NARRATIVE REVIEW

Epigenetic Pharmacology in Precision Oncology: A Narrative Review of DNA Methyltransferase and Histone-Targeting Therapies

Khalida Rizwan[1] | **Zafar Junaid**[2]*

[1]Biomedical Sciences, University of Pavia, Italy | [2]Allied Health Sciences, DUHS, Karachi, Pakistan

***Correspondence:** Zafar Junaid (zafarjunaid493@gmail.com)

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ABSTRACT

Epigenetic changes contribute to cancer initiation, progression, and therapeutic resistance, as they control the expression of genes without affecting their DNA sequence. Epigenetic regulators are potential targets for precision oncology as they are involved in the progression of tumors, immune escape, and resistance to therapy, all of which are associated with aberrant DNA methylation and chromatin modifications. DNA methyltransferase (DNMT) inhibitors and histone-targeting drugs like histone deacetylase (HDAC) inhibitors have been clinically beneficial, particularly in hematological malignancies. However, they have a limited number of drawbacks, such as lack of specificity, toxicity, resistance, and lack of predictive biomarkers. With recent developments in multi-omics profiling, single-cell epigenomics, and targeted epigenome editing, more personalized therapeutic strategies are becoming a reality. This narrative review outlines the molecular mechanisms, clinical applications, and drawbacks in the use of DNA methyltransferase and histone-targeting therapies, and introduces novel strategies for patient selection based on biomarkers and for combination therapy. The combination of epigenomic technologies and precision medicine strategies could enable more effective therapeutic strategies and help develop more targeted, more durable types of cancer therapies.

Keywords: Chromatin Assembly and Disassembly, DNA Methylation, Epigenomics, Histone Deacetylase Inhibitors, Molecular Targeted Therapy, Neoplasms; Precision Medicine.

INTRODUCTION

Protein and other genetic changes are not the only mechanisms that can cause cancer. There are also complex changes in epigenetic regulation [1]. Gene expression is regulated by epigenetic mechanisms such as DNA methylation, modifications of the histones, chromatin remodeling and regulation by non-coding RNAs without changing the DNA sequence. In cancer, these processes are disrupted which leads to unchecked proliferation, immune evasion, genomic instability and resistance to therapy [2]. Many epigenetic alterations are potentially reversible, providing a rationale for therapeutic strategies aimed at restoring abnormal gene-regulatory patterns [1, 3]. The two important therapeutic targets include the DNA methyltransferases (DNMTs) and the histone-modifying enzymes, which are known to play a key role in controlling the structure of chromatin and the activity of transcription [4]. Cancer cells can turn off tumor suppressor genes and keep the cells in a cancerous state by altering the DNA methylation and histone modification patterns [5]. Epigenetic therapy has become a key therapeutic approach in modern oncology with the clinical success of DNMT inhibitors, such as azacitidine and decitabine, in hematological malignancies, as well as histone deacetylase (HDAC) inhibitors like vorinostat, romidepsin and panobinostat [6].

Despite the progress made, the epigenetic therapies have not yet overcome some of the clinical obstacles such as clinical non-responsiveness, toxicity, resistance mechanisms, and lack of predictive markers [7]. The use of precision oncology technologies, such as genomic, transcriptomic and epigenomic profiling, has helped to better identify vulnerabilities of tumors and generate more personalized therapeutic treatment plans [8]. Alongside these approaches, blood-based genomic profiling using circulating tumor DNA, cell-free DNA, and DNA methylation signatures is being investigated for the non-invasive detection of early molecular alterations associated with cancer development [9]. The present narrative review aimed to summarize advances in the field of DNA methyltransferase and histone targeting therapy, their molecular mechanism of action, clinical applications, limitations, and potential future applications in precision oncology. It also aimed to emphasizes the use of biomarker-based strategies, combination strategies and future directions in enhancing the efficacy and clinical translation of epigenetic cancer therapeutics.

A narrative literature review was conducted to evaluate recent advances in epigenetic pharmacology within precision oncology, focusing on DNA methyltransferase inhibitors and histone-targeting therapies. Relevant literature published primarily between 2020 and 2026 was identified through PubMed/MEDLINE, Scopus, and Web of Science using keywords related to epigenetics, DNA methylation, histone modification, chromatin regulation, and cancer therapy. Original research articles, clinical trials, and high-quality reviews addressing molecular mechanisms, therapeutic applications, biomarkers, resistance mechanisms, and emerging strategies were included. The collected evidence was critically analyzed and synthesized to provide an updated overview of current developments, challenges, and future perspectives in epigenetic cancer therapeutics.

EPIGENETIC DYSREGULATION AS A THERAPEUTIC VULNERABILITY IN CANCER

A combination of genetic changes and epigenetic reprogramming that alters cell identity and transcriptional control is responsible for the progression of cancer. Epigenetic changes affect the expression of a gene without altering the DNA sequence, such as DNA methylation, other modifications of the histones, and control of chromatin structure and function by non-coding RNAs (**Figure 1**). These processes are extensively

altered in malignant cells, allowing them to proliferate indefinitely, to fail to differentiate, to evade the immune system, to spread to other parts of the body and to develop resistance to treatment [10]. Epigenetic abnormalities are potentially reversible and can therefore be good targets for pharmaceutical modulation. One of the best studied epigenetic processes in tumour development is DNA methylation. It is controlled by DNA methyltransferases (DNMTs), which include DNMT1, DNMT3A and DNMT3B, involved in maintenance and establishment of methylation patterns. A loss of DNA methylation (global hypomethylation) and gain of methylation (promoter hypermethylation) are common features of abnormal methylation in cancer cells. Genomic hypomethylation is associated with genomic instability, activation of repetitive elements in the genome and chromosomal abnormalities, while hypermethylation of promoters causes transcriptional repression of tumor suppressor genes which regulate the cell cycle, DNA repair, apoptosis and immune surveillance. This epigenetic silencing can have functional consequences of genetic loss-of-function mutations and give malignant cells a selective growth advantage [4].

Another important layer of regulation of chromatin structure and activity is provided by modifications of the histones. Chromatin accessibility is regulated by the dynamic interplay between the histone acetyltransferases (HATs) and histone deacetylases (HDACs) that regulate the interaction between DNA and histone proteins. In various cancers, higher levels of HDAC activity led to more gene silencing and increased condensation of chromatin, which results in repression of genes associated with differentiation, apoptosis, and cellular stress response [11]. Likewise, deregulated histone methylation via enzymes like enhancer of zeste homolog 2 (EZH2), lysine demethylases and protein arginine methyltransferases is linked to oncogenic transcriptional programs and tumor progression [12].

Because the epigenetic state of the genome is important for the maintenance of cancer cells' malignant phenotype, epigenetic dysregulation is important for therapeutic purposes. Epigenetic enzyme targeting can reactivate silenced gene expression, induce tumour differentiation, improve the immune-mediated recognition and sensitivity to other anticancer treatments. This idea has already been realized in the clinic, as DNMT inhibitors and histone deacetylase inhibitors are active in hematological malignancies [13].

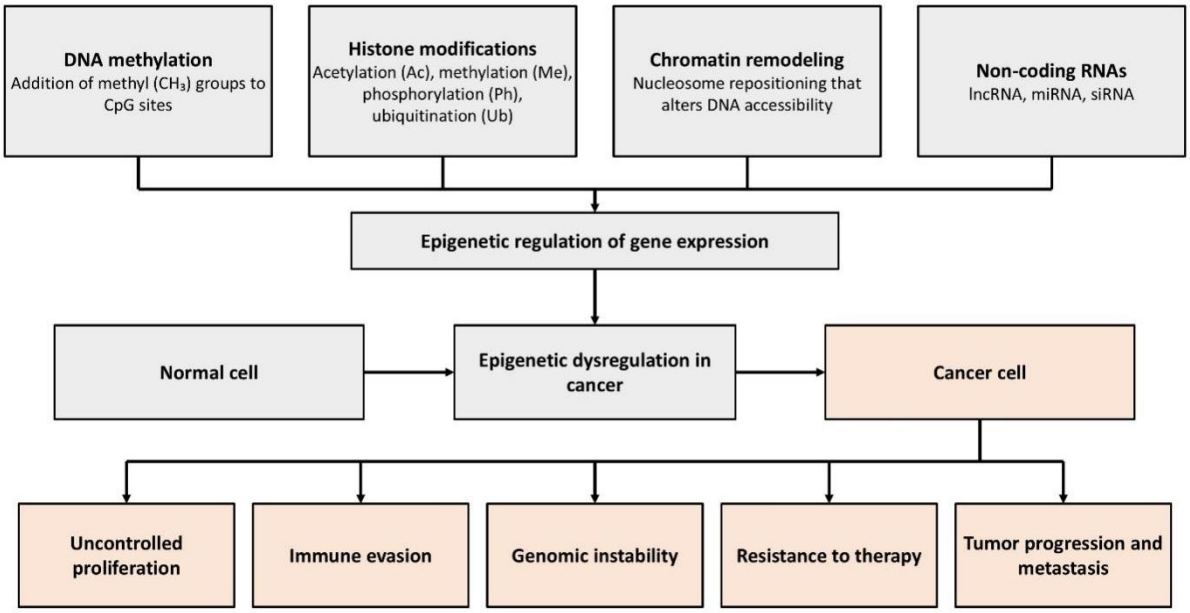


Figure 1: Epigenetic regulation of gene expression and its contribution to cancer progression.

The field of cancer epigenomics has moved from a 'one size fits all' approach to epigenetic modulation to precision-based therapeutic approaches in recent years. The combination of DNA methylation profiling with chromatin accessibility sequencing, single-cell epigenomics, and multi-omics is helping identify epigenetic vulnerabilities and predictive biomarkers in tumors [14]. These advances will help to enhance treatment efficacy, overcome therapeutic resistance, and enable better patient selection and the next generation of personalized epigenetic-based cancer treatments (**Table I**).

Table I: Major Epigenetic Targets, Mechanisms, and Clinically Relevant Therapeutic Agents in Precision Oncology

Study (Reference)	Epigenetic target/regulator	Molecular mechanism and biological effect	Representative therapeutic agents	Clinical relevance in oncology
Short et al., 2022 [15]	DNA methyltransferases (DNMT1, DNMT3A, DNMT3B)	Aberrant DNA methylation contributes to transcriptional silencing and malignant cellular programs. DNMT inhibitors induce hypomethylating and cytotoxic effects through DNA methyltransferase inhibition.	Azacitidine, Decitabine	Azacitidine and decitabine are established hypomethylating agents used in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).
Kalinkova et al., 2023 [16]	DNA methylation pathway in myeloid malignancies	Hypomethylating agents alter abnormal DNA methylation and can modify leukemic differentiation and gene-expression programs; resistance limits therapeutic efficacy.	Azacitidine, Decitabine	HMAs constitute an important therapeutic approach in AML and MDS, with ongoing investigation of combinations and strategies to overcome resistance.
Parveen et al.,	Histone	HDAC inhibition increases histone	Vorinostat,	Several HDAC inhibitors have

2023 [17]	deacetylases (HDACs)	acetylation and alters chromatin accessibility and gene-expression programs, promoting cell-cycle arrest and apoptosis in malignant cells.	Romidepsin, Belinostat, Panobinostat	received regulatory approval for hematological malignancies, including cutaneous/peripheral T-cell lymphomas and multiple myeloma.
Julia & Salles, 2021 [18]	EZH2 histone methyltransferase / PRC2 complex	EZH2 catalyzes H3K27 trimethylation through PRC2, promoting transcriptional repression. EZH2 dysregulation contributes to abnormal B-cell programs and follicular lymphomagenesis.	Tazemetostat	Tazemetostat provides targeted therapy for selected patients with EZH2-mutated follicular lymphoma and has also demonstrated activity in EZH2-wild-type disease.
Morschhauser et al., 2020 [19]	EZH2 as an oncogenic epigenetic driver	Pharmacological EZH2 inhibition reduces aberrant PRC2-mediated chromatin repression and can restore expression of genes involved in cellular differentiation and growth control.	Tazemetostat	Phase II clinical evidence demonstrated activity of tazemetostat in relapsed/refractory follicular lymphoma, supporting its clinical development and approval.
Bhat et al., 2021 [20]	Histone lysine methyltransferases (KMTs)	Dysregulated protein lysine methylation alters transcriptional regulation and cellular states; KMTs represent druggable epigenetic "writer" enzymes in cancer and other diseases.	EZH2 inhibitors and other KMT inhibitors	KMTs constitute an expanding class of therapeutic targets, with selected inhibitors reaching clinical development while many remain in preclinical investigation.

DNA METHYLTRANSFERASE-TARGETING THERAPIES: MECHANISMS AND CLINICAL APPLICATIONS

DNA methyltransferases (DNMTs) are one of the most clinically validated epigenetic targets in oncology because they are pivotal for the abnormal DNA methylation that is characteristic of cancer cells. Mammalian DNMTs are mainly composed of the maintenance DNMT1, the de novo DNMT3A and DNMT3B involved in cellular differentiation and malignant transformation. In cancer, dysregulated DNMT activity leads to the widespread hypermethylation of promoters, silencing of tumor suppressor genes, and the establishment of malignant cell states [21]. This has thus become a strategy to overcome epigenetic repression and reactivate normal gene expression programs, and targeting these enzymes has become a priority. Azacitidine is incorporated predominantly into RNA, although a proportion is converted into a deoxyribonucleotide and incorporated into DNA, whereas decitabine is incorporated directly into DNA. Following DNA incorporation, both agents form covalent complexes with DNMTs, resulting in DNMT depletion and passive DNA demethylation during subsequent cell divisions [22]. These drugs have been mainly epigenetic, acting by the re-expression of silenced genes at lower therapeutic concentrations, and directly cytotoxic at higher concentrations by pathways of DNA damage. This dose-dependent dual mechanism has affected their application in the clinic, especially in diseases in which epigenetic abnormalities play an important role in malignant transformation [23].

DNMT inhibitors have been most clearly shown to have clinical utility in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Azacitidine and decitabine are now proven therapeutic choices for the patient who has higher-risk MDS and AML who is not being considered for intensive chemotherapy. They have been shown to have clinical advantages such as better hematological responses, disease delay, and prolongation of survival in certain patient groups. Therapeutic strategies recently developed are aimed at using DNMT inhibitors together with other targeted drugs to improve the effects [24]. One of the recent breakthroughs is the use of hypomethylating agents in conjunction with a B-cell lymphoma 2 (BCL-2) inhibitor, venetoclax, which has led to a significant increase in response rates in older or medically unfit AML patients. The molecular markers such as TP53 modifications, IDH mutations, and DNA methylation signatures that affect sensitivity to these combinations are still under investigation [25]. Resistant tumor cells can develop through a variety of mechanisms: they may become more resistant to drugs because they take them up and metabolize them in different ways, they may recover methylation patterns, they may increase the expression of DNMTs, they may increase DNA repair capacity, and they may select for the drug-resistant tumor clones. Moreover, traditional DNMT inhibitors are not genome-specific and cause methylation changes throughout the genome which could lead to unintended side effects and unpredictable biological responses [26].

Another novel idea is to combine DNMT inhibitors with immunotherapies. Epigenetic reprogramming could improve the immunogenicity of the tumors by up-regulation of genes involved in immune response, antigen presentation pathways and endogenous retroviral elements. This has led to clinical trials testing hypomethylating agents in conjunction with the immune checkpoint inhibitors, especially in solid tumors where epigenetic therapy has minimal activity [27]. In summary, epigenetic drugs have paved the way for epigenetic therapy as an important clinical aspect of precision oncology. Further advancements in biomarker discovery, improved combination designs and the development of selective agents that will affect only specific methylation aberrations and lessen the effects on the rest of the body will be important for future developments.

HISTONE-TARGETING THERAPIES: HDAC, HISTONE METHYLTRANSFERASE, AND EMERGING CHROMATIN MODULATORS

Histone modifications are an important chromatin regulation mechanism that influences chromatin structure, transcription, DNA repair and cell differentiation. In cancer, hyperactive histone-modifying enzymes help to maintain oncogenic pathways and inhibit genes that provide growth control and apoptosis. In contrast to DNA methylation-directed therapies, histone-targeting therapies modulate the accessibility of chromatin by targeting enzymes that add, remove, or recognize histone modifications [28]. One of the most well-studied classes of histone-modifying enzymes in oncology is the histone deacetylases (HDACs). HDACs deacetylate lysine residues on histones, leading to condensation of the chromatin and

repression of transcription. Increased HDAC activity has been observed in many malignancies, leading to suppression of tumour suppressor pathways, and to changes in cell cycle progression, in differentiation and in immune responses. HDAC inhibitors can reverse acetylation of histones and elicit changes in gene expression that can lead to differentiation, apoptosis, and growth inhibition of tumor cells [29].

A number of HDAC inhibitors have been clinically approved, especially for hematological malignancies. Vorinostat has proven effective in the treatment of Cutaneous T-cell Lymphoma (CTCL) and was the first HDACi to be approved for clinical use [30]. Romidepsin is a selective class I HDAC inhibitor with activity in cutaneous and peripheral T-cell lymphomas, in combination with other drugs in multiple myeloma [31]. Although these successes have been achieved, there are still limited applications of HDAC inhibitors in solid tumors because of low response rates, toxicity, and resistance. The side effects that are commonly encountered are hematological, fatigue, gastrointestinal, and lack of tumor selectivity [32]. Recent studies have focused on isoform-selective HDAC inhibitors to increase therapeutic accuracy. Selective targeting of specific HDACs, e.g., HDAC6, could offer greater anti-tumour activity with less systemic toxicity from global HDAC inhibition. These events are part of the evolution from epigenetic, "broad" modification to molecularly targeted therapy [33].

Histone methylation has also proven to be a promising drug target since methylation can have either activating or repressive effects depending upon the type of histone that is modified. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of polycomb repressive complex 2 (PRC2) that is responsible for trimethylation of histone H3 lysine 27 (H3K27me3), involved in silencing transcription. Dysregulated EZH2 activity, including gain-of-function mutations or overexpression in selected malignancies, can promote abnormal PRC2-mediated transcriptional repression and contribute to tumor progression [34]. In addition to HDACs and EZH2, multiple novel chromatin regulators are the subject of study as potential therapeutic targets. The bromodomain and extraterminal domain (BET) proteins function as epigenetic readers that can identify acetylated histones and control transcription of cancer-related genes. BET inhibitors have been shown to have biological activity in selected solid tumors and hematological malignancies, but clinical development has been impeded by acquired resistance and short-lived responses [35]. Also, inhibitors of lysine-specific demethylase 1 (LSD1), protein arginine methyltransferases (PRMTs), and other chromatin-modifying enzymes are under investigation because they are involved in tumor progression, stemness, and therapeutic resistance [36].

The combination strategy is becoming a critical step in achieving the best clinical outcomes with histone-directed therapies. A combination of HDAC inhibitors and DNA methyltransferase inhibitors could be used to evoke synergistic epigenetic remodeling via simultaneous changes to chromatin and to DNA methylation [37]. In addition, an effort to integrate with immune checkpoint inhibitors is underway since epigenetic modulation could improve antigen presentation, immune recognition, and the immunogenicity of tumors [38]. These strategies will need to be implemented with biomarker-based patient selection of tumors with defined epigenetic vulnerabilities. In summary, the development of HTT has broadened the therapeutic options in epigenetic oncology beyond targeting DNA methylation. Selective inhibitors, combinations, and molecular biomarkers are being developed, and the clinical benefits have been proven principally for haematological cancers.

PRECISION ONCOLOGY INTEGRATION: BIOMARKERS, MULTI-OMICS AND PATIENT SELECTION

Epigenetic therapies will become an integral part of precision oncology if molecular characteristics can be identified which can predict therapeutic sensitivity, therapeutic resistance and clinical outcome. DNMT and histone-targeting agents are clinically active but many have variable activity, which may depend on the tumor biology, epigenetic dependency, and microenvironment. Thus, current epigenetic oncology has bypassed the empirical approach to chromatin-modifying drugs and has moved towards the identification of biomarkers to allow rational selection of patients [39]. Epigenetic biomarkers provide important opportunities for predicting response to targeted therapies. Epigenetic changes such as altered methylation and chromatin patterns can result from genetic mutations in epigenetic regulators, including isocitrate dehydrogenase (IDH1/2), ten-eleven translocation (TET) enzymes, DNMT3A, and EZH2, and offer unique therapeutic opportunities. IDH mutations produce abnormal metabolites that block DNA and histone demethylation pathways, causing broad epigenetic remodeling [40]. Likewise, mutations in EZH2 or its overexpression may lead to dependence on polycomb repression for the survival of certain malignancies, thus justifying the use of EZH2 inhibitors in these settings. These molecular properties are indicative of the close relationship between genetic and epigenetic changes in the determination of treatment response [41].

The methylation signatures are also beginning to be found as clinically useful markers for tumor classification and therapeutic stratification. The molecular subgroups that can be detected by methylation profiling might not be separable by standard histopathological analysis. For central nervous system tumors, DNA-based methylation has already proved useful for better diagnostics, and similar studies are underway to determine the predictive value of methylation for response to epigenetic therapies in hematological and solid malignancies. Moreover, liquid biopsy methods using methylation in the blood of circulating tumor DNA are currently being investigated to detect disease evolution and treatment efficacy in a minimally invasive manner [42]. The emergence of multi-omics technologies has greatly contributed to the advancement of knowledge regarding epigenetic regulation in cancer. The integration of whole-genome sequencing, transcriptomics, DNA methylation profiling, chromatin accessibility assays (e.g., ATAC-seq), and proteomics offers a comprehensive insight into tumor biology. These methods allow for the discovery of sets of functional epigenetic dependencies, not just individual molecular changes [14]. Single-cell epigenomic technologies have also shown that there is a lot of intratumoral heterogeneity, with different cellular populations in the same tumor having different chromatin states and vulnerabilities [43].

Analytical techniques that rely on artificial Intelligence (AI) are becoming a more common feature in epigenomic precision medicine. AI algorithms, such as machine learning models, can be used to uncover predictive patterns and trends in complex molecular data that can help identify potential drug resistance mechanisms, tumor evolution, and the predictive nature of drug response. AI analysis of methylation, chromatin state, and transcriptomic signatures could improve biomarker discovery and allow personalized treatment selection. But clinical translation will require standardization in datasets, external validation, and incorporation into the clinical oncology workflow [44]. However, a number of challenges that restrict the broad use of epigenetic biomarkers in the clinic exist. The epigenomes of tumors are very dynamic and the epigenome can evolve throughout the course of disease and when exposed to treatments, so it is crucial to perform longitudinal monitoring. Moreover, the relationship between specific epigenetic changes and drug response is context-specific and can depend on tumor type, co-existing mutations, and/or combinations of treatments. Thus, implementation of precision epigenetic therapy will need to involve multiple layers of molecules instead of relying on single molecules as biomarkers [45].

Overall, the future of epigenetic pharmacology depends on combining targeted therapies with advanced molecular profiling strategies. The use of a biomarker to select the appropriate patient, the integration of multi-omics technologies, and computational methods are important steps that will facilitate the transition from epigenetic therapies that act globally to targeted and personalized cancer treatments (**Table II**).

Table II: Emerging Epigenetic Therapeutic Strategies and Precision Oncology Applications

Study (Reference)	Therapeutic strategy / target	Molecular mechanism	Current clinical development status	Precision oncology relevance
Wu et al., 2022 [46]	Protein arginine methyltransferase (PRMT) inhibition	PRMT inhibition alters arginine methylation-dependent transcriptional regulation and immune-related signaling, including induction of a viral-mimicry response that can enhance antitumor immune activity.	Preclinical development with increasing translational interest in PRMT-targeted therapy.	Supports biomarker-guided targeting of tumors with PRMT-dependent transcriptional or immune-regulatory programs.
Carter et al., 2023 [47]	PRMT5 inhibition combined with PARP blockade	PRMT5 inhibition disrupts DNA damage-response pathways and increases tumor-cell sensitivity to PARP inhibition, providing a mechanistic basis for combination therapy.	Preclinical combination studies; PRMT5 inhibitors and PARP inhibitors are being investigated as therapeutic strategies.	Supports synthetic-lethal approaches based on tumor-specific DNA-repair vulnerabilities.
Bhat et al., 2021 [20]	Histone lysine methyltransferase (KMT) inhibition	Targeting aberrant lysine methyltransferase activity alters histone and non-histone methylation programs that regulate transcription, chromatin state, and tumor-cell survival.	Multiple KMT inhibitors are undergoing clinical and preclinical evaluation.	Enables targeting of cancers characterized by specific chromatin dependencies and oncogenic methylation programs.
Chen et al., 2022 [48]	BET bromodomain inhibition	BET proteins recognize acetylated histones and regulate oncogenic transcription through chromatin-reader functions. Selective BET inhibition disrupts aberrant transcriptional programs while potentially improving selectivity over pan-BET inhibition.	Clinical trials and translational development across hematological malignancies and solid tumors.	Potentially useful for tumors exhibiting transcriptional addiction or BET-dependent epigenetic programs.
Shen et al., 2024 [49]	LSD1 (KDM1A) inhibition	LSD1 inhibition alters histone demethylation and transcriptional regulation, promoting differentiation and potentially reducing cancer stem-cell-associated properties. Combination and dual-target approaches may enhance therapeutic activity.	Several LSD1 inhibitors have entered clinical investigation; combination and dual-target strategies remain under development.	Particularly relevant to malignancies characterized by differentiation blockade and LSD1-dependent transcriptional programs.
Guan & Quek, 2025 [50]	Multi-omics-guided precision therapy	Integration of single-cell genomic, transcriptomic, epigenomic, and other molecular layers can resolve tumor heterogeneity and identify cell-state-specific therapeutic vulnerabilities.	Emerging precision-oncology framework with increasing translational application.	Supports individualized treatment selection by linking molecular heterogeneity and epigenetic states with therapeutic vulnerabilities.

COMBINATION STRATEGIES AND RESISTANCE MECHANISMS

Epigenetic therapies have demonstrated their clinical utility, but there are often incomplete responses, acquired resistance and disease relapse as the main limitations with their use as single agents. Therefore, rational combination strategies have been increasingly investigated in the current research, which take advantage of the interactions between epigenetic regulation and other cancer-driving pathways. Epigenetic agents could increase the efficacy of targeted therapies, chemotherapy and immunotherapies by changing the state of transcription and resilencing silenced genes [51]. The most clinically successful combination therapy has been the use of hypomethylating agents with venetoclax, a selective inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (BCL-2). This combination has enhanced response results in older patients and those not suitable for intensive chemotherapy in the case of AML. The therapeutic mechanism is complementary: DNMT inhibitors bring a change in the epigenetic landscape and make the cells more susceptible, while venetoclax is a mitochondrial apoptosis agent by blocking survival signals mediated by BCL-2. In addition to apoptosis regulation, alterations in mitochondrial metabolism, including oxidative phosphorylation and fatty acid oxidation, may contribute to tumor-cell survival and metabolic adaptation, providing further potential targets for cancer therapy [52]. Continuing research seeks molecular predictors to identify the benefit that this approach may provide to patients.

Epigenetic therapies are also being studied with immune therapies. Tumor immune escape can be induced by abnormal epigenetic regulation, which may lead to a decrease in antigen presentation, interferon signal transduction and immune-related gene expression. These effects can be reversed by DNMT inhibitors, which lead to increased expression of tumour-associated antigens and endogenous retroviral elements, possibly improving immune recognition. This has sparked clinical trials on the combination of immune checkpoint inhibitors and HDAC inhibitors in various solid tumors and hematological malignancies. Despite these differences in tumor immune microenvironment and states of epigenetics, however, identifying patients most likely to respond is still a significant hurdle [53]. Beyond epigenetic modulation, therapeutic strategies targeting the tumor microenvironment (TME) have also gained attention as potential approaches to overcome resistance to immune checkpoint inhibition. These strategies aim to modify immunosuppressive cellular and molecular interactions within the TME and may complement conventional PD-1/PD-L1-directed therapies [54]. These innovations have not stopped resistance from being a major obstacle to sustainable solutions, however. Epigenetic therapies can be resisted in several ways, such as changes in the metabolism of the drugs, decreased entry of the drug into the cell, re-expression of abnormal chromatin, and the emergence of resistant tumor clones. Cancer cells can undergo adaptive epigenetic remodeling and continue to survive under the pressure of continued therapy. Furthermore, pre-existing resistant sub-populations can grow in response to treatment to allow for tumor heterogeneity and lead to relapse.

Future strategies are going to include the use of combinations of epigenetic agents using biomarkers, sequential uses, and the development of more selective epigenetic agents. Longitudinal molecular monitoring, such as the use of liquid biopsy as a tool for methylation assessment and single-cell molecular profiling, could result in the early detection of resistance and treatment adaptation. In summary, combination strategies are a middle ground that can serve as a prime pathway to unlock the therapeutic potential of epigenetic pharmacology and to realize more lasting effects in precision oncology (**Figure 2**).

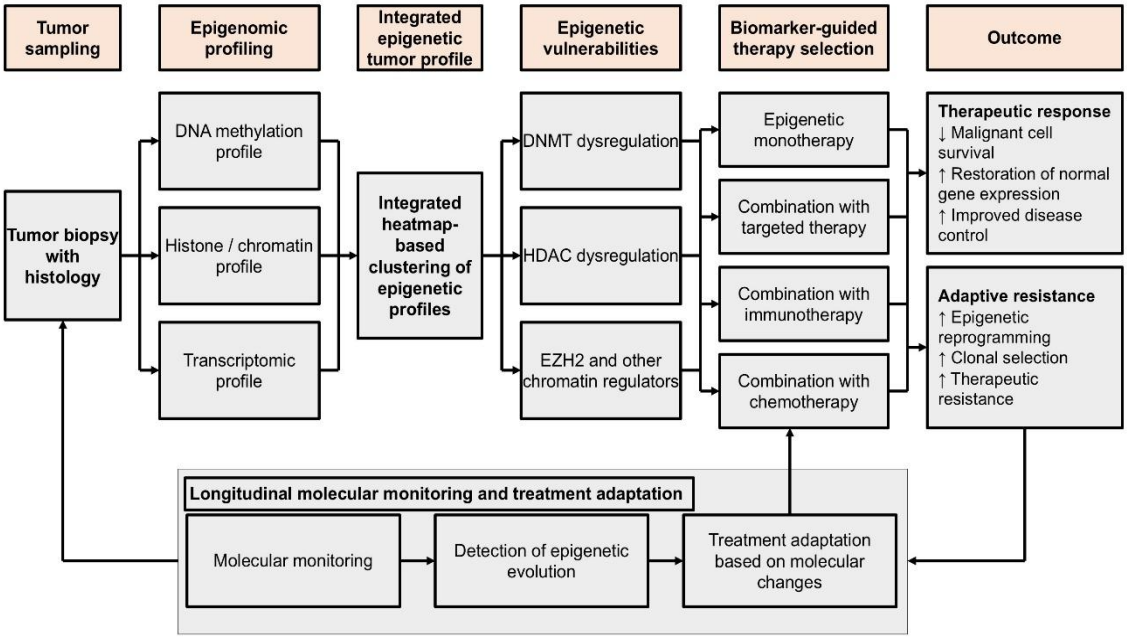


Figure 2: Biomarker-guided integration of epigenomic profiling into precision oncology.

CURRENT CHALLENGES AND FUTURE THERAPEUTIC DIRECTIONS

While great strides have been made in the understanding of epigenetic pharmacology, there are numerous biological and clinical challenges that still exist that hinder the widespread use of epigenome-targeting therapies in precision oncology. One of the drawbacks is the absence of absolute specificity of the agents that are available. To date, most approved epigenetic drugs have effects on multiple genomic and cellular pathways, and not necessarily on disease-relevant epigenetic abnormalities. This is a broad activity that can adversely affect therapeutic windows and/or toxicity, especially if administered for extended periods of time.

Another important challenge is the heterogeneity of tumors, which is the second obstacle to clinical translation of epigenetic therapies. Malignant tumors are heterogeneous collections of cells that have a mixture of different genetic and epigenetic characteristics in different areas, leading to different sensitivities of the cells to drugs. Moreover, epigenetic landscapes change over time, with changes that can occur as the disease progresses or occur in response to different treatments. This plasticity enables cancer cells to change their response to treatment by adopting different transcriptomic programs and can help them become resistant [56]. Targeted epigenome editing is making new gains toward increased treatment precision. Locus-specific modification of epigenetic marks without DNA sequence modification is possible using a catalytically inactive CRISPR-associated protein (dCas9) fused to a DNA methyltransferase or demethylase domain [57]. These are still mostly experimental, but offer a conceptual framework for the correction of pathogenic epigenetic states in particular genomic regions without off-target effects. To achieve clinical translation, additional enhancements in delivery systems, efficiency, and safety will be crucial.

There will also be a big shift in epigenetic drug development and patient selection with the integration of AI and computational biology. Complex multi-omics data can be used to identify treatment response, resistance, and disease evolution signatures using machine learning approaches [58]. These methods, coupled with single-cell sequencing and spatial profiling technologies, can enable spatio-temporal characterization of tumor epigenetics and direct adaptive therapeutic strategies. Selective epigenetic drugs may be used in conjunction with molecularly guided treatment in the future, which is likely to be essential for the further development of epigenetic oncology. Future optimizations of targeted inhibitors of chromatin regulators, novel biomarker platforms and logical combination treatments could provide new opportunities [39]. Finally, for clinical translation to be successful, epigenetic information should become part of routine oncology care, allowing epigenetic-based therapies to shift from generic chromatin modulations to truly personalized cancer therapies.

CONCLUSION

Epigenetic pharmacology has emerged as a key area in precision oncology due to its focus on reversible mechanisms that drive the progression and resistance to therapy in cancer. Emerging chromatin modulators provide new therapeutic opportunities, and DNMT inhibitors and histone-targeting therapies have proven to be clinically useful, especially in hematological malignancies. But resistance/tolerance, toxicity, tumor heterogeneity, and lack of markers are still issues. The use of advances in multi-omics profiling, single-cell epigenomics and targeted epigenome editing will bring improved patient selection and treatment precision. However, the development of selective agents, as well as rational combinations, will be crucial to achieve durable clinical responses in the future.

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