THE FUTURE OF EPIGENETICS

Emerging technologies and clinical applications

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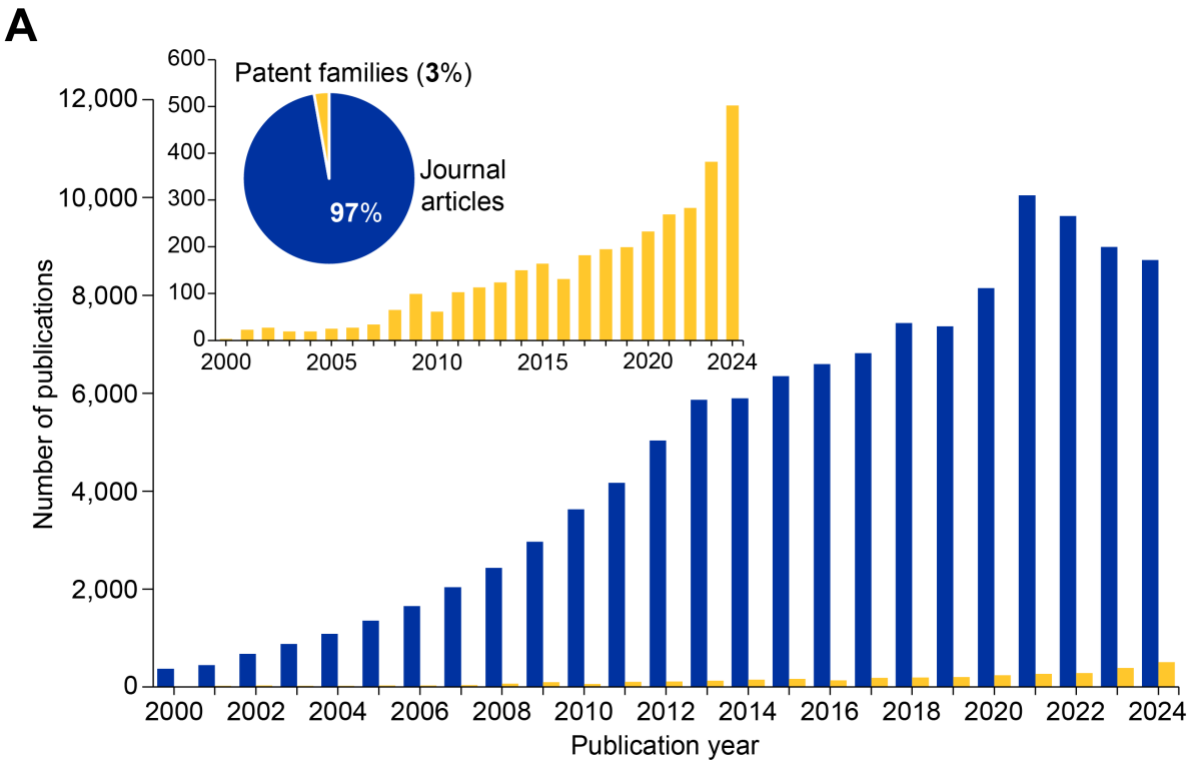
Epigenetics, the study of heritable changes in gene expression that do not involve alterations to the DNA sequence, has emerged[1] as a transformative field in biology and medicine, revealing how gene expression is modulated in response to internal and external cues. Epigenetic regulation is fundamental to developmental biology, disease pathogenesis, gene-environment interactions, transgenerational inheritance, and therapeutic development. By elucidating how genes are dynamically regulated beyond the static genome, epigenetics connects genetics and environmental influences, offering insights into disease mechanisms and innovative therapeutic strategies.

We analyzed the CAS Content Collection™, the largest human-curated repository of scientific information, to outline the progress made in epigenetic research and identify key emerging concepts and challenges. This comprehensive analysis examines the scientific foundations, clinical applications, and technological innovations impacting modern life sciences and healthcare.

Our analysis found steep and continual growth in publications over the last two decades with over 120,000 epigenetics-related publications now in the CAS Content Collection (see Figure 1). The field is dominated by journal articles (97%), with patents comprising only 3% of publications (see Figure 1A), indicating that epigenetics remains in the discovery and validation phase.



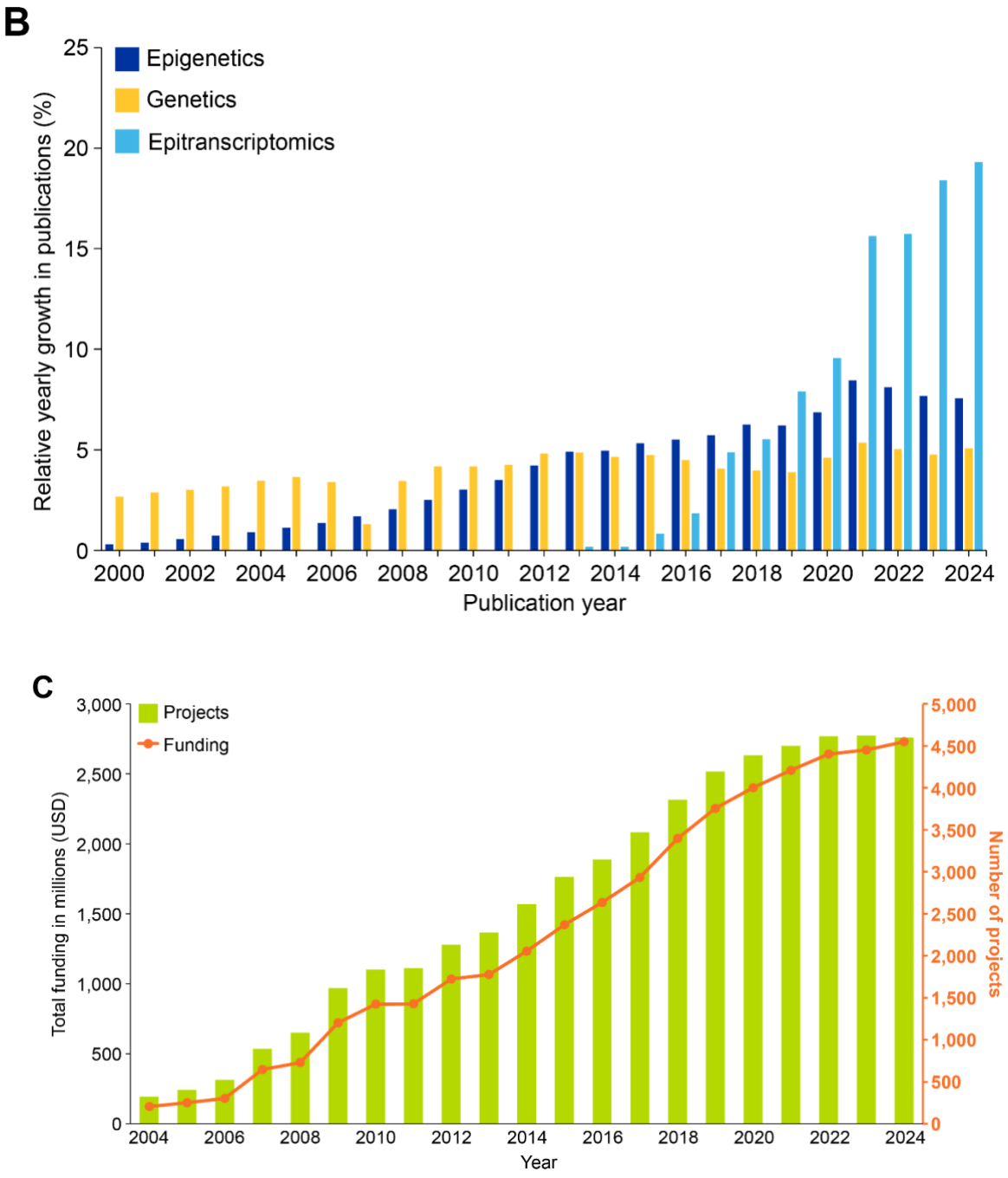


Figure 1. *(A) Publication trends for epigenetics related documents and (B) relative yearly growth in publications related to epigenetics, genetics, and epitranscriptomics. Source: CAS Content Collection. (C) Trends for the number of projects funded and total funding granted to epigenetics-related projects by the NIH.*
However, the sharp increase in patent publications (see inset graph in Figure 1A) indicates growing commercial interest and translational potential in this rapidly evolving field. Notably, epigenetics publications have outpaced genetics publications since 2014 (Figure 1B). The emergence of epitranscriptomics as a distinct field is noticeable after 2020 (Figure 1B).

This growth trajectory aligns with substantial funding increases — total research funding grew from USD $200 million in 2004 to over USD $4.5 billion in 2024, supporting approximately 2,700 projects annually (see Figure 1C). The consistent rise in project numbers and funding levels, with average project funding increasing from USD $1.2 million to USD $1.7 million, underscores sustained governmental and private sector commitment to advancing epigenetic research and its clinical translation.

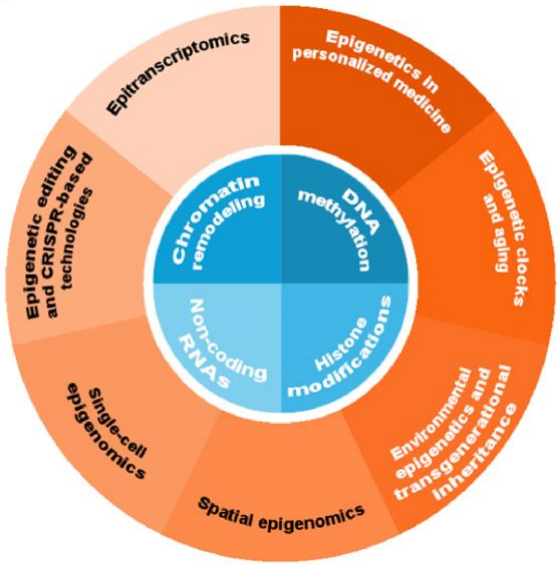
The commercial significance of epigenetics has expanded dramatically, with the global epigenetics market valued at USD $1.84 billion in 2023 and projected to reach USD $6.77 billion by 2033. This growth is driven[2] by more than ten FDA-approved epigenetic drugs including azacitidine (Vidaza®) and vorinostat (Zolinza®) for cancer treatment. There are also over 35 epigenetic therapies in clinical trials. These candidates predominantly target various malignancies but are starting to show diversification beyond cancer.

Let's explore epigenetics in more detail to understand how it's evolving and what it means for the future of medicine:

Core mechanisms of epigenetic regulation

Epigenetic mechanisms regulate gene expression through chemical modifications of DNA and chromatin structure without altering the DNA sequence. These mechanisms comprise four main classes: DNA methylation, histone modifications, non-coding RNA (ncRNA) regulation, and chromatin remodeling. As we examined epigenetics-related publications, we saw few publications addressing these mechanisms at first — an understandable result since the field was being established in the early 2000s (see Figure 2).

A



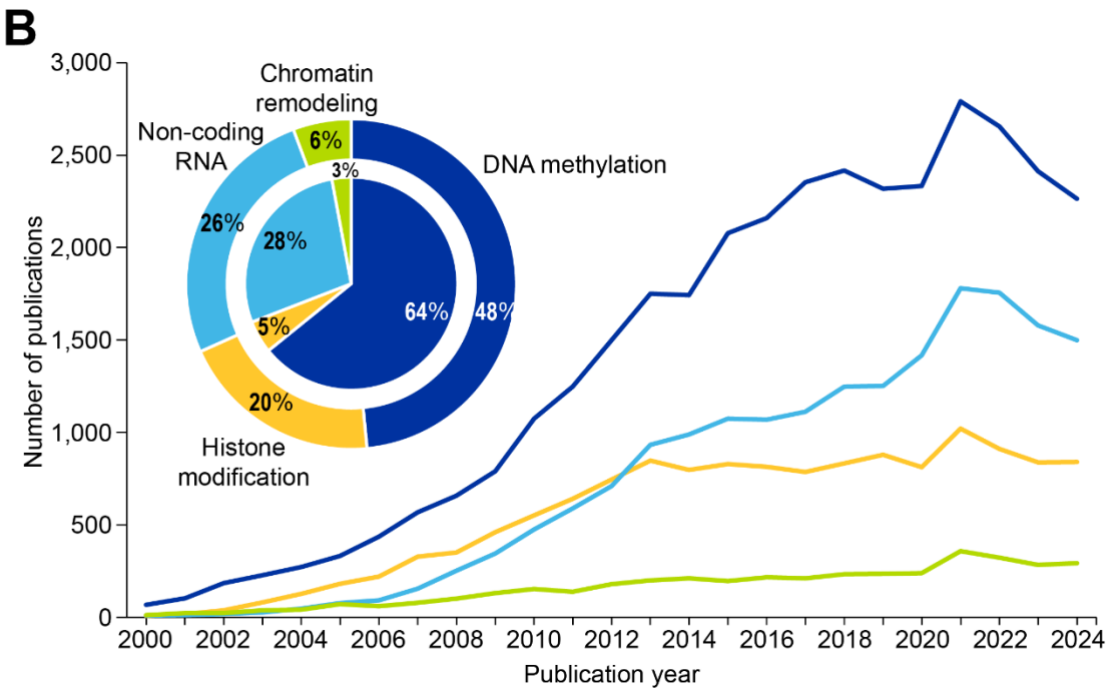


Figure 2: *(A) Core mechanisms of epigenetic regulation (inner pie chart) and recent advances (outer donut chart). (B) Publication trends of epigenetic mechanisms. The outer donut and inner pie chart in the inset image represent journal and patent publications, respectively. Source: CAS Content Collection.*

Subsequently, all four mechanisms showed accelerated growth, with DNA methylation experiencing the steepest increase and coming to dominate the research landscape, both in terms of journal and patent publications. All other mechanisms experienced an increase as well, suggesting the growing recognition of epigenetic targets for drug development.

DNA methylation

DNA methylation[3] is a fundamental epigenetic mechanism involving the addition of methyl groups ($–CH_3$) to the cytosine rings at CpG dinucleotides in DNA, resulting in transcriptional repression. This modification plays a critical role in X-chromosome inactivation, genomic imprinting, and transposon suppression.

DNA methylation is catalyzed by DNA methyltransferases (DNMTs). DNMT1 maintains existing methylation patterns during replication, while DNMT3a/3b establishes new methylation patterns during development or in response to environmental cues. DNMT3L, lacking catalytic activity and mainly expressed in early development, is restricted to the germ cells and thymus in adulthood. DNMTs target CpG islands, regions with high frequency of CpG dinucleotides, often located near gene promoters.

Aberrant methylation patterns have been identified[4] in various diseases including cancer, cardiovascular diseases, mental health disorders, Alzheimer's disease, autism, and metabolic syndromes. Hypermethylation of tumor suppressor gene promoters silences their expression promoting oncogenesis, while global hypomethylation can activate oncogenes and cause genomic instability. DNA methylation patterns change with age, including the accumulation of errors and loss of fidelity in methylation maintenance.

Histone modifications

Histone modifications[5] can be inherited through cell division and can be influenced by environmental factors, potentially impacting development and disease states. Post-translational histone modifications such as acetylation, methylation, phosphorylation, and ubiquitination alter chromatin structure and gene accessibility. Histone acetyltransferases (HATs) and deacetylases (HDACs) regulate acetylation by catalyzing the addition and removal of acetyl groups from histones, while methyltransferases (HMTs) and demethylases (HDMs) control methylation. These modifications primarily occur on lysine, arginine, serine, and threonine residues in histone tails, which are protrusions from the nucleosome core with increased accessibility.

Histone modifications affect the structure of chromatin, which is DNA packaged around histone proteins regulating gene expression, DNA repair, and chromosome condensation during mitosis. Aberrant histone modifications can disrupt gene expression patterns and contribute to tumor development and metastasis, and they are linked to other diseases and disorders such as Alzheimer's, Huntington's disease, autism, aging-associated chromatin changes, and immune dysregulation.

These changes often form a "histone code," with combinations of modifications on different residues synergizing or antagonizing fine-tune chromatin states. They are a dynamic and versatile system for regulating chromatin structure and gene expression, and their reversible nature makes them promising targets for therapeutic interventions.

Non-coding RNAs (ncRNAs)

ncRNAs constitute a diverse class of regulatory molecules that play critical regulatory roles in gene expression and chromatin dynamics without encoding proteins. These RNAs fine-tune gene processing by targeting[6] messenger RNA (mRNA) for degradation or modulating transcriptional machinery.
Three classes have emerged as primary epigenetic regulators: microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and PIWI-interacting RNAs (piRNAs). These ncRNAs orchestrate epigenetic regulation through five principal mechanisms:

- **Chromatin remodeling:** lncRNAs recruit chromatin-modifying complexes to specific genomic loci, influencing chromatin structure and gene expression. For example, X inactive specific transcript (XIST) mediates X-chromosome inactivation by recruiting polycomb repressive complex 2 (PRC2).
- **Transcriptional regulation:** miRNAs and lncRNAs modulate transcription by interacting with transcription factors or RNA polymerases. For example, the lncRNA HOX transcript antisense intergenic RNA (HOTAIR) recruits PRC2 to repress genes on a different chromosome.
- **Post-transcriptional control:** miRNAs bind to the 3′ untranslated regions (UTRs) of target messenger RNAs (mRNAs), leading to degradation or translational inhibition. lncRNAs can act as molecular sponges to sequester miRNAs, which prevents them from targeting mRNAs.
- **RNA modification:** Some ncRNAs guide RNA methylation (e.g., N6-methyladenosine, m6A) or editing, affecting RNA stability and translation.
- **Genome defense:** piRNAs and siRNAs suppress transposable elements, protecting genomic integrity. siRNAs can guide heterochromatin formation in regions with repetitive sequences.

Chromatin remodeling

Chromatin remodeling dynamically modifies[7] chromatin architecture between euchromatin (open, transcriptionally active) and heterochromatin (condensed, transcriptionally silent) states. The basic unit of chromatin is the nucleosome, composed of DNA wrapped around an octamer of histone proteins. Chromatin remodeling is carried out by ATP-dependent complexes, such as switch/sucrose nonfermentable (SWI/SNF), imitation switch (ISWI), chromodomain helicase DNA (CHD)-binding proteins, and INO80 families utilizing ATP hydrolysis to power repositioning, ejection, or restructuring of nucleosomes.

Remodeling mechanisms include nucleosome sliding, histone eviction/exchange, and chromatin compaction/decompaction. These processes work with DNA methylation and histone modifications to regulate gene expression, cell differentiation, and identity maintenance.

Chromatin remodeling dysregulation is linked to cancer, neurological disorders, and developmental diseases. For example, mutations in chromatin remodelers like AT-rich interaction domain 1A (ARID1A) (a component of the SWI/SNF complex) are frequently observed[8] in malignancies. Chromatin remodelers represent promising therapeutic targets for reversing aberrant gene expression.As such, chromatin remodeling is recognized as a mediator of environmental influences (diet, stress, toxins, etc.) on gene expression and health.

Recent advances in epigenetics

Recent progress has shown how epigenetic modifications including DNA methylation, histone modifications, ncRNA regulation, and chromatin remodeling contribute to disease pathogenesis, particularly in cancer. Emerging research on miRNAs and other ncRNAs as epigenetic regulators has identified new therapeutic targets, while advances in individual epigenetic profiling are aiding advancements in personalized medicine approaches. Publication trends show the leading fields of interest (see Figure 3).

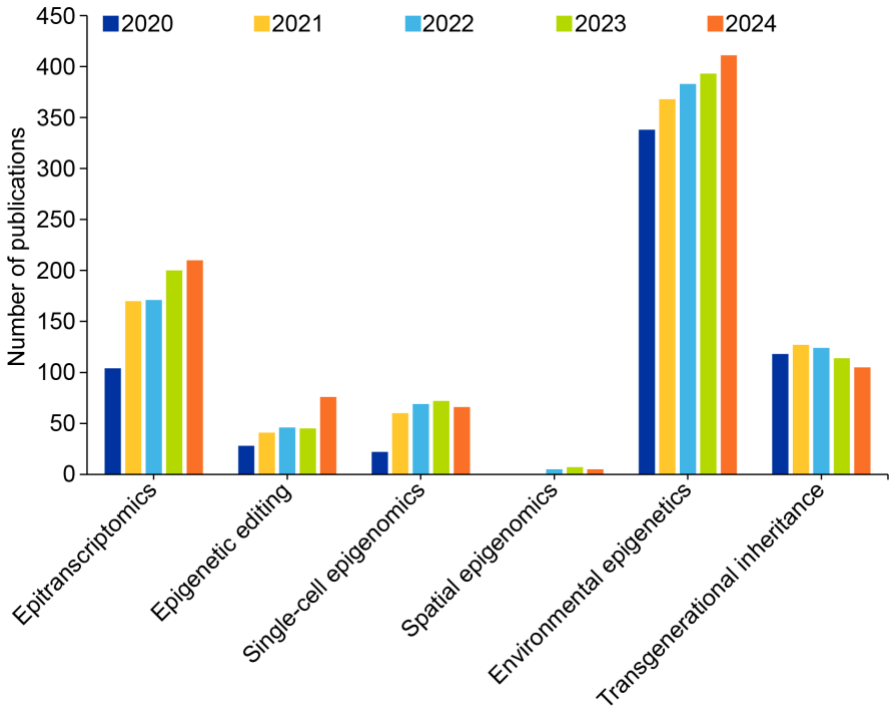


Figure 3: *Publication trends for recent advances in epigenetics research. Source: CAS Content Collection.*

Environmental epigenetics

Environmental factors such as diet, stress, toxins, and lifestyle can induce[9] epigenetic changes through the various mechanisms discussed previously. These modifications might contribute to the development of diseases such as cancer, metabolic disorders, and neurological conditions by altering cellular function and tissue homeostasis. Specific influences include:

- Nutrient availability (e.g., folate, vitamin B12) affecting DNA methylation patterns.
- Chemical exposures (e.g., bisphenol A, pesticides, air pollutants) altering epigenetic marks leading to long-term health consequences.
- Psychological and physiological stress inducing epigenetic changes in stress-response genes and modulating mental health.
- Lifestyle factors (e.g., smoking, alcohol, physical activity levels) influencing disease risk via modulating epigenetic states.

Epitranscriptomics

Epitranscriptomics focuses[10] on the study of chemical modifications to RNA molecules and their role in regulating gene expression and cellular functions. Just as epigenetics explores modifications to DNA and histones that influence gene activity without altering the underlying DNA sequence, epitranscriptomics investigates how RNA modifications affect RNA stability, translation, splicing, and other processes.

Over 170 distinct RNA modifications across mRNA, tRNA, rRNA, and ncRNAs have been identified, with N6-methyladenosine (m6A) being the most abundant and extensively studied modification in eukaryotic mRNA. Key modifications include: m6A methylation at the N6 position of adenosine, influencing mRNA stability, splicing, export, and translation; m5C methylation at the N5 position of cytosine in mRNA and tRNA, affecting RNA stability and translation; pseudouridine (Ψ), an isomer of uridine, enhancing RNA stability and translation efficiency; and adenosine-to-inosine deamination, altering base pairing properties and affecting splicing and protein coding.

The epitranscriptomic machinery comprises three main protein classes:

- "Writers": enzymes that add modifications (e.g., METTL3/METTL14 complex for m6A methylation).
- "Erasers": enzymes that remove modifications (e.g., fat mass- and obesity-associated protein (FTO) and alkB homolog 5, RNA demethylase (ALKBH5) for m6A demethylation).
- "Readers": proteins that recognize and bind to modified RNA (e.g., YTH domain proteins for m6A recognition), which collectively regulate RNA modification dynamics.

RNA modifications regulate multiple cellular processes, and dysregulation of these modifications contributes to various pathologies. In cancer, m6A modifications are often altered[11] in tumors and linked to tumor progression, metastasis, and drug resistance. Aberrant RNA editing and modifications are associated with neurodegenerative diseases including Alzheimer's, Parkinson's, and ALS. Additionally, RNA viruses, including HIV and SARS-Cov-2, exploit host RNA modification machinery to regulate viral replication and immune evasion, including epigenetic modifications.

High-throughput sequencing technologies enable genome-wide mapping of RNA modifications, complemented by mass spectrometry and chemical labeling techniques for modification detection and quantification. These advances facilitate therapeutic development targeting RNA modification enzymes.

Targeting components of RNA modification machinery (writers, erasers, and readers) is being explored as a strategy for treating diseases. For example, inhibitors of FTO, which are m6A demethylases, have shown promise in cancer therapy, while modified nucleotides in mRNA vaccines enhance stability and translation efficiency.

Overall, current research focuses on deciphering the "epitranscriptome code", developing tools for precise *in vivo* manipulation of RNA modifications, and exploring modifications in ncRNAs. Single-cell epitranscriptomics is revealing cell-type-specific RNA modification patterns and their functional consequences. An emerging technology, multi-omics integration, combines epigenomic data with transcriptomics, proteomics, and metabolomics using technologies like CUT&RUN and Hi-C integration, providing holistic cellular function views. These approaches enable comprehensive pathway analysis and biomarker discovery in complex diseases.

Transgenerational inheritance

Transgenerational inheritance refers to the transmission[12] of environmentally induced epigenetic changes across multiple generations independent of DNA sequence alterations. This phenomenon has been observed in plants and animals, suggesting that environmental exposures experienced by one generation can affect the health and development of subsequent generations. However, verifying the extent and significance of this process in humans is challenging.

Examples of transgenerational epigenetic inheritance include the Dutch Hunger Winter[13] (1944-1945), where altered DNA methylation patterns and increased metabolic risks were observed in subsequent generations of individuals who were subject to famine exposure in the Netherlands. Animal studies have also provided examples of transgenerational effects of endocrine disruptors (e.g., vinclozolin) on reproduction, behavior, and disease susceptibility, while in humans paternal smoking and maternal stress have been linked to epigenetic changes in offspring.

While the mechanisms underlying transgenerational epigenetic inheritance are not fully understood, their effect on raising the risk profile for diseases such as obesity, diabetes, and cardiovascular disorders in descendants of exposed individuals means that it remains an area of active research. Understanding transgenerational effects can also inform policies to reduce exposure to harmful environmental factors, particularly during critical windows of development (e.g., pregnancy).

Epigenetic editing and CRISPR-based technologies

The advent of CRISPR-Cas9 technology has revolutionized genetic engineering, and its application[14] to epigenetics is no exception. Epigenetic editing involves the targeted modification of epigenetic marks without altering the DNA sequence, offering a powerful tool for studying gene regulation and developing novel therapies.

The CRISPR-Cas9 system employs guide RNAs (gRNAs) to direct catalytically inactive Cas9 (dCas9) fused with epigenetic effector domains to specific genomic loci. Key effector domains include DNMT (e.g., DNMT3A), DNA demethylases (e.g., TET1), histone modifiers (e.g., p300, HDACs), and chromatin remodelers, enabling precise addition or removal of epigenetic modifications.

CRISPR-Cas9 technology enables selective activation or repression of gene expression by targeting regulatory elements including enhancers and promoters, allowing researchers to directly test the causal roles of specific epigenetic marks in gene regulation, cellular differentiation, and disease. Additionally, it allows for the examination of epigenetic inheritance across cell divisions, development, and the generation of disease models driven by epigenetic dysregulation.

Therapeutic applications include silencing disease-causing genes (oncogenes, viral genes) and reactivating beneficial silenced genes (tumor suppressors) in cancer and hypercholesterolemia, among others. This approach offers the potential of highly personalized therapies with minimal off-target effects and applications in cellular reprogramming for regenerative medicine. Key advantages of CRISPR-based epigenome editing include high targeting precision, versatility through interchangeable effector domains, and reduced mutagenic risk compared to gene editing.

Advancing this technology requires developing high-fidelity Cas variants and optimized gRNA designs to minimize off-target effects. Furthermore, multiplexed targeting will enable the investigation of complex regulatory networks, while improved delivery methods (viral vectors, nanoparticles) will facilitate clinical translation. Emerging technologies in this space include epigenome editing tools, particularly CRISPR/dCas9-based systems fused with epigenetic effectors (DNMTs, TETs, HDACs). Alternative platforms include TALE549 and zinc-finger proteins for locus-specific targeting.

Single-cell epigenomics

Single-cell epigenomic technologies enable[15] the profiling of epigenetic modifications at the resolution of individual cells. This provides unprecedented insights into cellular diversity and function and overcomes the drawbacks of traditional bulk sequencing methods, which look at average epigenetic marks across millions of cells.

Techniques including single-cell ATAC-seq (assay for transposase-accessible chromatin using sequencing) and single-cell ChIP-seq (chromatin immunoprecipitation sequencing) profile chromatin accessibility, and histone modifications in individual cells are at the forefront of this trend. Applications include mapping epigenetic landscapes during embryogenesis, cellular and tissue differentiation, cell fate decisions, and immune system heterogeneity.

In cancer research, single-cell epigenomics can uncover intratumoral epigenetic heterogeneity relevant to clonal evolution, drug resistance, and metastasis. The technology is also used to elucidate epigenetic changes in neurodevelopment, neurodegeneration, and immune cell differentiation, informing our understanding of autoimmune diseases and immunotherapy responses.

Future directions include integration with spatial transcriptomics, temporal profiling of epigenetic marks in response to cellular processes or environmental stimuli, and clinical applications for biomarker identification and personalized medicine.

Spatial epigenomics

Spatial epigenomics is cutting-edge technology that combines[16] the study of epigenetic modifications with spatial context within tissues. This approach bridges single-cell epigenomics and histology, revealing how epigenetic regulation varies across tissue regions and influences cellular organization, function, and communication in health and disease.

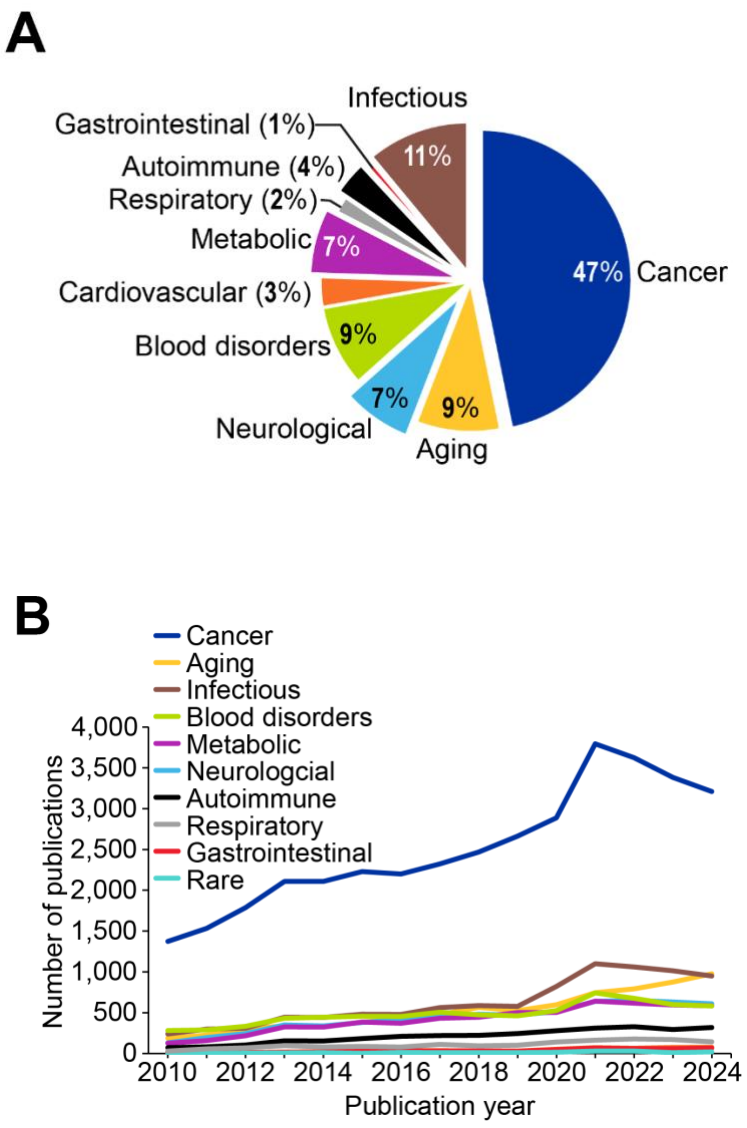
Applications include mapping tissue patterning during organogenesis guided by epigenetic changes; identifying spatially distinct epigenetic signatures within tumors (core versus invasive margins), which may drive metastasis or drug resistance; characterizing region-specific epigenetic changes in brain tissues or cell types providing insights into neurodevelopment, plasticity, and neurodegenerative diseases; understanding epigenetic regulation across immune cell niches; and the influence of epigenetic states in the tissue microenvironment.

Epigenetics in health and disease

Epigenetic modifications guide embryonic development and cell fate decisions by activating or silencing specific gene sets. Dysregulation of these processes impacts numerous pathologies, and while cancer has been the leading area of disease under investigation, the role of epigenetics in other conditions is being explored.

Cancer

Genetic mutations have long been recognized as drivers of cancer, and epigenetic alterations are now understood to play an equally critical role in tumorigenesis. The research landscape reveals cancer's dominance with 47% of publications, reflecting both the field's maturity and clinical translation success (see Figure 4).



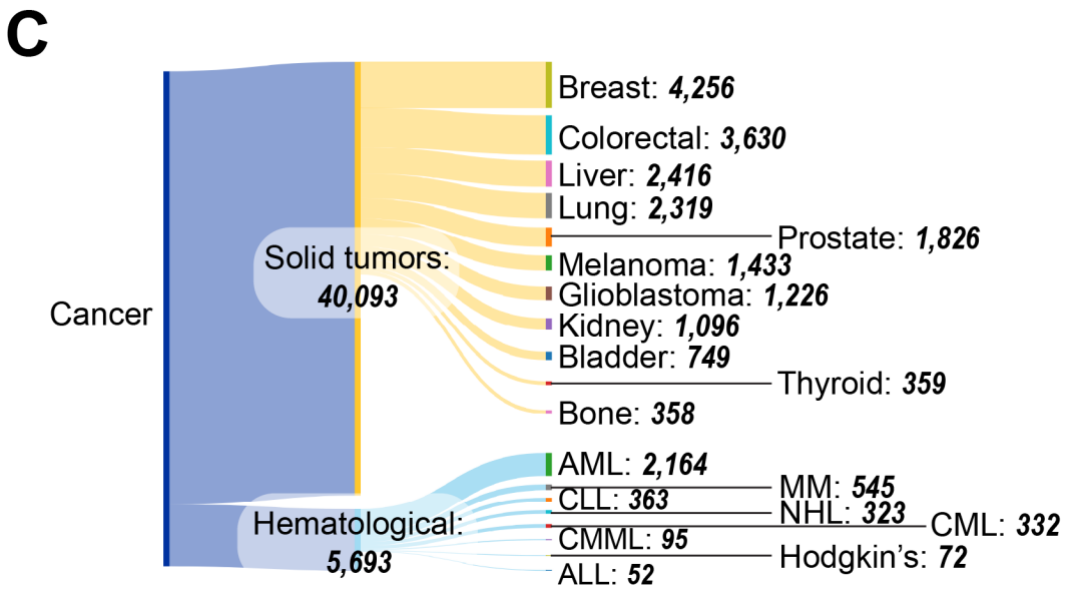


Figure 4: *(A) Relative distribution of epigenetics related publications among various disease types, (B) (B) yearly trends for publications of the broader disease categories shown in panel A, and (C) Sankey charts showing the distribution across various cancer subtypes. Source: CAS Content Collection.*

Solid tumors account for an overwhelming majority of publications (Figure 4C) with breast, colorectal, liver, and lung cancer leading in terms of research activity. Among hematological malignancies, acute myeloid leukemia (AML) dominates, followed by chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). This distribution based on publication data from the CAS Content Collection aligns with U.S. FDA-approved epigenetic therapies targeting these malignancies, including azacitidine[17] and decitabine[18] used for treatment of AML and vorinostat[19] for cutaneous T-cell lymphoma.

Epigenetic regulation in cancer involves three primary mechanisms:

- **DNA methylation:** Hypermethylation of promoter regions often leads to the silencing of tumor suppressor genes, whereas global hypomethylation can activate oncogenes and promote genomic instability.
- **Histone modifications:** Alterations in histone acetylation, methylation, and phosphorylation can change chromatin structure and gene expression.
- **ncRNAs:** Dysregulation of miRNAs (e.g., miR-21 overexpression) can promote cancer progression by targeting tumor suppressors or oncogenes.

The gene-epigenetic mechanism co-occurrence heatmap shown in Figure 5 reveals distinct patterns. For example, DNA methylation's dominance reflects its role as an important epigenetic mechanism. Chromatin remodeling shows minimal co-occurrence across most genes, suggesting its role in broader architectural changes rather than gene-specific regulation. Publications associated with ncRNA and histone modifications lie between the two extremes — DNA methylation and chromatin remodeling.

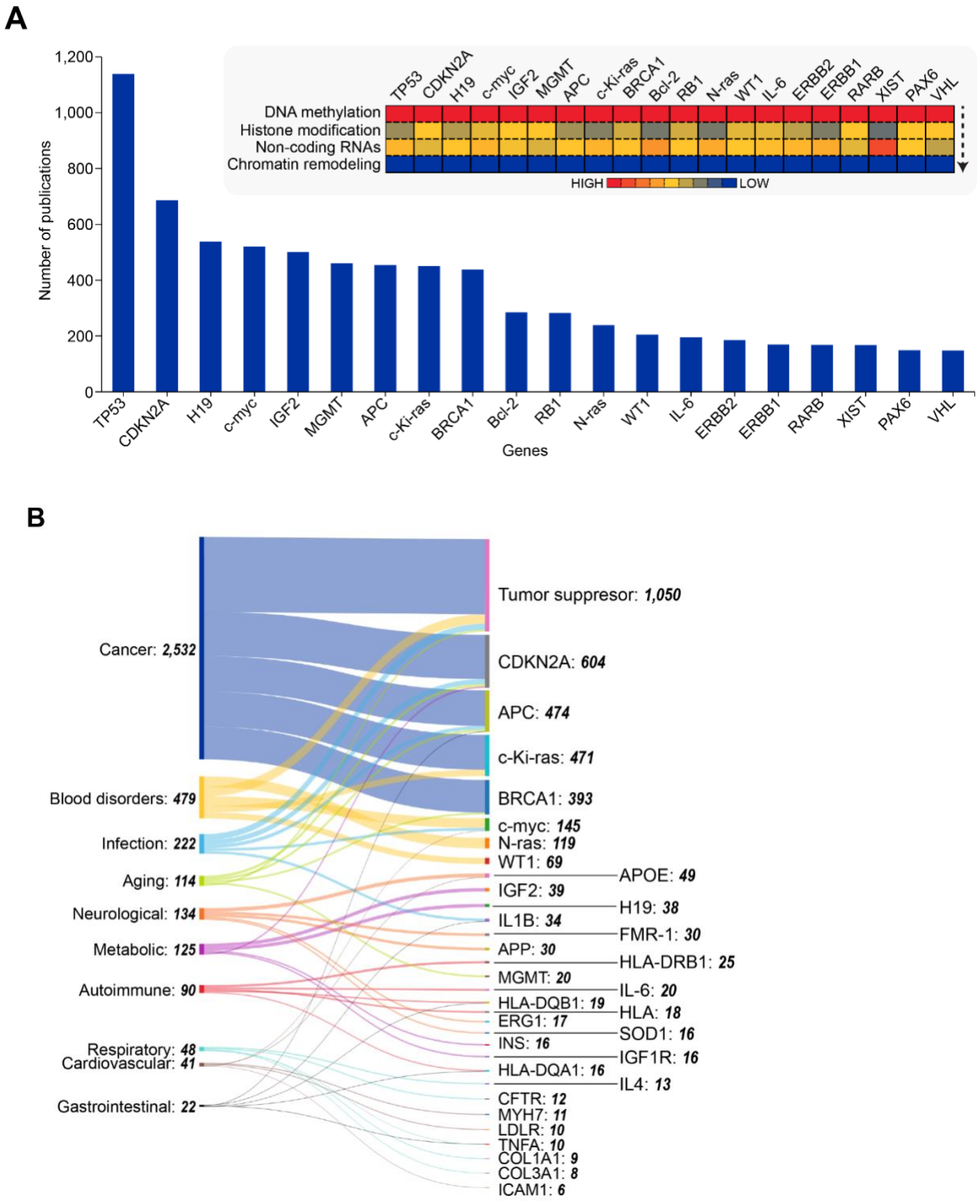


Figure 5: *(A) Leading genes associated with epigenetic publications based on CAS indexing. Inset heat map table shows co-occurrence of epigenetic mechanisms with individual genes. (B) Sankey graphs depicting disease and gene co-occurrences in the epigenetics dataset. Source: CAS Content Collection.*

Our analysis of gene and disease co-occurrences (Figure 5B) illustrates cancer's central position, with tumor suppressor genes showing the highest connectivity. Other genes with high co-occurrences across multiple cancers include CDKN2A, followed by APC and c-Ki-ras (KRAS325). This pattern reflects these genes' roles as epigenetic hubs subject to methylation-mediated silencing across diverse malignancies.

Epigenetic clocks and aging-related conditions

Epigenetic clocks are a groundbreaking concept[20] using computational models that predict biological age based on DNA methylation patterns. They can reveal discrepancies between an individual's biological age and chronological age, providing insights into the aging process and the impact of lifestyle and environmental factors. These models exploit predictable age-related changes in DNA methylation, where specific genomic regions become hypermethylated or hypomethylated in reproducible patterns.

The first-generation epigenetic clock, Horvath's clock, was developed[21] by Steve Horvath in 2013 and utilizes DNA methylation data from 353 CpG sites across multiple tissues and cell types to estimate biological age. Hannum's clock[22], developed in the same year, employs 71 CpG sites, primarily in blood. More recent clocks like GrimAge and PhenoAge incorporate additional biomarkers (e.g., plasma proteins) to improve accuracy and predict mortality and disease risk.

In longevity research, centenarians and individuals with exceptional longevity often exhibit slower epigenetic aging, providing clues to the genetic and environmental factors that promote healthy aging. Current research explores reversibility through senolytics and epigenetic regulator-targeting compounds.

Research publication trends seen in Figure 4A demonstrate that aging represents 9% of epigenetic research explicitly mentioning disease and aging, significantly smaller than cancer research (47%), yet showing consistent growth from 2010-2024, especially noticeable after 2019 (Figure 4B). This proportion reflects aging research's specialized but expanding role within the broader epigenetic landscape dominated by cancer applications.

Neurodegenerative diseases

Epigenetic modifications have been linked to neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS, as well as mental health disorders such as depression and schizophrenia (Figure 6). The substantial research output reflects growing recognition of epigenetic mechanisms in neuropsychiatric and neurodegenerative pathologies (see Figure 4A).

Epigenetic alterations affect[23] genes involved in amyloid-beta (Aβ) production and tau phosphorylation in Alzheimer's disease, with dysregulation of miRNAs such as miR-29352 and miR-34354 being associated with cognitive decline. Parkinson's disease shows epigenetic changes in mitochondrial function genes (e.g., PINK1355) and α-synuclein aggregation pathways. Histone acetylation and DNA methylation patterns are disrupted in Parkinson's disease models, affecting neuronal survival.

Autism spectrum disorders exhibit dysregulation of synaptic genes (e.g., SHANK3360) through aberrant DNA methylation and histone modifications, with environmental factors such as prenatal exposure to valproic acid shown[24] to induce epigenetic changes in animal models. In epilepsy, epigenetic mechanisms regulate ion channel genes and synaptic plasticity genes, contributing to seizure susceptibility, with histone modifications and miRNA dysregulation being observed. Neurodevelopmental disorders exemplify critical epigenetic regulation as exhibited by mutations in the MECP2 gene, encoding a methyl-CpG-binding protein, causing Rett syndrome and FMR1 hypermethylation in Fragile X syndrome.

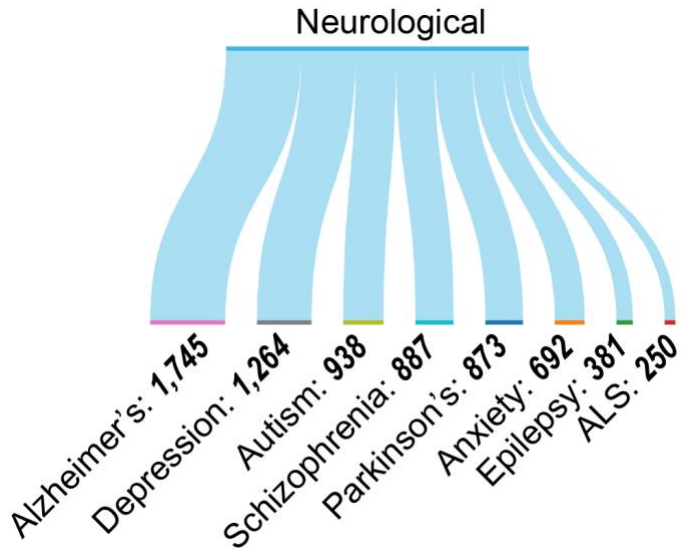


Figure 6: *Sankey graph depicting breakdown of publications across various neurological diseases in the epigenetics dataset. Source: CAS Content Collection.*

Epigenetic alterations are increasingly recognized as biomarkers for neurological disorders. Methylation patterns of genes such as BDNF372 and COMT374 are associated with cognitive function and psychiatric disorders, while specific histone marks (e.g., H3K27me3) are linked to gene regulatory networks in neurodegeneration. Circulating miRNAs, particularly miR-132376 and miR-124378, have shown potential as non-invasive biomarkers for diagnosis of Alzheimer's and Parkinson's disease, respectively, offering potential for early detection and therapeutic monitoring.

Cardiovascular disease

Epigenetic mechanisms contribute to the pathogenesis of various cardiovascular diseases, though our analysis of publication data suggests a smaller fraction of research interest when compared to cancer (see Figure 4A). For instance, in atherosclerosis[25], DNA methylation and histone modifications regulate genes involved in inflammation, lipid metabolism, and endothelial function. Hypomethylation of pro-inflammatory genes (e.g., IL-6384) and hypermethylation of anti-inflammatory genes (e.g., PPARγ385) promote plaque formation.

Epigenetic changes in genes regulating vascular tone and sodium homeostasis contribute to hypertension, while environmental factors such as a high-salt diet and stress can induce these epigenetic alterations. Epigenetic regulation of ion channel genes (e.g., SCN5A and KCNQ1392) can predispose individuals to arrhythmias. Similarly, epigenetic modifications drive pathological cardiac remodeling, including hypertrophy and fibrosis. DNA methylation, histone modifications, and miRNAs are key regulators of these processes. In ischemic heart disease and stroke, DNA methylation and histone modifications alter the expression of genes that govern cell survival, stress responses, and inflammatory pathways.

As with neurological disorders, these alterations are increasingly documented as biomarkers. Methylation patterns of genes such as F2RL3400 and AHRR401 are associated with cardiovascular risk and outcomes. Specific histone marks are linked to gene regulatory networks in heart failure and atherosclerosis. Circulating miRNAs are used as biomarkers for acute myocardial infarction and heart failure.

Metabolic disorders

Epigenetic modifications regulate[26] genes controlling insulin sensitivity, fat storage, and inflammation in metabolic diseases. Environmental factors including diet and exercise induce persistent epigenetic changes contributing to insulin resistance and metabolic dysfunction.

Metabolic diseases represent a sizable fraction of epigenetic research (see Figure 4A), with obesity studies and type 2 diabetes dominating this field. The substantial publication volume reflects the global epidemic of metabolic diseases and a growing understanding of epigenetic contributions to metabolic dysfunction. The steady but modest growth in metabolic epigenetics research is comparable to neurological and blood disorders (Figure 4B) but contrasts with the exponential increase in cancer studies, suggesting significant untapped potential in this area.

Epigenetics have been found to play a key role in:

- **Obesity:** DNA methylation and histone modifications regulating adipogenesis, appetite control, and energy expenditure genes, with dysregulated miRNAs associated with obesity and adipose tissue dysfunction. DNA methylation and histone modifications regulating adipogenesis, appetite control, and energy expenditure genes, with dysregulated miRNAs being associated with obesity and adipose tissue dysfunction.
- **Type 2 diabetes (T2D):** Epigenetic changes in pancreatic β cells, liver, and skeletal muscle affecting insulin production and sensitivity, including DNA methylation of PPARGC1A and IRS1 genes.
- **Non-alcoholic fatty liver disease (NAFLD):** DNA methylation and histone modifications regulate hepatic lipid metabolism and inflammation, with miRNAs contributing to disease progression.
- **Metabolic syndrome:** Epigenetic changes affect glucose metabolism, lipid metabolism, and blood pressure regulation genes.
- **Cardiometabolic diseases:** Epigenetic mechanisms link metabolic dysregulation to cardiovascular complications through DNA methylation of genes including FTO418 and ABCA1419 associated with atherosclerosis and hypertension risk.

Epigenetic biomarkers for metabolic diseases include methylation patterns of TXNIP and SREBF1 genes associated with T2D and NAFLD; specific histone marks linked to metabolic gene regulatory networks; and circulating miRNAs serving as biomarkers for T2D and obesity. These biomarkers enable early detection, risk stratification, and therapeutic monitoring in metabolic disorders.

Autoimmune diseases

Aberrant methylation of immune tolerance genes can activate self-reactive T cells, leading to autoimmune conditions. Despite their clinical importance, autoimmune diseases represent a modest portion of epigenetic research (see Figure 4A), with steady but limited growth from 2010-2024 compared to the exponential increase in cancer studies (Figure 4B). This research gap suggests significant potential for expanded investigation into autoimmune epigenetics.

Within autoimmune diseases, certain conditions have emerged as primary research areas (Figure 7):

- **Systemic lupus erythematosus** (SLE) pathogenesis associated with dysregulated miRNAs.
- **Rheumatoid arthritis** (RA) involves DNA methylation changes in synovial fibroblasts and immune cells promoting joint inflammation, while histone modifications regulate pro-inflammatory cytokine production.
- **Multiple sclerosis** (MS) exhibits epigenetic changes in T and B cells affecting immune regulation and myelin destruction genes, with miRNA dysregulation linked to disease progression.

- **Type 1 diabetes** (T1D) involves DNA methylation and histone modifications in pancreatic β cells and immune cells contributing to autoimmune destruction of insulin-producing cells, with miRNAs (e.g., miR-21, miR-34a) implicated in pathogenesis.
- **Inflammatory bowel disease** (IBD) such as Crohn's and ulcerative colitis exhibit epigenetic changes in intestinal epithelial and immune cells, driving chronic inflammation alongside association with miRNA dysregulation.

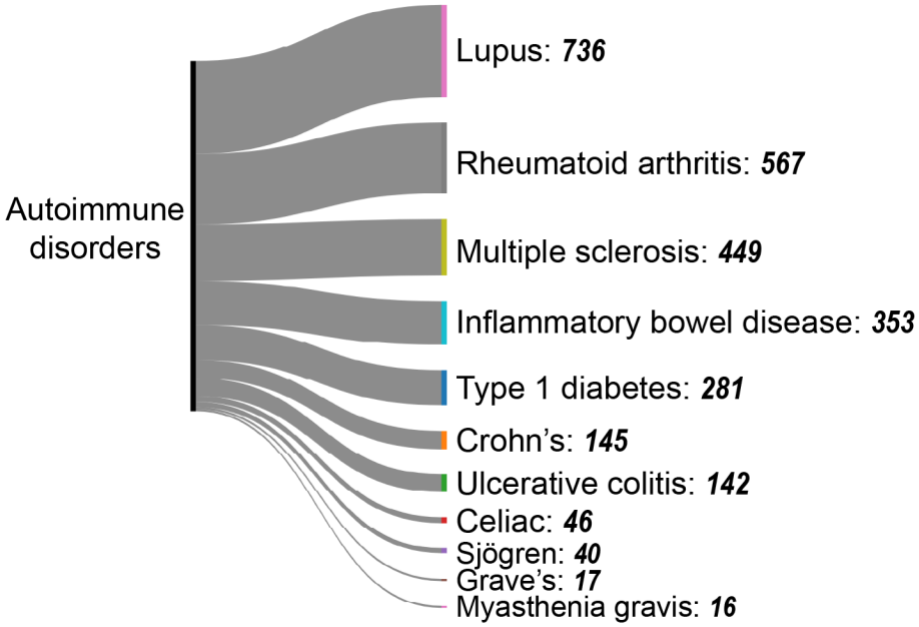


Figure 7: *Sankey graph depicting breakdown of publications across various autoimmune disorders in the epigenetics dataset. Source: CAS Content Collection.*

Epigenetics therapeutics: clinical applications of epi-drugs

Epigenetic drugs (epi-drugs) reverse aberrant epigenetic modifications to restore normal gene expression in diseases characterized by epigenetic dysregulation. The therapeutic landscape (see Figure 8A) reveals HDAC inhibitors dominating with 59% of publications, followed by DNMT inhibitors (18%), and RNA modulators (8% each for ncRNA modulators).

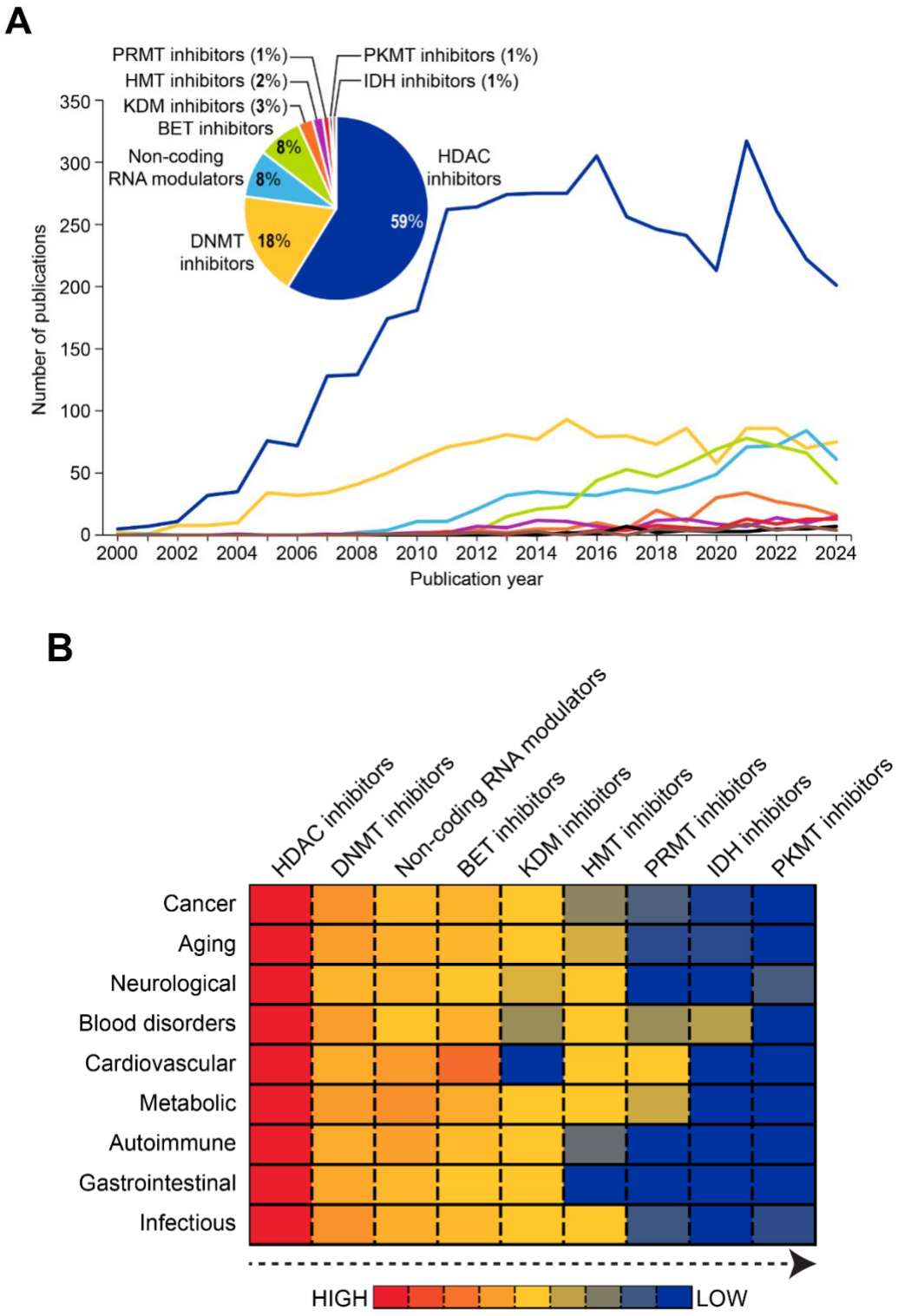


Figure 8: *(A) Distribution and publication trends of epi-drug classes in the epigenetics dataset. (B) Heat map showing co-occurrence of epi-drug classes with diseases. Abbreviations used: HDAC, histone deacetylase; DNMT, DNA methyltransferase; BET, bromodomain and extra-terminal domain; KDM, histone lysine demethylase; HMT, histone methyltransferase; PRMT, arginine methyltransferase; PKMT, lysine methyltransferase; IDH, isocitrate dehydrogenase. Source: CAS Content Collection.*

Current epi-drugs:

- **Histone deacetylase (HDAC) inhibitors** prevent[27] removal of acetyl groups from histones, promoting relaxed chromatin structures and increased gene expression, including tumor suppressor genes. HDAC inhibitors also affect non-histone proteins, such as transcription factors and chaperone proteins, further contributing to their anticancer effects.
- **DNA methyltransferases (DNMT) inhibitors** represent the second-largest drug class in terms of associated research publications. They block DNMTs, thereby aiding in the reactivation of silenced tumor suppressor genes in cancer. DNMT inhibitors currently approved for clinical use are azacitidine (Vidaza®) and decitabine (Dacogen®), which are nucleoside analogs that incorporate DNA during replication, irreversibly bind DNMTs, and prevent methylation.
- **ncRNA modulators** target miRNAs or lncRNAs to influence gene regulation. RNA modulators appear to be a fast-growing category, especially since 2018 (Figure 8A), reflecting recognition of miRNAs and lncRNAs as druggable targets for precision medicine.
- **Bromodomain and extra-terminal domain (BET) inhibitors** block the binding of BET proteins to acetylated histones, disrupting the transcriptional activation of oncogenes. BET proteins (e.g., BRD2, BRD3, BRD4) are involved in the recognition and binding of acetylated lysines on histones and acting as "readers" of epigenetic marks.
- **Histone lysine demethylases (KDMs) inhibitors** block enzymes belonging to lysine demethylases (LSDs) or the Jumonji domain containing (JmjC) family of N-methyl lysine demethylases enzymes. There are no approved KDM inhibitors so far, however, a KDM4 inhibitor is currently in a clinical trial (zavondemstat[28]) with ongoing research directed toward developing more.
- **Histone methyltransferase (HMT) inhibitors** target enzymes that add methyl groups to specific lysine or arginine residues on histone proteins, which can either activate or repress gene expression depending on the specific histone and the location of the methylation.
- **Protein arginine methyltransferase (PRMT) inhibitors** target protein methyltransferases — enzymes responsible for adding methyl groups to proteins and impacting gene expression and cellular processes. HMT inhibitors and protein methyltransferase inhibitors such as PRMT and PKMT inhibitors remain in early development, while KDM inhibitors show emerging therapeutic potential.
- **Isocitrate dehydrogenase (IDH) inhibitors** target mutant forms of IDH enzymes, such as IDH1 and IDH2, that produce the oncometabolite 2-hydroxyglutarate. These enzymes cause DNA hypermethylation and block cellular differentiation by accumulating in cells and inhibiting enzymes involved in epigenetic regulation, such as TET proteins and histone demethylases.
- **Enhancer of zeste homolog 2 (EZH2) inhibitors** function as specific HMT inhibitors, reducing H3K27me3 levels and reactivating silenced tumor suppressor genes, which can restore normal cellular differentiation and inhibit tumor growth, particularly in cancers with EZH2 mutations or overexpression.
- **Dual-action or multi-epigenetic modulators** combine mechanisms targeting multiple epigenetic pathways. These drugs may enhance therapeutic efficacy in complex diseases.

Co-occurrence analysis

The clinical landscape of epigenetic therapeutics demonstrates regulatory success, with13 U.S. FDA-approved drugs targeting key epigenetic regulators (see Figure 9).

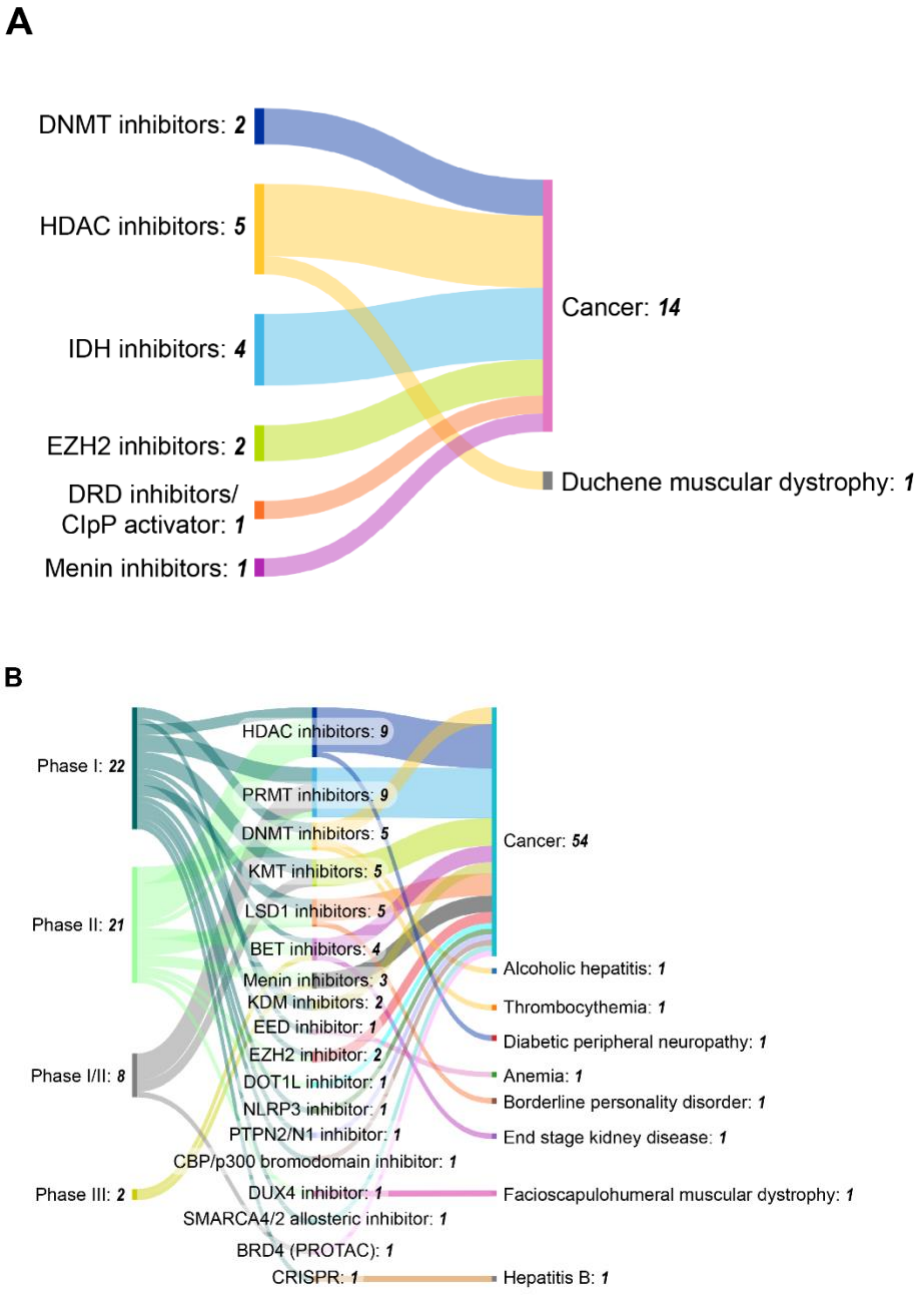


Figure 9: *Distribution of (A) FDA-approved epigenetic therapeutics and (B) those currently in clinical trials across disease conditions. Does not include combination therapies currently in clinical trials. Each drug/therapy has been counted once in the highest phase trial. Source: CAS, publicly available information on clinicaltrials.gov.*

HDAC inhibitors lead with five approvals, and hematological malignancies represent the primary therapeutic application, accounting for 12 of 15 approved indications. This concentration reflects the sensitivity of blood cancers to epigenetic dysregulation and the accessibility of hematologic targets compared to solid tumors.

DNMT inhibitors azacitidine (2004) and decitabine (2006) were among the first approved epigenetic drugs, establishing proof-of-concept for targeting DNA methylation in myelodysplastic syndromes and AML. HDAC inhibitors including vorinostat, romidepsin, and belinostat have shown efficacy across multiple hematologic malignancies, validating histone modification as a therapeutic target.

Epigenetic drugs in clinical trials

The landscape of epigenetic drugs in clinical trials has expanded dramatically over 25 years, with nearly 2,200 trials registered on clinicaltrials.gov (see Figure 10). There has been a sustained increase from a single trial in 2000 to just under 200 clinical trials a year in 2024, with notable oscillations reflecting regulatory milestones and market dynamics. Following azacitidine's U.S. FDA approval in 2004, trial activity demonstrated waxing and waning patterns with overall upward trajectory. This growth pattern indicates sustained pharmaceutical investment despite periodic consolidation phases.

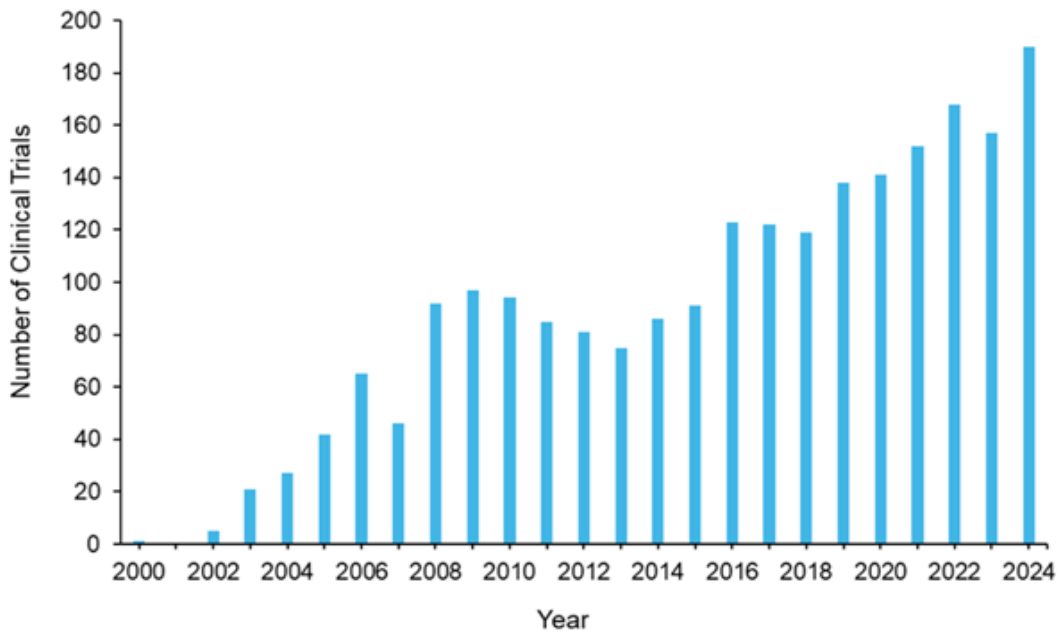


Figure 10: Number of therapeutic epigenetic drug clinical trials by year, characterized by first posted date. Source: CAS, publicly available information from clinicaltrials.gov.

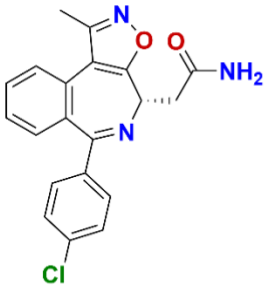
Analysis of therapeutic epigenetic clinical trials with respect to phase distribution reveals that Phase II trials dominate at 57%, followed by Phase I (32%) and Phase III (9%). This distribution is typical of drug development and reflects the high attrition rate in epigenetic drug development and the exploratory nature of many combination strategies. Notably, 62% of trials involve U.S. FDA-approved drugs, suggesting extensive label expansion efforts and combination therapy exploration beyond initial indications. The remaining 38% of clinical trials are for newer/novel unapproved drugs.

The clinical development pipeline reveals robust activity with more than 50 ongoing trials across three phases. Phase I and II trials dominate (more than 20 trials each) with DNMT and HDAC inhibitors maintaining a strong clinical presence with 5 and 9 candidates in trials, respectively. There is also diversification beyond DNMT and HDAC inhibitors, with LSD1, BET and menin inhibitors being increasingly explored (see Figure 9B). Additionally, a BRD4 PROTAC and CRISPR based epigenetic therapy are also currently in Phase I. This distribution demonstrates both continued optimization of established targets and expansion into novel epigenetic regulators. Cancer applications continue to predominate with more than 50 trials, though data suggests encouraging diversification into non-oncologic conditions including thrombocythemia, alcoholic hepatitis, anemia, and diabetic peripheral neuropathy.

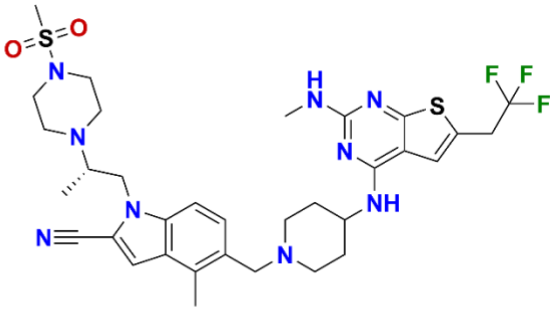
Promising agents in clinical development

Of the various drugs in development, several stand out as promising for cancer and other conditions:

- **Oncology agents:**
  - Pelabresib (CPI-0610), an advanced BET inhibitor, reached Phase III trials for myelofibrosis.
  - Ziftomenib (KO-539), a selective small-molecule inhibitor of the menin-KMT2A protein-protein interaction, received U.S. FDA Breakthrough Therapy designation[29] in March 2024 for relapsed or refractory NPM1-mutant AML.

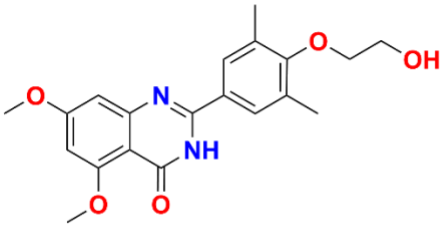


Pelabresib (CPI-0610)
CAS RN: 1380087-89-7

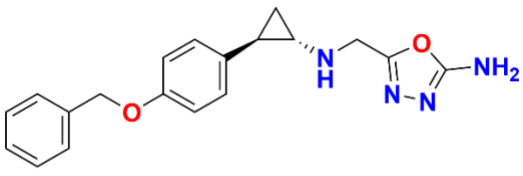


Ziftomenib (KO-539)
CAS RN: 2134675-36-6

- **Non-oncology agents:**
  - Apabetalone (RVX-208), a selective BET inhibitor targeting BD2 domains, is currently in Phase I/II for end-stage kidney disease.
  - Larsucosterol (DUR-928), an endogenous sulfated oxysterol and first-in-class epigenetic regulator, is in Phase II trials for alcoholic hepatitis.
  - Vafidemstat (ORY-2001) is a selective LSD1 inhibitor that is currently being evaluated in Phase II clinical trials for borderline personality disorder.

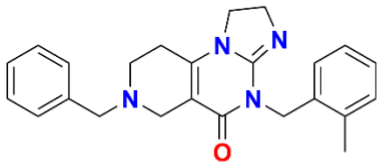


Apabetalone (RVX-208)
CAS RN: 1044870-39-4

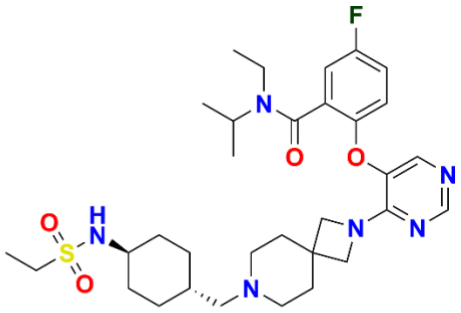


Vafidemstat (ORY-2001)
CAS RN: 1357362-02-7

- **Recently approved agents:**
    - Modeyso (Dordaviprone) received U.S. FDA accelerated approval in August 2025 H3K27M-mutant diffuse midline gliomas in patients over the age of one.
    - Revuforj (Revumenib) gained U.S. FDA approval in November 2024 for relapsed/refractory KMT2A-rearranged AML in adults and pediatric patients.



Modeyso (Dordaviprone)
CAS RN: 1616632-77-9



Revuforj (Revumenib)
CAS RN: 2169919-21-3

Epigenetics in personalized medicine

The integration of epigenetic data aids in the development of highly precise diagnostic tools, prognostic markers, and therapeutic approaches, particularly for complex diseases. As noted, epi-drugs including DNMT inhibitors and HDAC inhibitors are clinically established and continue to be developed. Combination therapies integrating epigenetic drugs with chemotherapy and immunotherapy are also enhancing treatment efficacy, representing a key advancement in personalized therapeutic approaches.

Another key breakthrough in epigenetics is the use of these modifications as tissue-specific biomarkers. Examples of these disease-specific patterns include tumor suppressor gene hypermethylation[30] in cancer, and aberrant methylation and histone modifications in patients with Alzheimer's or Parkinson's disease.

Identifying these epigenetic biomarkers enables early disease detection and diagnosis. For example, it could accomplish this through liquid biopsies used for detecting cancer-specific DNA methylation patterns in blood or other bodily fluids for non-invasive diagnosis and monitoring and prenatal testing via epigenetic markers in maternal blood to assess fetal health. Prognostically epigenetic markers can predict disease outcomes and response to therapy. For example, methylation status predicts outcomes and metastasis likelihood in some cancers[31], while epigenetic changes in psychiatric disorders may predict medication response.

Clinical applications of epigenetic biomarkers

Epigenetic biomarkers are therefore important for disease diagnosis, prognosis, and therapeutic decision-making. We analyzed publications in the CAS Content Collection specific to epigenetic biomarkers, and we found a sharp increase starting around 2008-2009 marked by a few periods of plateauing (2015-2017 and 2023-2024) (see Figure 11).

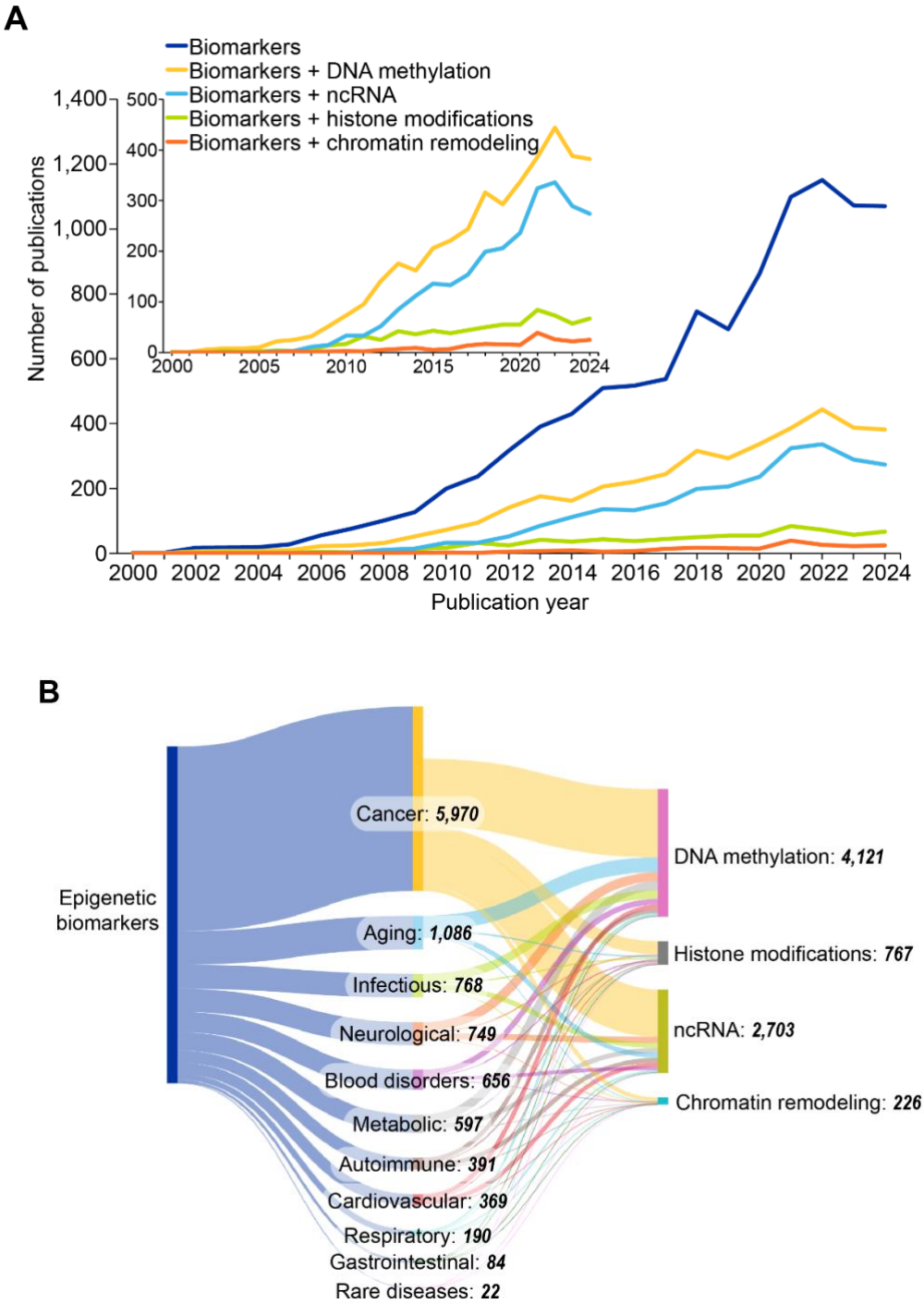


Figure 11: *(A) Publication trends for publications related to biomarkers and specific epigenetic mechanisms and (B) their co-occurrences with specific disease types and epigenetic mechanisms. Source: CAS Content Collection.*

Among the four main epigenetic mechanisms, DNA methylation and ncRNA appear to be the most well-studied with publications related to DNA methylation and ncRNA biomarkers doubling between 2015 and 2022, while histone modifications and chromatin remodeling remain comparatively underexplored in this context. As seen in Figure 11B, cancer appears to co-occur most extensively with publications related to epigenetic biomarkers, reflecting the well-established role of epigenetic dysregulation in oncogenesis and the clinical utility of methylation markers such as MGMT516 and VIM517 for diagnosis and prognosis. The substantial representation of aging research aligns with recent advances in epigenetic clock development and their applications in biological age assessment.

DNA methylation biomarkers

Aberrant DNA methylation patterns serve as disease hallmarks, particularly hypermethylation of tumor suppressors being a common biomarker of various cancers. For example, SEPT9 methylation enables non-invasive colorectal cancer screening through blood-based detection as an alternative to colonoscopy. MGMT methylation predicts[32] temozolomide response in glioblastoma, with hypermethylation being associated with better outcomes. BRCA1 methylation serves as a diagnostic and prognostic marker associated with increased risk of breast and ovarian cancer. Notably, DNA methylation co-occurs most predominantly with epigenetic biomarker research, likely due to its chemical stability, established detection methodologies, and direct clinical translation through FDA-approved tests.

Histone modification biomarkers

Histone modifications influence chromatin structure and gene expression, and specific histone marks are associated with disease states. The relatively modest co-occurrence of histone modifications we see in Figure 11B suggests untapped potential, particularly given their dynamic nature and responsiveness to therapeutic interventions.

Loss of histone H4 acetylation predicts poor prognosis in certain cancers, while histone H3 lysine 27 trimethylation (H3K27me3) reflects PRC2 dysregulation and correlates with poor prognosis in prostate and bladder cancers. Histone H3/H4 citrullination is linked to the production of anti-citrullinated protein antibodies (ACPAs), a hallmark of rheumatoid arthritis enabling diagnosis and monitoring.

Despite these promising findings, challenges remain such as the highly labile nature of histone modifications and their susceptibility to enzymatic degradation causing rapid signal loss within minutes of sample collection. Current protocols require specialized preservation buffers containing protease, deacetylase, and demethylase inhibitors, complicating routine clinical implementation.

ncRNA biomarkers

ncRNAs, including miRNAs like miR-21529 and miR-155530, are overexpressed in various cancers and serve as diagnostic and prognostic biomarkers through bodily fluids.[33] The substantial ncRNA co-occurrence with epigenetic biomarker research reflects growing interest in circulating miRNAs and lncRNAs as minimally invasive biomarkers.

For example, miR-21 overexpression is associated with tumor growth, invasion, metastasis, and chemotherapy resistance across breast, lung, and colorectal cancer. Elevated miR-208a levels serve as a biomarker for acute myocardial infarction (heart attack). HOTAIR lncRNA overexpression is also associated with metastasis and poor prognosis in breast, colorectal, and pancreatic cancers.

Chromatin remodeling biomarkers

Chromatin remodeling patterns predict therapeutic resistance, with open chromatin regions in drug-resistant cancer cells being used to predict[34] treatment failure. Similar to histone modifications, the relatively low co-occurrence of chromatin remodeling suggests untapped potential.

Overall, the future of epigenetic biomarkers lies in the development of robust, high-throughput technologies and integrative approaches. Multi-omic integration combining epigenetic, genomic, transcriptomic, and proteomic data will enhance biomarker discovery and validation. Non-invasive detection of epigenetic biomarkers in bodily fluids will revolutionize early diagnosis and monitoring.

Advanced computational tools are expected to aid in identifying complex epigenetic signatures for patient stratification. For example, CRISPR-based epigenome editing may enable manipulation of disease-associated epigenetic marks for therapeutic purposes, potentially transitioning biomarkers from diagnostic to therapeutic tools.

Ethical, legal, and social implications of epigenetics in medicine

Epigenetics has the potential to transform our understanding of health and disease, but it also raises significant ethical, legal, and social challenges. Addressing these challenges requires a proactive and collaborative approach that balances the benefits of epigenetic research with the need to protect individual rights and promote social justice. By developing robust ethical guidelines, legal protections, and public engagement strategies, we can harness the power of epigenetics to improve health and well-being while minimizing potential harms.

Ethical considerations

- **Privacy and discrimination:** Epigenetic information, like genetic data, is highly personal and can reveal sensitive information about an individual's health, lifestyle choices, and environmental exposures, and therefore requires robust privacy protections. For instance, epigenetic markers predicting disease risk could enable discrimination by health insurers through premium increases or coverage denial. Similarly, the ability to detect epigenetic modifications from past behaviors raises concerns about retroactive health assessments and employment discrimination.
- **Individual responsibility and transgenerational impacts:** Relatedly, epigenetic information could lead to blaming individuals for their health conditions, ignoring broader social and environmental determinants of health. Epigenetic changes induced by environmental factors can sometimes be passed to future generations. This raises ethical concerns about the long-term consequences of interventions that alter epigenetic markers.

Legal requirements

- **Regulatory oversight:** The proliferation of direct-to-consumer epigenetic testing kits raises concerns about accuracy, interpretation, and regulation. Legal frameworks must ensure that these applications are evidence-based and ethically sound while preventing premature commercialization of unproven technologies.

- **Liability and intellectual property:** Epigenetic modifications linked to environmental exposure raise complex liability questions. For example, should toxin-induced harm be the responsibility of employers, manufacturers, or governments? Potential legal accountability for epigenetic harm to fetuses through parental or third-party negligence or environmental exposures would require careful consideration. The commercialization of epigenetic research, such as biomarkers or therapies, raises questions about patenting and ownership, requiring a balance between innovation and maintaining public access to epigenetic technologies.

Social implications

- **Public understanding and equity:** Limited public understanding of epigenetics enables misconceptions and exploitation through unproven therapies (e.g., "epigenetic diets"). Comprehensive education and robust scientific communication are essential to address this issue and to improve informed decision-making. Epigenetic research linking environmental exposures to disease may also contribute to the stigmatization of certain communities or populations, particularly those exposed to high levels of pollution or toxins. Ensuring equitable access to epigenetic therapies and preventing exacerbation of health disparities requires deliberate policy interventions addressing socioeconomic barriers.

- **Implementation strategies:** Effective governance requires clear ethical guidelines for epigenetic data collection, use, and sharing; updated legal frameworks addressing unique challenges of epigenetic information; public engagement fostering trust and informed consent; and international cooperation ensuring consistent standards across jurisdictions. By developing robust protections while promoting responsible innovation, society can harness epigenetics' transformative potential while safeguarding individual rights and promoting health equity.

Future directions for epigenetics

The landscape of epigenetics research has undergone a remarkable transformation over the past decade, evolving from a specialized area of molecular biology into a mainstream biomedical discipline with profound implications for human health and therapeutic intervention. The clinical translation of epigenetic research has achieved remarkable success, with 15 FDA-approved drugs validating epigenetic targets as therapeutically viable. The 36 ongoing clinical trials across multiple development phases indicate sustained investment and confidence in epigenetic therapeutics with encouraging diversification beyond oncology — trials are now spanning metabolic, neurological, inflammatory, and rare diseases.

This shift reflects the growing recognition that environmental factors such as diet, stress, toxins, and lifestyle choices induce heritable epigenetic changes with transgenerational implications. The integration of environmental exposure data with individual epigenetic profiles enables personalized risk assessment and intervention strategies, representing a fundamental shift toward preventive, precision medicine approaches.

The future of epigenetics is bright, with immense potential for advancing our understanding of biology and improving human health. However, realizing this potential will require overcoming significant challenges, including technological limitations, ethical concerns, and the complexity of epigenetic regulation. By fostering interdisciplinary collaboration, investing in innovative technologies, and addressing ethical and social implications, the field of epigenetics can continue to make groundbreaking discoveries and translate them into meaningful clinical and societal benefits.

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