase and histone deacetylase hybrid inhibitors for cancer therapy. *J Med Chem*. 2019;62(7):3171–83.
39. Daigle SR, Olhava EJ, Therkelsen CA, Basavapathruni A, Jin L, Boriack-Sjodin PA, et al. Potent Inhibition of DOT1L as treatment of MLL-fusion leukemia. *Blood*. 2013;122(6):1017–25.
40. Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR, et al. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. *Blood*. 2018;131(24):2661–9.
41. Chen J, Glasser CL. New and emerging targeted therapies for pediatric acute myeloid leukemia (AML). *Child (Basel)*. 2020;7(2).
42. Lim SH, Dubielecka PM, Raghunathan VM. Molecular targeting in acute myeloid leukemia. *J Transl Med*. 2017;15(1):183.
43. Nassa G, Salvati A, Tarallo R, Gigantino V, Alexandrova E, Memoli D, et al. Inhibition of histone methyltransferase DOT1L silences ERα gene and blocks proliferation of antiestrogen-resistant breast cancer cells. *Sci Adv*. 2019;5(2):eaav5590.
44. Salvati A, Gigantino V, Nassa G, Giurato G, Alexandrova E, Rizzo F, et al. The histone methyltransferase DOT1L is a functional component of Estrogen receptor alpha signaling in ovarian cancer cells. *Cancers (Basel)*. 2019;11(11).
45. Alexandrova E, Salvati A, Pecoraro G, Lamberti J, Melone V, Sellitto A, et al. Histone methyltransferase DOT1L as a promising epigenetic target for treatment of solid tumors. *Front Genet*. 2022;13:864612.
46. Zhang Y, Wang Y, Valdivia A, Huang H, Matei D. DOT1L regulates ovarian Cancer stem cells by activating β-catenin signaling. *Mol Cancer Res*. 2023;21(2):140–54.
47. Rodon J, Rodriguez E, Maitland ML, Tsai FYC, Socinski MA, Berlin JD, et al. A phase I study to evaluate the safety, pharmacokinetics, and pharmacodynamics of PF-06939999 (PRMT5 inhibitor) in patients with selected advanced or metastatic tumors with high incidence of splicing factor gene mutations. *ESMO Open*. 2024;9(4):102961.
48. Yun M, Wu J, Workman JL, Li B. Readers of histone modifications. *Cell Res*. 2011;21(4):564–78.
49. Franklin KA, Shields CE, Haynes KA. Beyond the marks: reader-effectors as drivers of epigenetics and chromatin engineering. *Trends Biochem Sci*. 2022;47(5):417–32.
50. Eissenberg JC. Structural biology of the chromodomain: form and function. *Gene*. 2012;496(2):69–78.
51. Vermeulen M, Mulder KW, Denissov S, Pijnappel WWMP, van Schaik FMA, Varier RA, et al. Selective anchoring of TFIIID to nucleosomes by trimethylation of histone H3 lysine 4. *Cell*. 2007;131(1):58–69.
52. Zhu H, Wei T, Cai Y, Jin J. Small molecules targeting the specific domains of histone-mark readers in cancer therapy. *Molecules*. 2020;25(3).
53. Zhang Y, Jang Y, Lee J-E, Ahn J, Xu L, Holden MR, et al. Selective binding of the PHD6 finger of MLL4 to histone H4K16ac links MLL4 and MOF. *Nat Commun*. 2019;10(1):2314.
54. Mio C, Bulotta S, Russo D, Damante G. Reading cancer: chromatin readers as druggable targets for cancer treatment. *Cancers (Basel)*. 2019;11(1).
55. Zheng Z-Z, Xia L, Hu G-S, Liu J-Y, Hu Y-H, Chen Y-J, et al. Super-enhancer-controlled positive feedback loop BRD4/ERα-RET-ERα promotes ERα-positive breast cancer. *Nucleic Acids Res*. 2022;50(18):10230–48.
56. Jain P, Ballare C, Blanco E, Vizán P, Di Croce L. PHF19 mediated regulation of proliferation and invasiveness in prostate cancer cells. *eLife*. 2020;9.
57. Salvati A, Giurato G, Lamberti J, Terenzi I, Crescenzo L, Melone V, et al. Essential gene screening identifies the bromodomain-containing protein BRPF1 as a new actionable target for endocrine therapy-resistant breast cancers. *Mol Cancer*. 2024;23(1):160.
58. Cochran AG, Conery AR, Sims RJ. Bromodomains: a new target class for drug development. *Nat Rev Drug Discov*. 2019;18(8):609–28.
59. Shapiro GI, LoRusso P, Dowlati A, Do T, Jacobson K, Vaishampayan CA. A phase I study of RO6870810, a novel bromodomain and extra-terminal protein inhibitor, in patients with NUT carcinoma, other solid tumours, or diffuse large B-cell lymphoma. *Br J Cancer*. 2021;124(4):744–53.
60. Ramasamy K, Nooka A, Quach H, Httut M, Popat R, Liedtke M, et al. A phase 1b dose-escalation/expansion study of BET inhibitor RO6870810 in patients with advanced multiple myeloma. *Blood Cancer J*. 2021;11(9):149.
61. Yang Y, Zhang M, Wang Y. The roles of histone modifications in tumorigenesis and associated inhibitors in cancer therapy. *J Natl Cancer Cent*. 2022;2(4):277–90.
62. Sterling J, Menezes SV, Abbassi RH, Munoz L. Histone lysine demethylases and their functions in cancer. *Int J Cancer*. 2021;148(10):2375–88.
63. Kruidenier L, Chung C, Cheng Z, Little J, Che K, Joberty G, et al. A selective Jumonji H3K27 demethylase inhibitor modulates the Proinflammatory macrophage response. *Nature*. 2012;488(7411):404–8.

64. de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, van Kuilenburg ABP. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J*. 2003;370(Pt 3):737–49.
65. Zucconi BE, Cole PA. Allosteric regulation of epigenetic modifying enzymes. *Curr Opin Chem Biol*. 2017;39:109–15.
66. March E, Farrona S. Plant deubiquitinases and their role in the control of gene expression through modification of histones. *Front Plant Sci*. 2017;8:2274.
67. McClurg UL, Robson CN. Deubiquitinating enzymes as oncotargets. *Oncotarget*. 2015;6(12):9657–68.
68. Li K-Q, Bai X, Ke A-T, Ding S-Q, Zhang C-D, Dai D-Q. Ubiquitin-specific proteases: from biological functions to potential therapeutic applications in gastric cancer. *Biomed Pharmacother*. 2024;173:116323.
69. Yeamin Khusbu F, Chen F-Z, Chen H-C. Targeting ubiquitin specific protease 7 in cancer: A deubiquitinase with great prospects. *Cell Biochem Funct*. 2018;36(5):244–54.
70. Nervi C, De Marinis E, Codacci-Pisanelli G. Epigenetic treatment of solid tumours: a review of clinical trials. *Clin Epigenetics*. 2015;7:127.
71. Yang T, Yang Y, Wang Y. Predictive biomarkers and potential drug combinations of epi-drugs in cancer therapy. *Clin Epigenetics*. 2021;13(1):113.
72. Jin N, George TL, Otterson GA, Verschraegen C, Wen H, Carbone D, et al. Advances in epigenetic therapeutics with focus on solid tumors. *Clin Epigenetics*. 2021;13(1):83.
73. Ganesan A, Arimondo PB, Rots MG, Jeronimo C, Berdasco M. The timeline of epigenetic drug discovery: from reality to Dreams. *Clin Epigenetics*. 2019;11(1):174.
74. Dai X-J, Ji S-K, Fu M-J, Liu G-Z, Liu H-M, Wang S-P, et al. Degradors in epigenetic therapy: protacs and beyond. *Theranostics*. 2024;14(4):1464–99.
75. Capece M, Tessari A, Mills J, Vinguerra GLR, Louke D, Lin C, et al. A novel auxin-inducible Degron system for rapid, cell cycle-specific targeted proteolysis. *Cell Death Differ*. 2023;30(9):2078–91.
76. Martín-Acosta P, Xiao X. PROTACs to address the challenges facing small molecule inhibitors. *Eur J Med Chem*. 2021;210:112993.
77. Békés M, Langley DR, Crews CM. PROTAC targeted protein degraders: the past is prologue. *Nat Rev Drug Discov*. 2022;21(3):181–200.
78. Ciulli A, Trainor N. A beginner's guide to protacs and targeted protein degradation. *Biochem (Lond)*. 2021.
79. Syding LA, Nickl P, Kasperek P, Sedlacek R. Crispr/cas9 epigenome editing potential for rare imprinting diseases: A review. *Cells*. 2020;9(4).
80. Bhat AA, Nisar S, Mukherjee S, Saha N, Yarravarapu N, Lone SN, et al. Integration of CRISPR/Cas9 with artificial intelligence for improved cancer therapeutics. *J Transl Med*. 2022;20(1):534.
81. Yang Y, Mei H, Han X, Zhang X, Cheng J, Zhang Z, et al. Synthetic CRISPR/dCas9-KRAB system driven by specific PSA promoter suppresses malignant biological behavior of prostate cancer cells through negative feedback inhibition of PSA expression. *Cell Mol Biol Lett*. 2023;28(1):96.
82. Tejedor JR, Peñarroya A, Gancedo-Verdejo J, Santamarina-Ojeda P, Pérez RF, López-Tamargo S, et al. CRISPR/dCas9-mediated DNA demethylation screen identifies functional epigenetic determinants of colorectal cancer. *Clin Epigenetics*. 2023;15(1):133.
83. Cavalcante BRR, Freitas RD, Siquara da Rocha L, de O, Santos R, de Souza SBD, de Ramos BS. In Silico approaches for drug repurposing in oncology: a scoping review. *Front Pharmacol*. 2024;15:1400029.
84. Montalvo-Casimiro M, González-Barrios R, Meraz-Rodríguez MA, Juárez-González VT, Arriaga-Canon C, Herrera LA. Epidrug repurposing: discovering new faces of old acquaintances in cancer therapy. *Front Oncol*. 2020;10:605386.
85. Kirtonia A, Gala K, Fernandes SG, Pandya G, Pandey AK, Sethi G, et al. Repurposing of drugs: an attractive Pharmacological strategy for cancer therapeutics. *Semin Cancer Biol*. 2021;68:258–78.
86. Weth FR, Hoggarth GB, Weth AF, Paterson E, White MPJ, Tan ST, et al. Unlocking hidden potential: advancements, approaches, and obstacles in repurposing drugs for cancer therapy. *Br J Cancer*. 2024;130(5):703–15.
87. Moreira-Silva F, Camilo V, Gaspar V, Mano JF, Henrique R, Jerónimo C. Repurposing old drugs into new epigenetic inhibitors: promising candidates for cancer treatment? *Pharmaceutics*. 2020;12(5).
88. Xia Y, Sun M, Huang H, Jin W-L. Drug repurposing for cancer therapy. *Signal Transduct Target Ther*. 2024;9(1):92.
89. Kallingal A, Olszewski M, Maciejewska N, Brankiewicz W, Baginski M. Cancer immune escape: the role of antigen presentation machinery. *J Cancer Res Clin Oncol*. 2023;149(10):8131–41.
90. Saleh R, Toor SM, Sasidharan Nair V, Elkord E. Role of epigenetic modifications in inhibitory immune checkpoints in cancer development and progression. *Front Immunol*. 2020;11:1469.
91. Santini V, Lübbert M, Wierzbowska A, Ossenkoppele GJ. The clinical value of decitabine monotherapy in patients with acute myeloid leukemia. *Adv Ther*. 2022;39(4):1474–88.
92. Huang KC-Y, Chiang S-F, Chen WT-L, Chen T-W, Hu C-H, Yang P-C et al. Decitabine augments chemotherapy-induced PD-L1 upregulation for PD-L1 Blockade in colorectal cancer. *Cancers (Basel)*. 2020;12(2).
93. Taib N, Merhi M, Inchakalody V, Mestiri S, Hydrose S, Makni-Maalej K, et al. Treatment with decitabine induces the expression of stemness markers, PD-L1 and NY-ESO-1 in colorectal cancer: potential for combined chemoimmunotherapy. *J Transl Med*. 2023;21(1):235.
94. Guo Z, Wang H, Meng F, Li J, Zhang S. Combined trabectedin and anti-PD1 antibody produces a synergistic antitumor effect in a murine model of ovarian cancer. *J Transl Med*. 2015;13:247.
95. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Commun Signal*. 2020;18(1):59.
96. Xie Z, Zhou Z, Yang S, Zhang S, Shao B. Epigenetic regulation and therapeutic targets in the tumor microenvironment. *Mol Biomed*. 2023;4(1):17.
97. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell*. 2011;146(6):904–17.
98. Meng S, Zhang L, Tang Y, Tu Q, Zheng L, Yu L, et al. BET inhibitor JQ1 blocks inflammation and bone destruction. *J Dent Res*. 2014;93(7):657–62.
99. Pang Y, Bai G, Zhao J, Wei X, Li R, Li J, et al. The BRD4 inhibitor JQ1 suppresses tumor growth by reducing c-Myc expression in endometrial cancer. *J Transl Med*. 2022;20(1):336.
100. Adeegbe DO, Liu S, Hattersley MM, Bowden M, Zhou CW, Li S, et al. BET bromodomain inhibition cooperates with PD-1 Blockade to facilitate antitumor response in Kras-Mutant Non-Small cell lung Cancer. *Cancer Immunol Res*. 2018;6(10):1234–45.
101. Wang H, Liu G, Jin X, Song S, Chen S, Zhou P, et al. BET inhibitor JQ1 enhances anti-tumor immunity and synergizes with PD-1 Blockade in CRC. *J Cancer*. 2022;13(7):2126–37.
102. Nong S, Han X, Xiang Y, Qian Y, Wei Y, Zhang T, et al. Metabolic reprogramming in cancer: mechanisms and therapeutics. *MedComm*. 2023;4(2):e218.
103. Lanzetti L. Oncometabolites at the crossroads of genetic, epigenetic and ecological alterations in cancer. *Cell Death Differ*. 2024;31(12):1582–94.
104. Gonzalez-Lopez C, Wojcik BS. Role of Metformin in the management of type 2 diabetes: recent advances. *Pol Arch Intern Med*. 2023;133(6).
105. Oh S, Cho Y, Chang M, Park S, Kwon H. Metformin decreases 2-HG production through the MYC-PHGDH pathway in suppressing breast cancer cell proliferation. *Metabolites*. 2021;11(8).
106. Neophytou CM, Panagi M, Stylianopoulos T, Papageorgis P. The role of tumor microenvironment in cancer metastasis: molecular mechanisms and therapeutic opportunities. *Cancers (Basel)*. 2021;13(9).
107. Chen JF, Yan Q. The roles of epigenetics in cancer progression and metastasis. *Biochem J*. 2021;478(17):3373–93.
108. Duvic M, Vu J. Update on the treatment of cutaneous T-cell lymphoma (CTCL): focus on Vorinostat. *Biologics*. 2007;1(4):377–92.
109. Chiu H-W, Yeh Y-L, Wang Y-C, Huang W-J, Chen Y-A, Chiou Y-S, et al. Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, enhances radiosensitivity and suppresses lung metastasis in breast cancer in vitro and in vivo. *PLoS ONE*. 2013;8(10):e76340.
110. Chu X, Tian W, Ning J, Xiao G, Zhou Y, Wang Z, et al. Cancer stem cells: advances in knowledge and implications for cancer therapy. *Signal Transduct Target Ther*. 2024;9(1):170.
111. Phi LTH, Sari IN, Yang Y-G, Lee S-H, Jun N, Kim KS, et al. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in Cancer treatment. *Stem Cells Int*. 2018;2018:5416923.
112. Kumar B, Yadav A, Lang JC, Teknos TN, Kumar P. Suberoylanilide hydroxamic acid (SAHA) reverses chemoresistance in head and neck cancer cells by targeting cancer stem cells via the downregulation of Nanog. *Genes Cancer*. 2015;6(3–4):169–81.
113. Sullivan JK, Fahey PP, Agho KE, Hurley SP, Feng Z, Day RO, et al. Valproic acid as a radio-sensitizer in glioma: A systematic review and meta-analysis. *Neurooncol Pract*. 2023;10(1):13–23.
114. Shirbhate E, Patel P, Patel VK, Veerasamy R, Sharma PC, Rajak H. The combination of histone deacetylase inhibitors and radiotherapy: a promising novel approach for cancer treatment. *Future Oncol*. 2020;16(30):2457–69.

115. PDQ Adult Treatment Editorial Board. Breast Cancer Treatment (PDQ®): Patient Version. PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); 2002.
116. Bodriagova O, Previs RA, Gaba L, Shankar A, Vidal L, Saini KS. Recent advances in gynecological malignancies: focus on ASCO 2023. *Oncol Ther*. 2023;11(4):397–409.
117. Habibi S, Bahramian S, Zare Jalise S, Mehri S, Ababzadeh S, Kavianpour M. Novel strategies in breast cancer management: from treatment to long-term remission. *Crit Rev Oncol Hematol*. 2025;211:104715.
118. Liu B, Zhou H, Tan L, Siu KTH, Guan X-Y. Exploring treatment options in cancer: tumor treatment strategies. *Signal Transduct Target Ther*. 2024;9(1):175.
119. Gandhi A, Andrick B, Darling J, Truong T, Signorelli J. Oral antineoplastics in acute myeloid leukemia: A comprehensive review. *Clin Lymphoma Myeloma Leuk*. 2022;22(12):e1033–49.
120. Feehley T, O'Donnell CW, Mendlein J, Karande M, McCauley T. Drugging the epigenome in the age of precision medicine. *Clin Epigenetics*. 2023;15(1):6.
121. Momparler RL. Pharmacology of 5-Aza-2'-deoxycytidine (decitabine). *Semin Hematol*. 2005;42(3 Suppl 2):S9–16.
122. Jabbour E, Issa J-P, Garcia-Manero G, Kantarjian H. Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer*. 2008;112(11):2341–51.
123. Xu Y, Li P, Liu Y, Xin D, Lei W, Liang A, et al. Epi-immunotherapy for cancers: advanced of epi-drugs in combination with immunotherapy and advances in clinical trials. *Cancer Commun (Lond)*. 2022;42(6):493–516.
124. Connolly RM, Li H, Jankowitz RC, Zhang Z, Rudek MA, Jeter SC, et al. Combination epigenetic therapy in advanced breast Cancer with 5-Azacitidine and entinostat: A phase II National Cancer institute/stand up to Cancer study. *Clin Cancer Res*. 2017;23(11):2691–701.
125. Bear HD, Deng X, Bandyopadhyay D, Idowu M, Jenkins TM, Kmiecik M et al. T-cell immune checkpoint Inhibition plus hypomethylation for locally advanced HER2-negative breast cancer: a phase 2 neoadjuvant window trial of decitabine and pembrolizumab followed by standard neoadjuvant chemotherapy. *J Immunother Cancer*. 2025;13(2).
126. Li W, Sun Z. Mechanism of action for HDAC Inhibitors-Insights from omics approaches. *Int J Mol Sci*. 2019;20(7).
127. Lyu H, Hou D, Liu H, Ruan S, Tan C, Wu J, et al. HER3 targeting augments the efficacy of Panobinostat in claudin-low triple-negative breast cancer cells. *NPJ Precis Oncol*. 2023;7(1):72.
128. Yervu SLH, Zhao F, Miller KD, Tevaarwerk AJ, Wagner LI, Gray RJ, et al. E2112: randomized phase III trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. *NPJ Breast Cancer*. 2018;4:1.
129. Munster PN, Thurn KT, Thomas S, Raha P, Lacey M, Miller A, et al. A phase II study of the histone deacetylase inhibitor Vorinostat combined with Tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br J Cancer*. 2011;104(12):1828–35.
130. Lian B, Chen X, Shen K. Inhibition of histone deacetylases attenuates tumor progression and improves immunotherapy in breast cancer. *Front Immunol*. 2023;14:1164514.
131. Lee EK, Tan-Wasielewski Z, Matulonis UA, Birrer MJ, Wright AA, Horowitz N, et al. Results of an abbreviated phase Ib study of the HDAC6 inhibitor Ricolinostat and Paclitaxel in recurrent ovarian, fallopian tube, or primary peritoneal cancer. *Gynecol Oncol Rep*. 2019;29:118–22.
132. Guo F, Wang H. Potential of histone deacetylase inhibitors for the therapy of ovarian cancer. *Front Oncol*. 2022;12:1057186.
133. Ovejero-Sánchez M, Asensio-Juárez G, González M, Puebla P, Vicente-Manzanares M, Pélaez R et al. Panobinostat synergistically enhances the cytotoxicity of microtubule destabilizing drugs in ovarian cancer cells. *Int J Mol Sci*. 2022;23(21).
134. Joseph R, Dasari SK, Umamaheswaran S, Mangala LS, Bayraktar E, Rodriguez-Aguayo C et al. EphA2- and HDAC-Targeted combination therapy in endometrial Cancer. *Int J Mol Sci*. 2024;25(2).
135. Bondarev AD, Attwood MM, Jonsson J, Chubarev VN, Tarasov VV, Schiöth HB. Recent developments of HDAC inhibitors: emerging indications and novel molecules. *Br J Clin Pharmacol*. 2021;87(12):4577–97.
136. Yoon S, Eom GH. HDAC and HDAC inhibitor: from cancer to cardiovascular diseases. *Chonnam Med J*. 2016;52(1):1–11.
137. Poole RM. Belinostat: first global approval. *Drugs*. 2014;74(13):1543–54.
138. Gryder BE, Sodji QH, Oyeler AK. Targeted cancer therapy: giving histone deacetylase inhibitors all they need to succeed. *Future Med Chem*. 2012;4(4):505–24.
139. Bose P, Dai Y, Grant S. Histone deacetylase inhibitor (HDACI) mechanisms of action: emerging insights. *Pharmacol Ther*. 2014;143(3):323–36.
140. Noerenberg D, Damm F. Beyond the code: the role of histone methylation in cancer resistance and therapy. *Signal Transduct Target Ther*. 2024;9(1):161.
141. Schram A, Eskander R, Sill M, Hagemann A, Waggoner S, Press J, et al. Clinical activity of tazemetostat, an EZH2 inhibitor, among patients with advanced endometrioid endometrial cancer and ovarian clear cell carcinoma with and without ARID1A mutations (NRG-GY014). *Gynecol Oncol*. 2024;190:S56–7.
142. Italiano A, Soria J-C, Toulmonde M, Michot J-M, Lucchesi C, Varga A, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol*. 2018;19(5):649–59.
143. Yap TA, Winter JN, Giulino-Roth L, Longley J, Lopez J, Michot J-M, et al. Phase I study of the novel enhancer of Zeste homolog 2 (EZH2) inhibitor GSK2816126 in patients with advanced hematologic and solid tumors. *Clin Cancer Res*. 2019;25(24):7331–9.
144. Yamagishi M, Kuze Y, Kobayashi S, Nakashima M, Morishima S, Kawamata T, et al. Mechanisms of action and resistance in histone methylation-targeted therapy. *Nature*. 2024;627(8002):221–8.
145. Keshari S, Barrodia P, Singh AK. Epigenetic perspective of immunotherapy for cancers. *Cells*. 2023;12(3).
146. Andrade F, de O, Nguyen NM, Warri A, Hilakivi-Clarke L. Reversal of increased mammary tumorigenesis by valproic acid and hydralazine in offspring of dams fed high fat diet during pregnancy. *Sci Rep*. 2019;9(1):20271.
147. Song Y, Zhang C. Hydralazine inhibits human cervical cancer cell growth in vitro in association with APC demethylation and re-expression. *Cancer Chemother Pharmacol*. 2009;63(4):605–13.
148. Arce C, Segura-Pacheco B, Perez-Cardenas E, Taja-Chayeb L, Candelaria M, Dueñas-Gonzalez A. Hydralazine target: from blood vessels to the epigenome. *J Transl Med*. 2006;4:10.
149. Buenostro JD, Wu B, Litzenburger UM, Ruff D, Gonzales ML, Snyder MP, et al. Single-cell chromatin accessibility reveals principles of regulatory variation. *Nature*. 2015;523(7561):486–90.
150. Stuart T, Satija R. Integrative single-cell analysis. *Nat Rev Genet*. 2019;20(5):257–72.
151. Ma J, Zhang X, Huang X, Luo S, Meggers E. Preparation of chiral-at-metal catalysts and their use in asymmetric photoredox chemistry. *Nat Protoc*. 2018;13(4):605–32.
152. Skene PJ, Henikoff JG, Henikoff S. Targeted in situ genome-wide profiling with high efficiency for low cell numbers. *Nat Protoc*. 2018;13(5):1006–19.
153. Kaya-Okur HS, Wu SJ, Codomo CA, Pledger ES, Bryson TD, Henikoff JG, et al. CUT&Tag for efficient epigenomic profiling of small samples and single cells. *Nat Commun*. 2019;10(1):1930.
154. Wu SZ, Al-Eryani G, Roden DL, Junankar S, Harvey K, Andersson A, et al. A single-cell and spatially resolved atlas of human breast cancers. *Nat Genet*. 2021;53(9):1334–47.
155. Paldi F, Cavalli G. 3D genome folding in epigenetic regulation and cellular memory. *Trends Cell Biol*. 2025.
156. Landt SG, Marinov GK, Kundaje A, Kheradpour P, Pauli F, Batzoglou S, et al. ChIP-seq guidelines and practices of the ENCODE and ModENCODE consortia. *Genome Res*. 2012;22(9):1813–31.
157. Henikoff S, Henikoff JG, Kaya-Okur HS, Ahmad K. Efficient chromatin accessibility mapping in situ by nucleosome-tethered tagmentation. *eLife*. 2020;9.
158. Hayashi-Takanaka Y, Yamagata K, Wakayama T, Stasevich TJ, Kainuma T, Tsurimoto T, et al. Tracking epigenetic histone modifications in single cells using Fab-based live endogenous modification labeling. *Nucleic Acids Res*. 2011;39(15):6475–88.
159. Stergachis AB, Debo BM, Haugen E, Churchman LS, Stamatoyannopoulos JA. Single-molecule regulatory architectures captured by chromatin fiber sequencing. *Science*. 2020;368(6498):1449–54.
160. Mumbach MR, Rubin AJ, Flynn RA, Dai C, Khavari PA, Greenleaf WJ, et al. HiChIP: efficient and sensitive analysis of protein-directed genome architecture. *Nat Methods*. 2016;13(11):919–22.
161. Janssens DH, Otto DJ, Meers MP, Setty M, Ahmad K, Henikoff S. CUT&Tag2for1: a modified method for simultaneous profiling of the accessible and silenced regulome in single cells. *Genome Biol*. 2022;23(1):81.
162. Zambanini G, Nordin A, Jonasson M, Pagella P, Cantù C. A new CUT&RUN low volume-urea (LoV-U) protocol optimized for transcriptional co-factors uncovers Wnt/β-catenin tissue-specific genomic targets. *Development*. 2022;149(23).

163. Huang Z, Shi J, Gao Y, Cui C, Zhang S, Li J, et al. HMDD v3.0: a database for experimentally supported human microRNA-disease associations. *Nucleic Acids Res.* 2019;47(D1):D1013–7.
164. Davis CA, Hitz BC, Sloan CA, Chan ET, Davidson JM, Gabdank I, et al. The encyclopedia of DNA elements (ENCODE): data portal update. *Nucleic Acids Res.* 2018;46(D1):D794–801.
165. Tomczak K, Czerwińska P. The Cancer genome atlas (TCGA): an immeasurable source of knowledge. *Contemp Oncol (Pozn).* 2015;19(1A):A68–77.
166. van der Meer D, Barthorpe S, Yang W, Lightfoot H, Hall C, Gilbert J, et al. Cell model Passports—a hub for clinical, genetic and functional datasets of preclinical cancer models. *Nucleic Acids Res.* 2019;47(D1):D923–9.
167. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012;2(5):401–4.
168. Liu C-J, Hu F-F, Xia M-X, Han L, Zhang Q, Guo A-Y. GSCALite: a web server for gene set cancer analysis. *Bioinformatics.* 2018;34(21):3771–2.
169. Modhukur V, Iljasenko T, Metsalu T, Lökk K, Laisk-Podar T, Vilo J. MethSurv: a web tool to perform multivariable survival analysis using DNA methylation data. *Epigenomics.* 2018;10(3):277–88.
170. Koch A, De Meyer T, Jeschke J, Van Criekinge W. MEXPress: visualizing expression, DNA methylation and clinical TCGA data. *BMC Genomics.* 2015;16(1):636.
171. Carini C, Seyhan AA. Tribulations and future opportunities for artificial intelligence in precision medicine. *J Transl Med.* 2024;22(1):411.
172. Wang J, Zeng Z, Li Z, Liu G, Zhang S, Luo C, et al. The clinical application of artificial intelligence in cancer precision treatment. *J Transl Med.* 2025;23(1):120.
173. Shen R, Olshen AB, Ladanyi M. Integrative clustering of multiple genomic data types using a joint latent variable model with application to breast and lung cancer subtype analysis. *Bioinformatics.* 2009;25(22):2906–12.
174. Wang B, Mezlini AM, Demir F, Fiume M, Tu Z, Brudno M, et al. Similarity network fusion for aggregating data types on a genomic scale. *Nat Methods.* 2014;11(3):333–7.
175. Rohart F, Gautier B, Singh A, Lê Cao K-A. mixOmics. An R package for 'omics feature selection and multiple data integration. *PLoS Comput Biol.* 2017;13(11):e1005752.
176. Gomez-Cabrero D, Tarazona S, Ferreirós-Vidal I, Ramírez RN, Company C, Schmidt A, et al. STATegra, a comprehensive multi-omics dataset of B-cell differentiation in mouse. *Sci Data.* 2019;6(1):256.
177. Nelson RS. The usefulness of the Gastrocamera. *Gastroenterology.* 1968;54(2):320–1.
178. Mohammadzadeh-Vardin T, Ghareyazi A, Gharizadeh A, Abbasi K, Rabiee HR. DeepDRA: drug repurposing using multi-omics data integration with autoencoders. *PLoS ONE.* 2024;19(7):e0307649.
179. Goswami CP, Nakshatri H. PROGMiR: a tool for identifying prognostic miRNA biomarkers in multiple cancers using publicly available data. *J Clin Bioinforma.* 2012;2(1):23.
180. Li J, Han L, Roebuck P, Diao L, Liu L, Yuan Y, et al. TANRIC: an interactive open platform to explore the function of lncRNAs in Cancer. *Cancer Res.* 2015;75(18):3728–37.
181. Anaya J. OncoLnc: linking TCGA survival data to mRNAs, miRNAs, and lncRNAs. *PeerJ Comput Sci.* 2016;2:e67.
182. Li J, Lu Y, Akbani R, Ju Z, Roebuck PL, Liu W, et al. TCPA: a resource for cancer functional proteomics data. *Nat Methods.* 2013;10(11):1046–7.
183. Borcherding N, Bormann NL, Voigt AP, Zhang W, TRGAted. A web tool for survival analysis using protein data in the Cancer genome atlas. [version 2; peer review: 2 approved]. *F1000Res.* 2018;7:1235.
184. Dong X, Liu H, Tong T, Wu L, Wang J, You T, et al. Personalized prediction of anticancer potential of non-oncology drugs through learning from genome derived molecular pathways. *NPJ Precis Oncol.* 2025;9(1):36.
185. Chaudhary K, Poirion OB, Lu L, Garmire LX. Deep Learning-Based Multi-Omics integration robustly predicts survival in liver Cancer. *Clin Cancer Res.* 2018;24(6):1248–59.
186. Ching T, Himmelstein DS, Beaulieu-Jones BK, Kalinin AA, Do BT, Way GP et al. Opportunities and obstacles for deep learning in biology and medicine. *J R Soc Interface.* 2018;15(141).
187. Libbrecht MW, Noble WS. Machine learning applications in genetics and genomics. *Nat Rev Genet.* 2015;16(6):321–32.
188. Zhang Y, Chen F, Creighton CJ. SVExpress: identifying gene features altered recurrently in expression with nearby structural variant breakpoints. *BMC Bioinformatics.* 2021;22(1):135.
189. Wang Y, Yang Y, Chen S, Wang J. DeepDRK: a deep learning framework for drug repurposing through kernel-based multi-omics integration. *Brief Bioinf.* 2021;22(5).
190. Carli F, Di Chiaro P, Morelli M, Arora C, Biscaglia L, De Oliveira Rosa N, et al. Learning and actioning general principles of cancer cell drug sensitivity. *Nat Commun.* 2025;16(1):1654.
191. Lähnemann D, Köster J, Szczurek E, McCarthy DJ, Hicks SC, Robinson MD, et al. Eleven grand challenges in single-cell data science. *Genome Biol.* 2020;21(1):31.
192. Lundberg S, Lee S-I. A unified approach to interpreting model predictions. *arXiv.* 2017.
193. Li H, Guan Y. Asymmetric predictive relationships across histone modifications. *Nat Mach Intell.* 2022;4(3):288–99.
194. Pantziarka P, Vandeborne L, Bouche G. A database of drug repurposing clinical trials in oncology. *Front Pharmacol.* 2021;12:790952.
195. Conte N, Mason JC, Halmagyi C, Neuhauser S, Mosaku A, Yordanova G, et al. PDX finder: A portal for patient-derived tumor xenograft model discovery. *Nucleic Acids Res.* 2019;47(D1):D1073–9.
196. Pan D, Guo Y, Fan Y, Wan H. Development and application of traditional Chinese medicine using AI machine learning and deep learning strategies. *Am J Chin Med.* 2024;52(3):605–23.
197. Zeng Y, Gu H, Wei W, Guo Y. Deep-full-range: a deep learning based network encrypted traffic classification and intrusion detection framework. *Ins Elec Electron Eng (IEEE);* 2019.
198. Zou J, Huss M, Abid A, Mohammadi P, Torkamani A, Telenti A. A primer on deep learning in genomics. *Nat Genet.* 2019;51(1):12–8.
199. Angermueller C, Lee HJ, Reik W, Stegle O. DeepCpG: accurate prediction of single-cell DNA methylation States using deep learning. *Genome Biol.* 2017;18(1):67.
200. Wang K, Zhou R, Li Y, Li M. DeepDTAF: a deep learning method to predict protein-ligand binding affinity. *Brief Bioinf.* 2021;22(5).
201. Singh R, Lanchantin J, Robins G, Qi Y. DeepChrome: deep-learning for predicting gene expression from histone modifications. *Bioinformatics.* 2016;32(17):i639–48.
202. Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, et al. Integrative analysis of 111 reference human epigenomes. *Nature.* 2015;518(7539):317–30.
203. Boros J, Arnoult N, Stroobant V, Collet J-F, Decottignies A. Polycomb repressive complex 2 and H3K27me3 cooperate with H3K9 methylation to maintain heterochromatin protein 1α at chromatin. *Mol Cell Biol.* 2014;34(19):3662–74.
204. Ernst J, Kellis M. Large-scale imputation of epigenomic datasets for systematic annotation of diverse human tissues. *Nat Biotechnol.* 2015;33(4):364–76.
205. Choudhary C, Kumar C, Gnäd F, Nielsen ML, Rehman M, Walther TC, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science.* 2009;325(5942):834–40.
206. Rampášek L, Hidru D, Smirnov P, Haibe-Kains B, Goldenberg A. DrVAE: improving drug response prediction via modeling of drug perturbation effects. *Bioinformatics.* 2019;35(19):3743–51.
207. Zhou L, Feng T, Xu S, Gao F, Lam TT, Wang Q et al. Ggmsa: a visual exploration tool for multiple sequence alignment and associated data. *Brief Bioinf.* 2022;23(4).
208. Picard M, Leclercq M, Bodein A, Scott-Boyer MP, Perin O, Droit A. Improving drug repositioning with negative data labeling using large Language models. *J Cheminform.* 2025;17(1):16.
209. Abualigah L, Alomari SA, Almomani MH, Zitar RA, Saleem K, Migdady H, et al. Artificial intelligence-driven translational medicine: a machine learning framework for predicting disease outcomes and optimizing patient-centric care. *J Transl Med.* 2025;23(1):302.
210. InsilicoMedicine's. AI uncovers 28 new potential drug targets for ALS [Internet]. Fierce Biotech. [cited 2022 Jul 7]. Available from: <https://www.fiercebiotech.com/medtech/insilico-medicines-ai-uncovers-28-new-potential-drug-targets-als>
211. InsilicoMedicine Announces Positive Top-line Results of ISM001-055. in IPF Phase IIa [Internet]. PR Newswire. [cited 2024 Nov 12]. Available from: <https://www.prnewswire.com/news-releases/insilico-medicine-announces-positive-topline-results-of-ism001-055-for-the-treatment-of-idopathic-pulmonary-fibrosis-ipf-developed-using-generative-ai-302302583.html>
212. Potential treatment for COVID-19 identified by BenevolentAI enters randomised clinical trial [Internet]. TechCrunch. [cited 2020 Apr 14]. Available from: <https://techcrunch.com/2020/04/14/potential-new-treatment-for-covid-19-uncovered-by-benevolentai-enters-trials/>

213. BarrowNeurological Institute uses Watson for Drug. Discovery to identify five novelALS genes [Internet]. PR Newswire. [cited 2016 Dec 14]. Available from: <https://www.prnewswire.com/news-releases/barrow-identifies-new-genes-responsible-for-als-using-ibm-watson-health-300378211.html>
214. DeepPurpose– A. Deep-learning toolkit for drug repurposing and virtual screening [Internet]. github. [cited 2025 Apr 1]. Available from: <https://github.com/kexinhuang12345/DeepPurpose>
215. Cyclicaforms multi-year drug-discovery partnership with the Genome Institute. of Singapore to apply Ligand Express [Internet]. BusinessWire. [cited 2020 Apr 14]. Available from: <https://www.businesswire.com/news/home/20200414005071/en/Cyclica-Forms-Multi-Year-and-Multi-Project-Drug-Discovery-Partnership-with-the-Genome-Institute-of-Singapore>
216. Himmelstein DS, Lizee A, Hessler C, Brueggeman L, Chen SL, Hadley D et al. Systematic integration of biomedical knowledge prioritizes drugs for repurposing. *BioRxiv*. 2016.
217. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*. 2019;18(1):41–58.
218. Ferreira FJN, Carneiro AS. AI-Driven drug discovery: A comprehensive review. *ACS Omega*. 2025;10(23):23889–903.
219. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov*. 2015;14(7):475–86.
220. Pantziarka P, Verbaanderd C, Sukhatme V, Rica Capistrano I, Crispino S, Gyawali B, et al. ReDO_DB: the repurposing drugs in oncology database. *Ecancermedicalscience*. 2018;12:886.
221. Marsh DJ, Shah JS, Cole AJ. Histones and their modifications in ovarian cancer - drivers of disease and therapeutic targets. *Front Oncol*. 2014;4:144.
222. Zhu R, Ni J, Ren J, Li D, Xu J, Yu X, et al. Transcriptomic era of cancers in females: new epigenetic perspectives and therapeutic prospects. *Front Oncol*. 2024;14:1464125.
223. Duan X, Xing Z, Qiao L, Qin S, Zhao X, Gong Y, et al. The role of histone post-translational modifications in cancer and cancer immunity: functions, mechanisms and therapeutic implications. *Front Immunol*. 2024;15:1495221.
224. Suraweera A, O'Byrne KJ, Richard DJ. Epigenetic drugs in cancer therapy. *Cancer Metastasis Rev*. 2025;44(1):37.
225. Zhang W, Ge L, Zhang Y, Zhang Z, Zhang W, Song F, et al. Targeted intervention of tumor microenvironment with HDAC inhibitors and their combination therapy strategies. *Eur J Med Res*. 2025;30(1):69.
226. Ren L, Yang Y, Li W, Yang H, Zhang Y, Ge B, et al. Recent advances in epigenetic anticancer therapeutics and future perspectives. *Front Genet*. 2022;13:1085391.
227. Shirbhate E, Singh V, Jahoriya V, Mishra A, Veerasamy R, Tiwari AK, et al. Dual inhibitors of HDAC and other epigenetic regulators: A novel strategy for cancer treatment. *Eur J Med Chem*. 2024;263:115938.
228. Tomuleasa C, Tigu A-B, Munteanu R, Moldovan C-S, Kegyes D, Onaciu A, et al. Therapeutic advances of targeting receptor tyrosine kinases in cancer. *Signal Transduct Target Ther*. 2024;9(1):201.
229. Tao L, Zhou Y, Luo Y, Qiu J, Xiao Y, Zou J et al. Epigenetic regulation in cancer therapy: from mechanisms to clinical advances. *MedComm– Oncol*. 2024;3(1).
230. Fang K, Ohiohoin AG, Liu T, Choppavarapu L, Nosirov B, Wang Q, et al. Integrated single-cell analysis reveals distinct epigenetic-regulated cancer cell States and a heterogeneity-guided core signature in tamoxifen-resistant breast cancer. *Genome Med*. 2024;16(1):134.
231. Han X, Gao Y, Jiang M, Li Z, Guo J, Li Y, et al. Single-cell and Spatial transcriptome sequencing uncover a platinum-resistant cluster overexpressed TACSTD2 in high-grade serous ovarian cancer. *J Cancer*. 2024;15(11):3427–40.
232. Hu Y, Shen F, Yang X, Han T, Long Z, Wen J, et al. Single-cell sequencing technology applied to epigenetics for the study of tumor heterogeneity. *Clin Epigenetics*. 2023;15(1):161.
233. Jayatunga M, Ayers M, Bruens L, Jayanth D, Meier C. How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons. *Drug Discov Today*. 2024;29(6):104009.
234. Wieder R, Adam N. Drug repositioning for cancer in the era of AI, big omics, and real-world data. *Crit Rev Oncol Hematol*. 2022;175:103730.
235. Abou Zahr A, Saad Aldin E, Barbarotta L, Podoltsev N, Zeidan AM. The clinical use of DNA methyltransferase inhibitors in myelodysplastic syndromes. *Expert Rev Anticancer Ther*. 2015;15(9):1019–36.
236. Sun Y, Han J, Wang Z, Li X, Sun Y, Hu Z. Safety and efficacy of bromodomain and Extra-Terminal inhibitors for the treatment of hematological malignancies and solid tumors: A systematic study of clinical trials. *Front Pharmacol*. 2020;11:621093.
237. Subramanian S, Bates SE, Wright JJ, Espinoza-Delgado I, Piekarz RL. Clinical toxicities of histone deacetylase inhibitors. *Pharmaceuticals (Basel)*. 2010;3(9):2751–67.
238. Facciottio C, Casado J, Turunen L, Leivonen S-K, Tumiatu M, Rantanen V, et al. Drug screening approach combines epigenetic sensitization with immunotherapy in cancer. *Clin Epigenetics*. 2019;11(1):192.
239. Plana D, Palmer AC, Sorger PK. Independent drug action in combination therapy: implications for precision oncology. *Cancer Discov*. 2022;12(3):606–24.
240. Hou X, Du C, Lu L, Yuan S, Zhan M, You P, et al. Opportunities and challenges of patient-derived models in cancer research: patient-derived xenografts, patient-derived organoid and patient-derived cells. *World J Surg Oncol*. 2022;20(1):37.

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