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Epigenetic Drugs: From Cancer to Aging

Q2 2022

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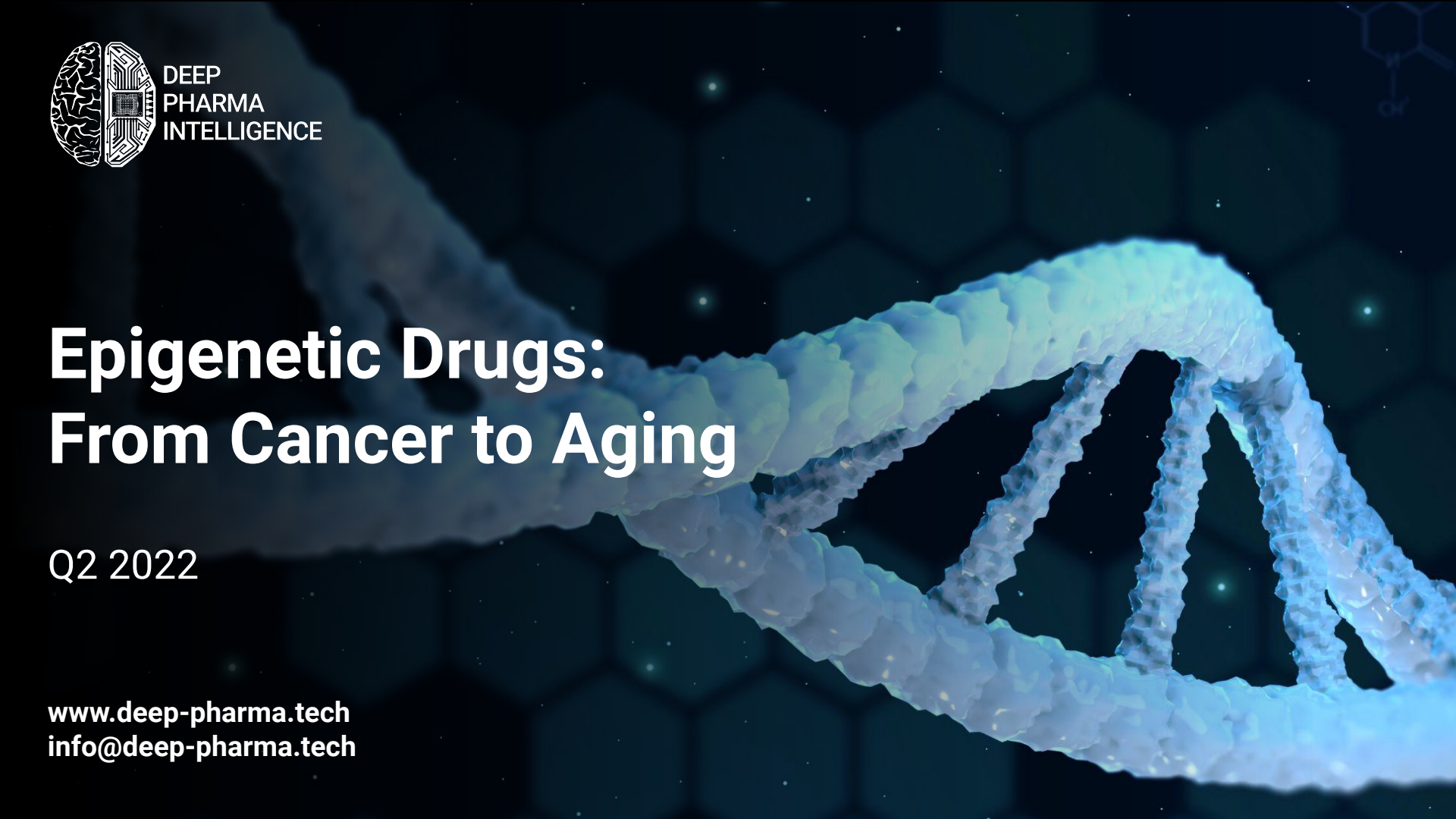

Table of Contents

Approach of the Report

Database

75	80	85
Drugs	Companies	R&D Centres

The database was formed based on:

- the **identification of companies** that conduct or have conducted clinical or preclinical research of drugs
- the **identification of companies** that research or develops biomarkers

Applied Research and Analytics Methods

Descriptive Analysis	**Mixed Data Research**	**Data Triangulation**
Comparative Analysis	**Qualitative Data Collection**	**Data Filtering**

Data Sources

Media Overview (Articles and Press Releases)	**Industry-Specialised Databases**	**Publicly Available Sources** (Websites)	**Industry Reports and Reviews**

Relying on various research methods and analytics techniques, the analysis provides a comprehensive overview of the Preclinical and Clinical Trials Industry. This approach has certain limitations, especially when using publicly available data sources and conducting secondary research. Deep Pis not responsible for the quality of the secondary data presented herein; however, we do our best to eliminate the said risks using different analytics techniques and cross-checking data. Please note that we did not deliberately exclude certain companies from our analysis. Nor was it due to the data-filtering method used or difficulties encountered. The main reason for their non-inclusion was incomplete or missing information in the available sources.

Executive Summary

Ever since being discovered, **epigenetics – which significantly influences gene expression, which means that to some extent, epigenetics is involved in almost all cellular processes** – have played a key role in our understanding of human biology. Because of their importance in cellular physiology, aberrant epigenetic regulations are associated with various human diseases, especially in different forms of malignancies. In addition, many studies have shown that epigenetics plays a central role in ageing.

The involvement of epigenetics in many essential cellular processes made enzymes that regulate epigenetic changes a **potential target**. Currently, more than **10 drugs targeting epigenetic regulators have been approved** for treating different diseases, and more than **60 other epigenetic drugs are in clinical trials**. These numbers will only grow through the years, making this research direction more and more promising. Currently, most of the epigenetic research is dedicated to cancer. However, in the last years, another prominent approach has appeared – **repurposing epigenetic drugs** for other diseases, including age-related diseases.

Main Features of the Analytical Case Study

- **Database of Key Market Players**
- **Role of Epigenetic in Cancer**
- **Role of Epigenetic in Aging and Aging-Related Diseases**
- **Overview of Clinical Trials for Epigenetics Drugs at All Phases**
- **In-depth Review of Epigenetic Drugs for Cancer**
- **Assessment of Epigenetic Drugs and Biomarkers for Aging**
- **Epigenetic Clinical Trial Market Review and Predictions**

Companies in EpiDrugs Development Q2 2022

Epigenetic Biomarkers for Aging

genknowme Personalized prevention solutions · Active Motif · MDxHealth · adela · AgelessLX · TECAN · MUHDO · VitaLife MD Add Vitality to Your Life · ELYSIUM · BioViva · GRAIL · Life Extension · TWIST Biosciences · Inherent Biosciences · RGCC · Capsulomics · Chronomics · Mayo Clinic Laboratories · Zymo Research · Modern Wellness Diagnostic Services · EPIFY · NUCLEIX · St. Mary's General Hospital · myDNAge · EarlyDx · EpigenDx · FOXO · CC Diagnostics · US EPI · FMI Friedrich Miescher Institute for Biomedical Research

Companies - 80

HDAC inhibitors

VANDA Pharmaceuticals Inc. · OnKure Therapeutics · MIRATI Therapeutics · AXIS Clinicals · XYNOMIC Pharma · abbvie · TITAN Pharmaceuticals · Chroma Therapeutics · SAMSUNG · Pharma Mar · BAYER · HELSINN · gsk · Bristol Myers Squibb · NOVARTIS · ONXEO The Orphan Oncology Innovator · 微芯生物 CHIPSCREEN · MSD · 4SC EpiScience for Life · janssen · ACROTECH Biopharma · CURIS · Celldex therapeutics · EOC

DNMT inhibitors

Innovent · NYU Langone Health · Bristol Myers Squibb · Ascentage Pharma · CANTEX Pharmaceuticals · Eisai · Pfizer · cti Biopharma · AMGEN · Salarius Pharmaceuticals · Takeda · GILEAD · Otsuka · SAMSUNG · Boehringer Ingelheim · BAYER · aprea therapeutics · janssen

Other inhibitors

ORYZON · gsk · janssen · Epizyme · morphosys · RESVERLOGIX · Roche · AstraZeneca · forma THERAPEUTICS · agios · Bristol Myers Squibb · abbvie · Abbott · Pfizer

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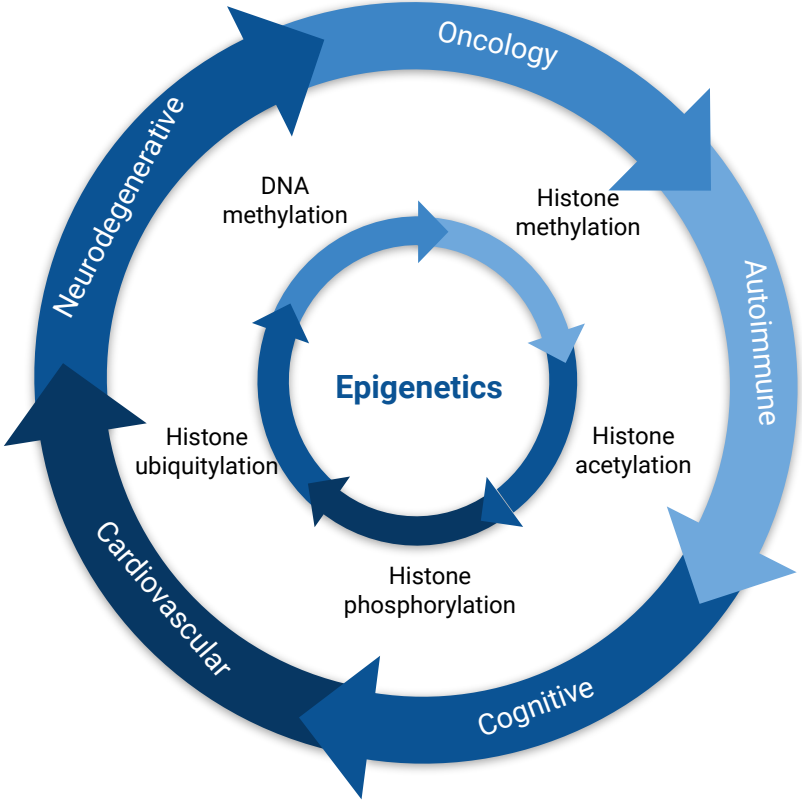
Introduction to Epigenetics

Epigenetics is the study of how cells control gene activity without changing the DNA sequence. The word “epigenetic” literally means “in addition to changes in genetic sequence.”

A vast range of diseases, behaviours, and other health markers, including malignancies of practically all sorts, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral ailments, already have some degree of evidence relating them to epigenetic processes. Currently, there are known many epigenetic processes, including **methylation**, **acetylation**, **phosphorylation**, **ubiquitylation**, and **sumoylation**.

The best-known epigenetic process is DNA methylation. This is the addition or removal of a methyl group (CH3), predominantly where cytosine bases occur consecutively (CpG islands). Another significant epigenetic process is chromatin modification. Chromatin is the complex of proteins (histones) and DNA that is tightly bundled to fit into the nucleus.

The **epigenome** consists of chemical compounds that modify or mark the genome in a way that tells it what to do, where to do it, and when to do it.

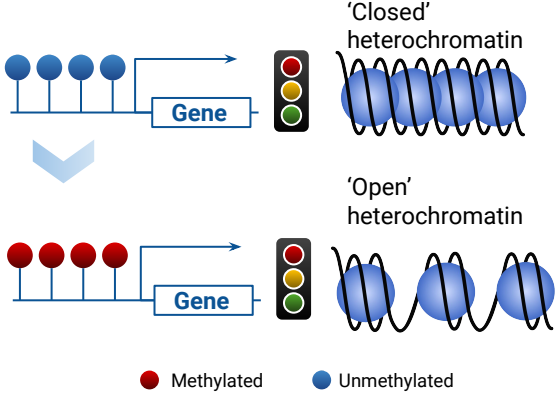


Sources: European Association for the Study of Diabetes, Environmental Health Perspectives, National Human Genome Research Institute

Epigenetic Processes: 3 Classes of Epigenetic Regulation

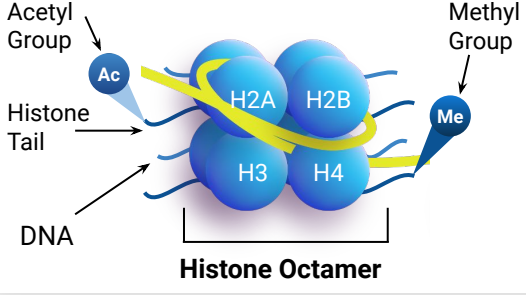
DNA Methylation

The process of DNA methylation involves the addition of a methyl (-CH3) group to DNA. This group is added to specific locations on DNA (CpG islands), where it prevents proteins from attaching to DNA and "reading" the gene. Demethylation is a method used to remove this chemical group. Methylation typically turns genes "off," while demethylation turns them "on."



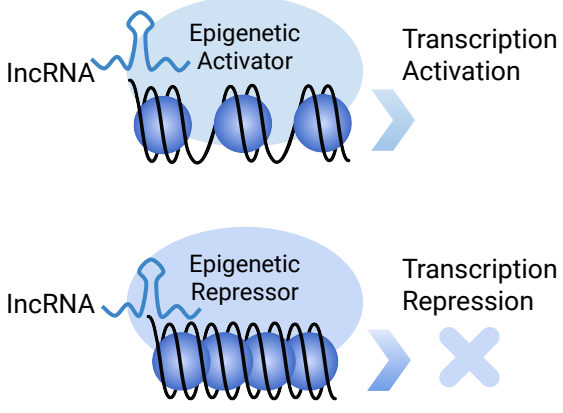
Histone Modifications

DNA wrapped around the proteins called histones. Proteins that "read" the gene cannot reach DNA wrapped tightly around histones. The genes that are wrapped tightly around the histone are turned "off", whereas others are turned "on" because they are loose around the histones and accessible to “readers”. Histones can have chemical groups added or deleted, affecting whether a gene is wrapped or unwrapped ("on" or "off").



Non-coding RNA action

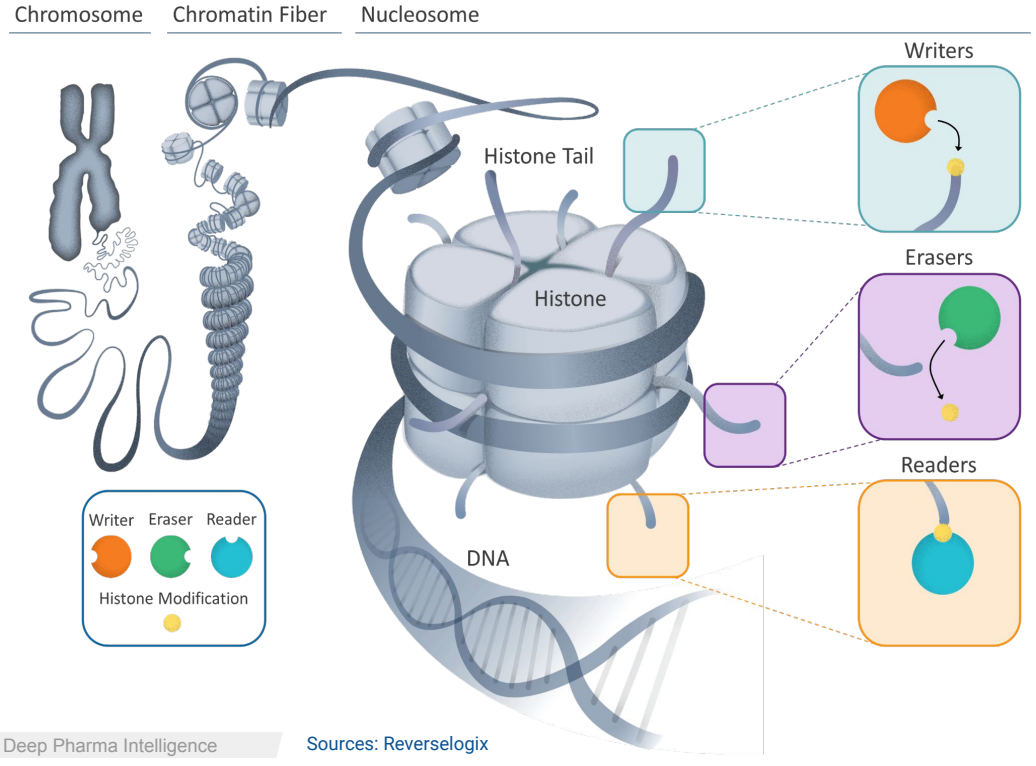
DNA is guide with instruction for creating coding and non-coding RNA. Proteins are made with coding RNA. The non-coding RNA regulates gene expression by binding to coding RNA and breaking it down, preventing it from being used to generate proteins. Proteins may be recruited by non-coding RNA to alter histones and switch genes "on" or "off."



Sources: European Association for the Study of Diabetes, Environmental Health Perspectives, National Human Genome Research Institute

Overview of the Epigenetic Regulation

Our chromosomes are made up of DNA wrapped around proteins and packed together in a beautiful hierarchical arrangement, which we inherit from our parents. Individual DNA strands are wrapped around specialized proteins in tightly coiled chromatin fibers, which are made up of smaller units (nucleosomes) than contain histones. The tail of the histone protein, which protrudes from the nucleosome, can be "marked."



Enzymes that add histone modifications such as acetylases, methylases, kinases

Enzymes that remove histone modifications such as deacetylases, demethylases

Proteins that bind to histone modifications and alter gene activity and protein production

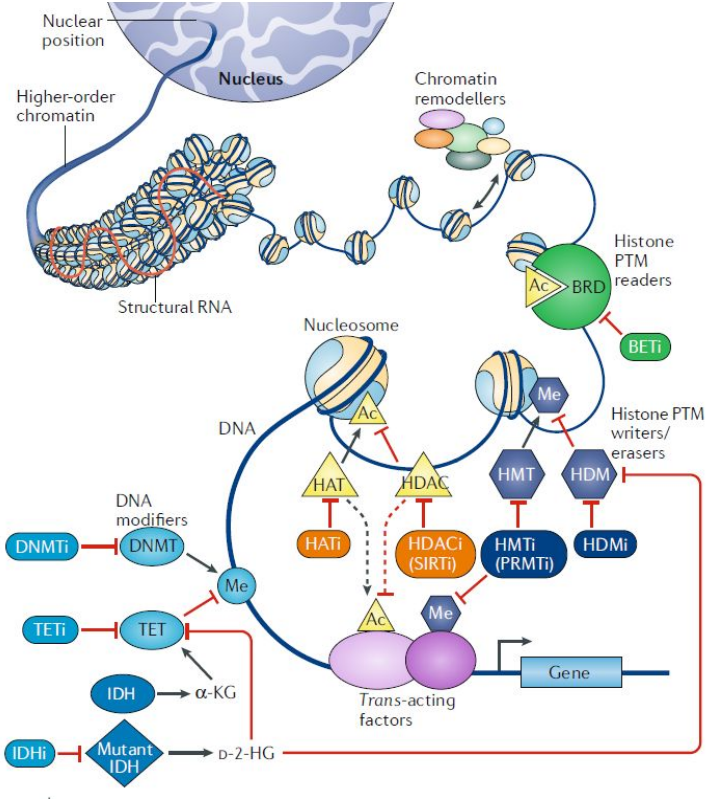
Sources: Reverselogix

Targets for EpiDrugs

More than 800 epigenetic enzymes affect genome activity at numerous levels. Epigenetic modifiers fall into four categories: '**writers**,' who add specific marks to DNA or the core histones H2A, H2B, H3, and H4; '**readers**,' who detect these marks; and '**erasers**,' who remove them. Epigenetic drugs (**EpiDrugs**) now target proteins in these three groups.

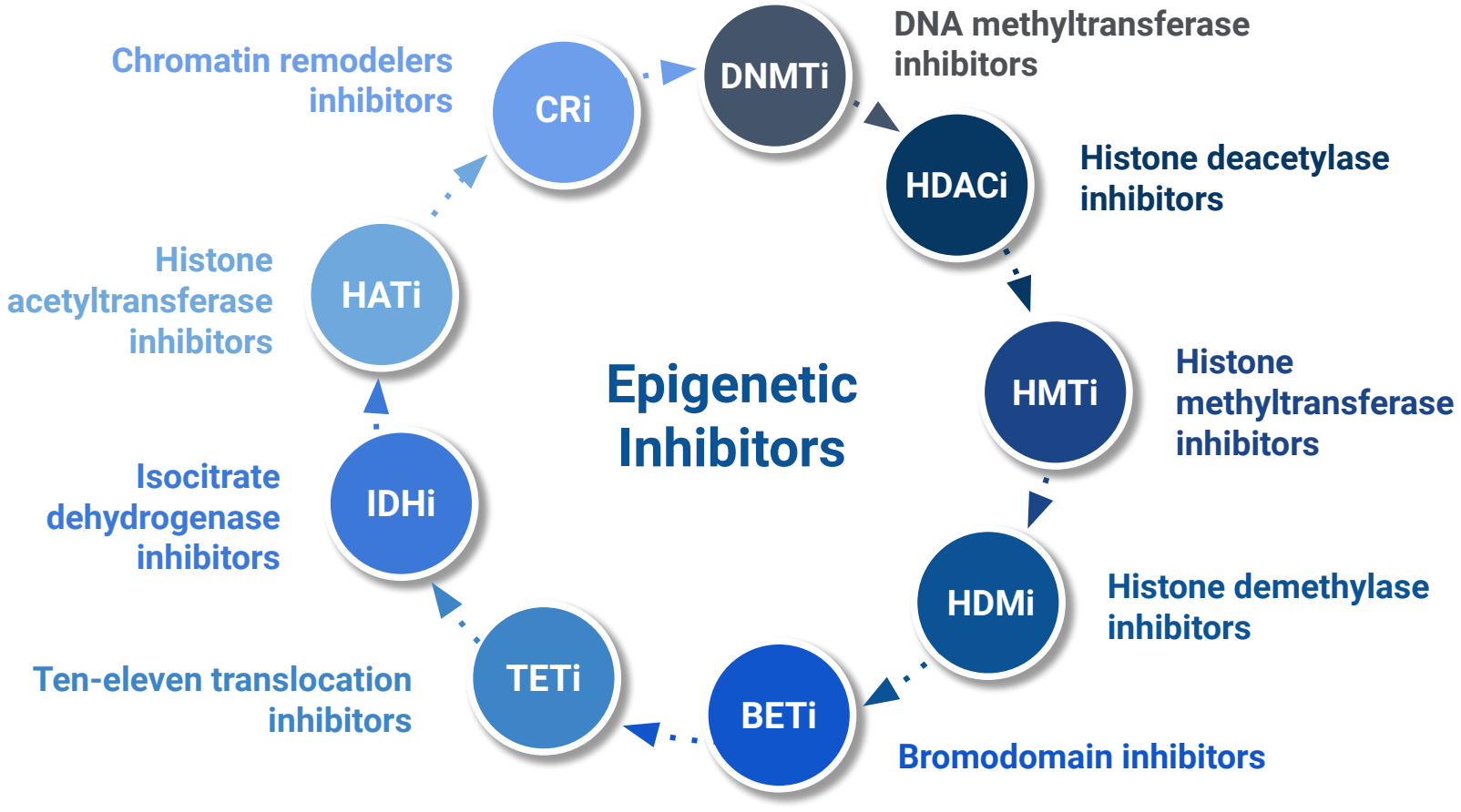
Inhibitors of DNA-modifying enzymes, such as **DNA methyltransferases** (**DNMTs**), which can methylate specific cytosine or adenosine nucleotides in DNA, inhibitors of **ten-eleven translocation (TET) enzymes** that catalyse the oxidation of 5-methylcytosine and inhibitors of mutant versions of **isocitrate dehydrogenase (IDH) enzymes**, are among these epi-drugs. Other epi-drugs, such as **histone acetyltransferases (HATs)**, **histone deacetylases (HDACs)**, **histone methyltransferases (HMTs)**, and other **protein arginine methyltransferases (PRMTs)** and **histone demethylases (HDMs)**, inhibit writers or erasers of histone arginine and/or lysine post-translational modifications (PTMs).

Readers of histone PTMs, such as **bromodomain and extra-terminal domain (BET) family proteins (BRDs)**, which bind acetylated lysine residues in histones, are inhibited by another class of epi-drugs. Epi-drugs that target **histone chaperones** and **chromatin remodeling factors** are also being developed.



Sources: Morel et al (2020). Nature Reviews Clinical Oncology

Classification of Epigenetic Inhibitors



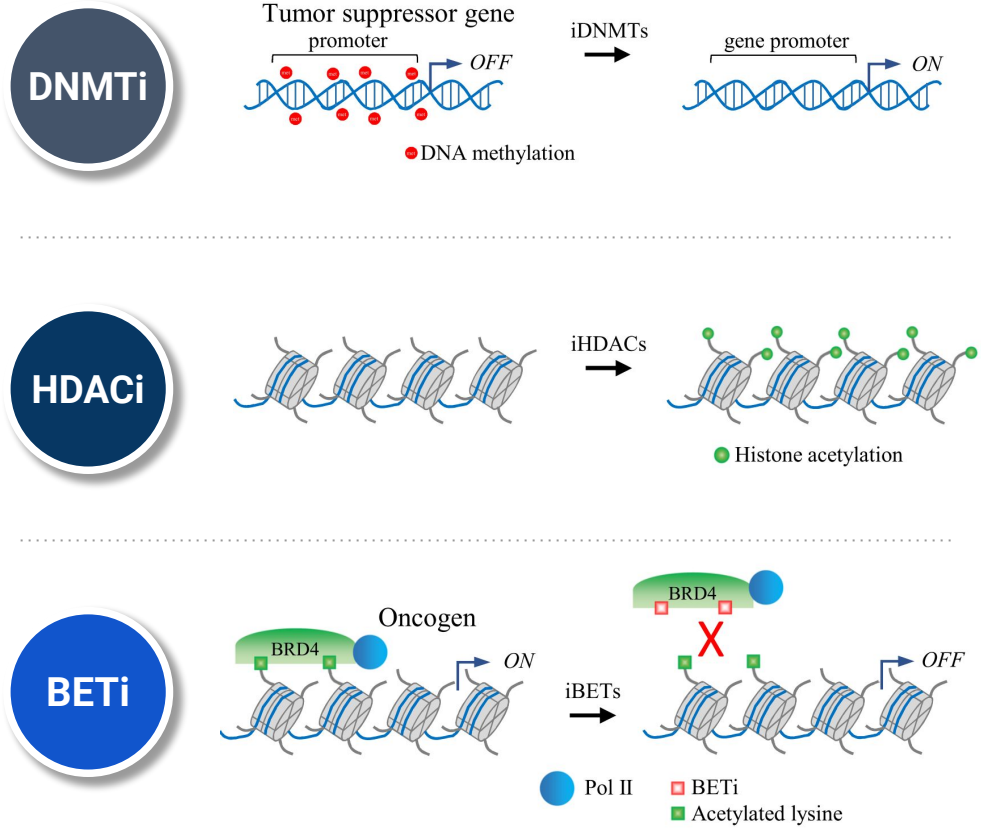
Epigenetic Inhibitors: Examples of Mechanism of Action

By blocking the activation of DNA methylation, **DNMTi** can **repair the expression activity and function** of tumour suppressor genes, consequently limiting tumor cell growth and triggering apoptosis.

HDACi are emerging as promising anti-cancer medications that regulate epigenetic and non-epigenetic factors in altered cells, causing cell death, apoptosis, cell cycle arrest, cell mobility inhibition, and antiangiogenesis.

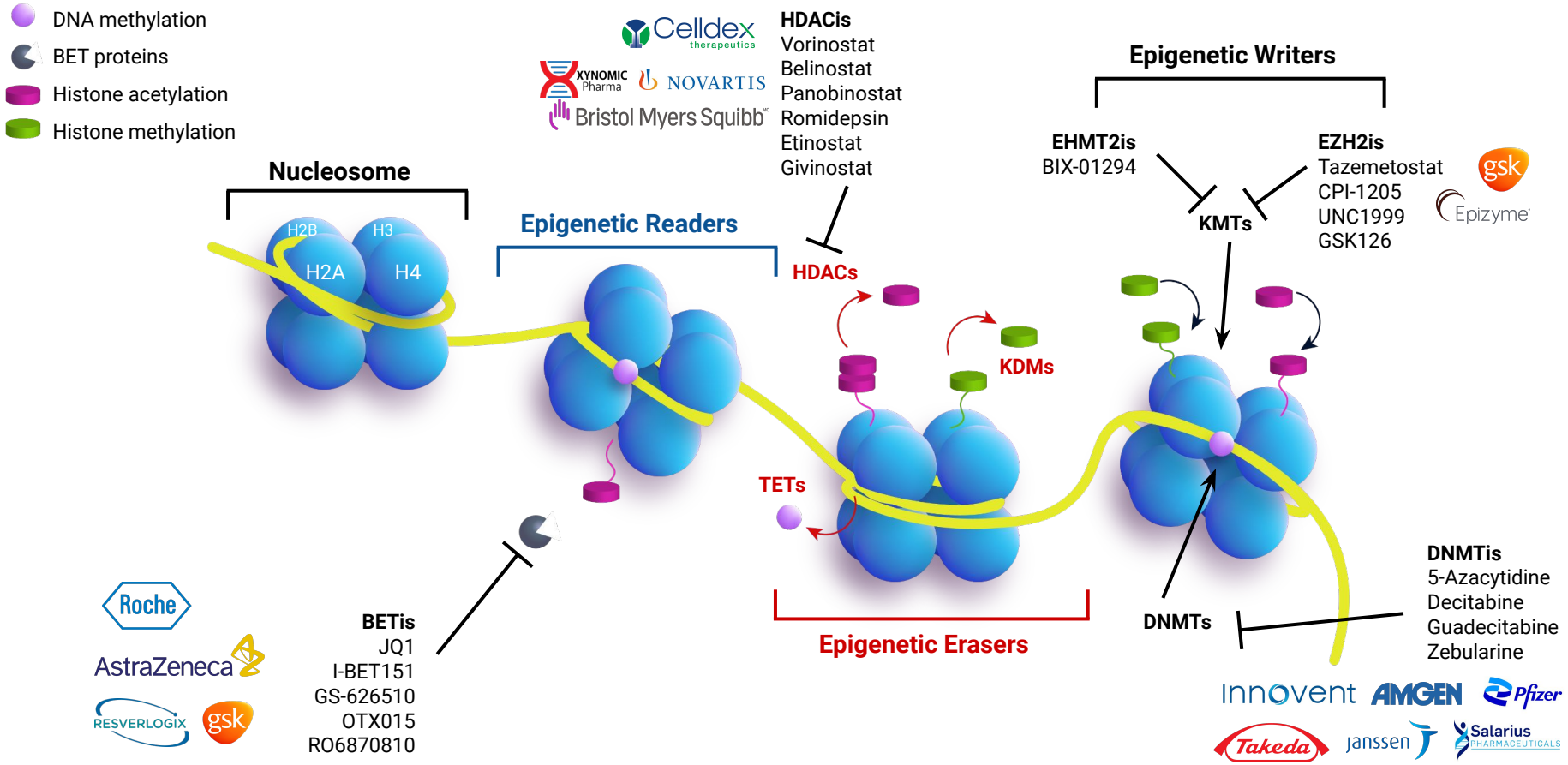
To create a repressive chromatin environment, HDACs remove acetylation marks from histone tails. **HDACi inhibits the activity of HDAC**, which renew histone acetylation.

Readers that identify acetylated lysine are **bromodomain and extra-terminal motif (BET) proteins**. **BETi** bind to the bromodomain of BET proteins in a reversible manner, disrupting crucial protein-histone interactions. **BRD4**, which is translocated in some malignancies, is required for the production of oncogenes like **MYC**, and one of the better-studied targets of BETi small molecules is the **pro-inflammatory gene NFKB**.



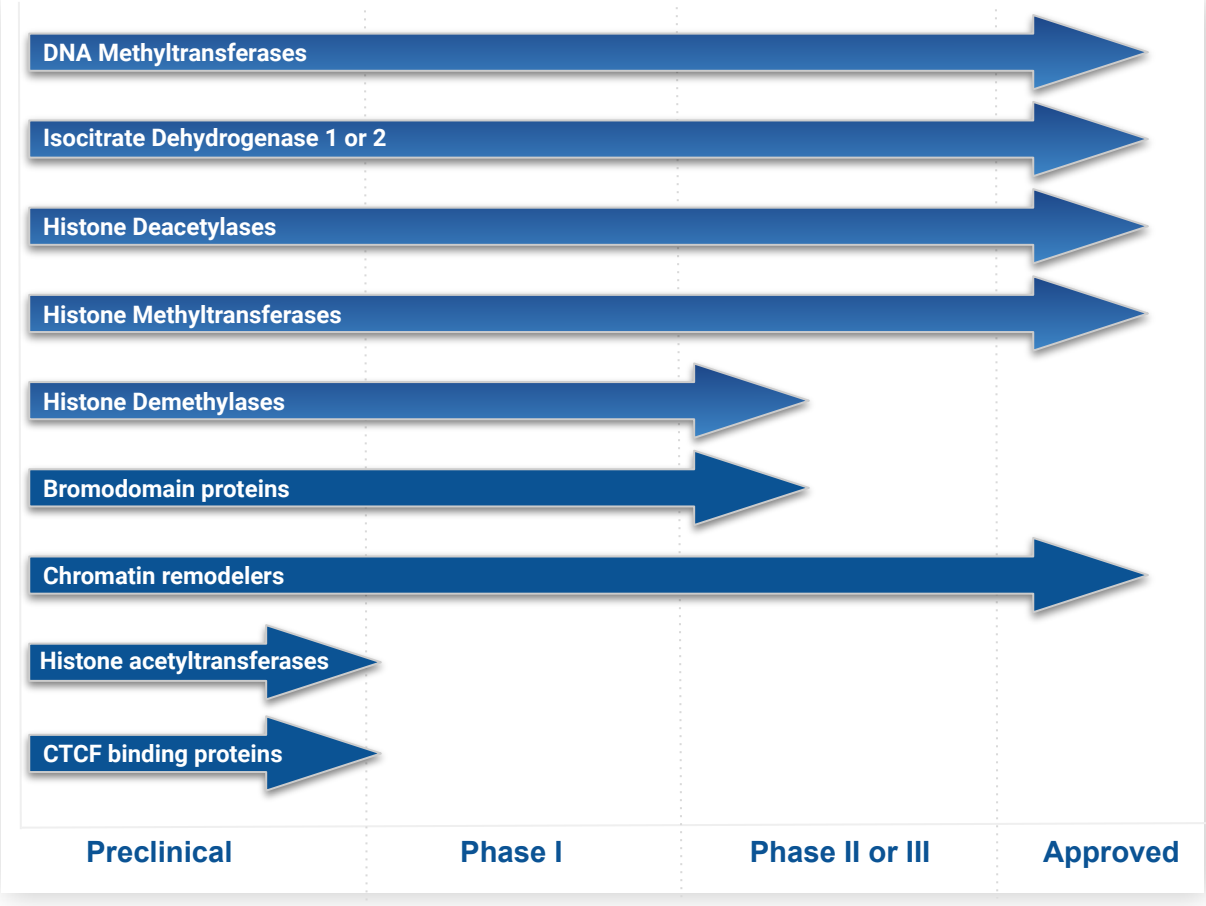
Sources: Roberti et al (2019). Clinical Epigenetics

Overview of Key Drugs



Sources: Citron, F.; Fabris, L. Targeting Epigenetic Dependencies in Solid Tumors: Evolutionary Landscape Beyond Germ Layers Origin. *Cancers* 2020

Rise of EpiDrug Development



On the graph, you can see epigenetic regulators under investigation or approved by the Food and Drug Administration (FDA), according to protein family.

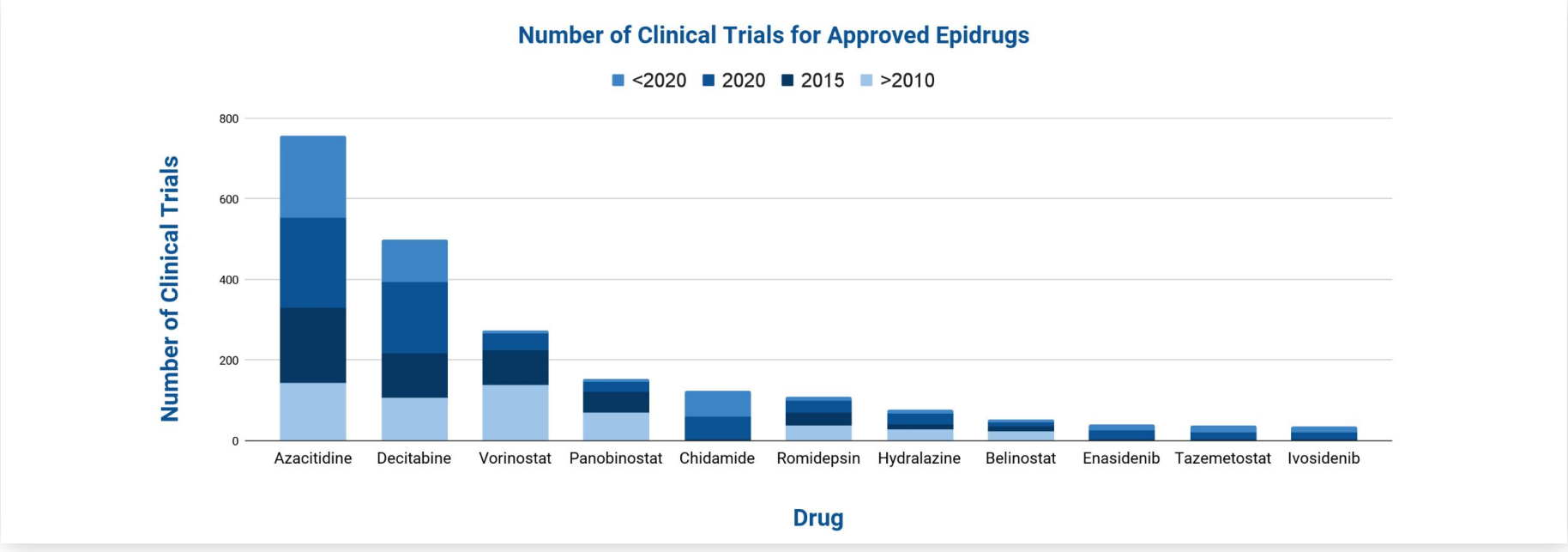
Eleven epigenetic agents are currently available for standard-of-care treatment:

- ➔ Three **DNMT inhibitors** (azacitidine, decitabine, hydralazine)
- ➔ Five **HDAC inhibitors** (belinostat, panobinostat, vorinostat, romidepsin, chidamide, the last one approved only in China)
- ➔ Two **IDH inhibitors** (enasidenib, ivosidenib)
- ➔ One **HMTi - EZH2 inhibitor** (tazemetostat)

Many more inhibitors of writers, erasers, and readers are in development.

Sources: Dan L. Longo (2020). The New England Journal of Medicine.

Rise of EpiDrugs Development



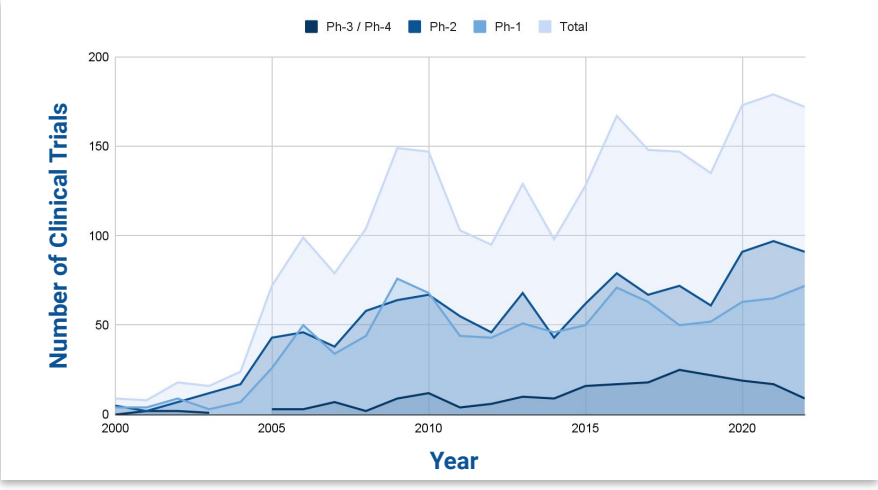
As of today, **2153 clinical trials** with approved EpiDrugs have been reported on **ClinicalTrials.gov. 653** of those clinical trials are **active/recruiting patients**. The biggest number of studies were started in the last decade: **1110 clinical trials** have been registered since **2015**.

The most popular drug is **Azacitidine**. From 2020 to nowadays, **204 clinical trials** have been using azacytidine alone or in combination or with other treatments. **Decitabine**, **Panobinostat** and **Chidamide** are the next most popular EpiDrugs in clinical studies.

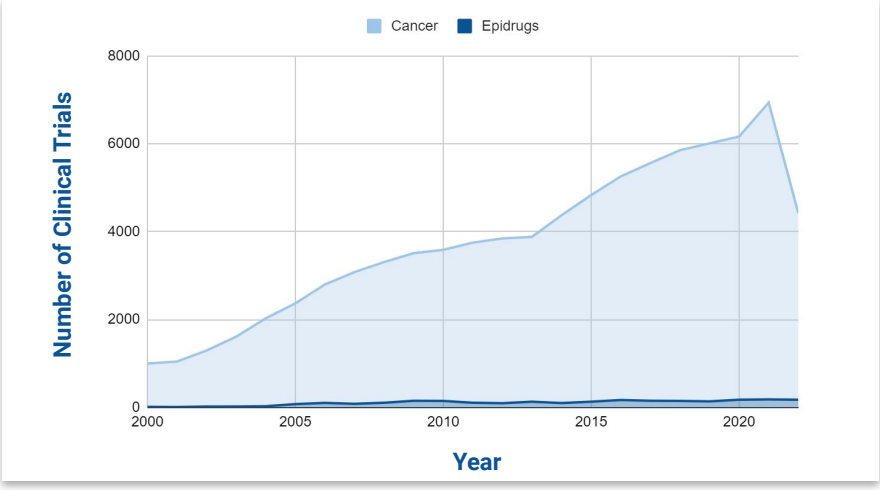
Sources: ClinicalTrials.gov

EpiDrugs in Cancer Clinical Trials

Total Number of Approved EpiDrugs Clinical Trials (2227 trials)



Share of EpiDrugs Clinical Trials in Cancer (86,478 trials)



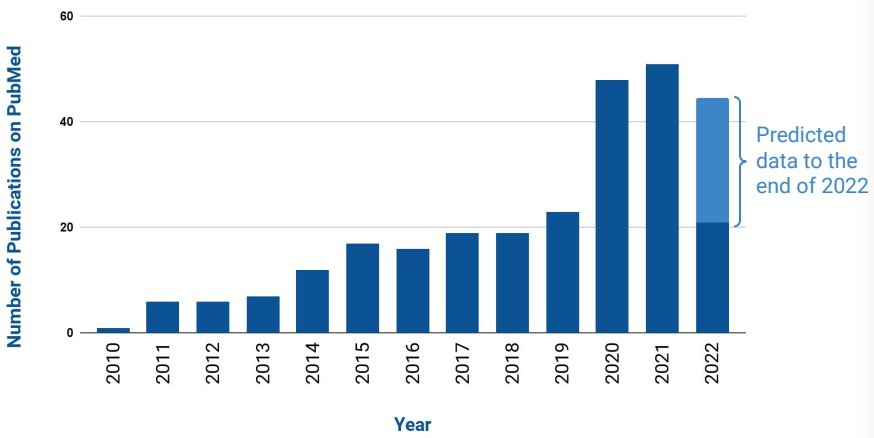
As of **2022**, the percentage of clinical trials with approved EpiDrugs **is negligible compared to trials with other drugs in treating cancer**. Of these, only 10% have reached **Phases 3 and 4**, the stages at which industry-ready products are feasible in the nearest future.

However, here we **did not include** all other EpiDrugs, that **were not approved before**. Therefore, the **role of the development of EpiDrugs in the treatment of cancer should not be neglected** nowadays.

Sources: ClinicalTrials.gov

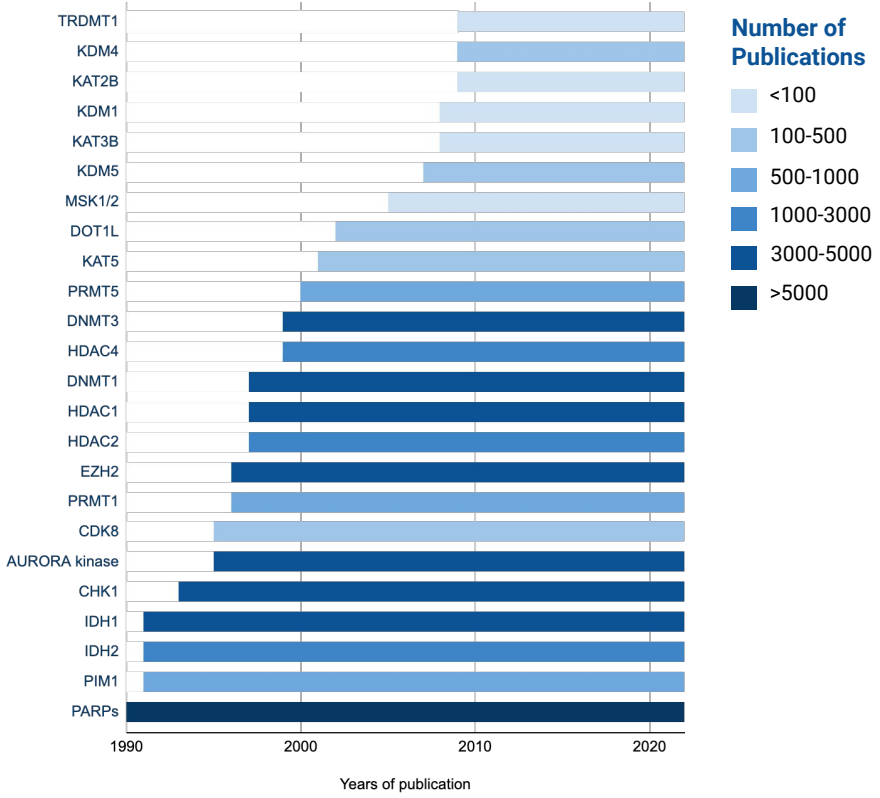
Growth of Scientific Interest in EpiDrugs

Total Scientific Interest in the EpiDrugs Development



Broadly speaking, scientific interest in epigenetic drugs and epigenetics growths through the years. Most papers investigate **classic epigenetic targets** such as **DNA Methyltransferases** (DNMT1, DNMT3a and DNMT3b), and **Histone deacetylases** (HDAC1 and HDAC3). These targets are very reliable, and a few already FDA-approved drugs target these enzymes. However, the interest in **non-classical targets** such as Histone acetyltransferase KAT2B is also very perspective and can bring the new first-in-class drugs.

Popularity of Epigenetic Targets in Time



Sources: pubmed.com, webofscience.com

Key Market Players

Key Companies

- Incyte (113 programs)
- Epizyme (20 programs)
- Eisai (35 programs)
- MIRATI THERAPEUTICS (25 programs)
- agios (9 programs)
- 4SC (7 programs)
- RESVERLOGIX (8 programs)
- CURIS (8 programs)
- ORYZON (13 programs)

Key R&D Centers *(Academia)*

- NIH NATIONAL CANCER INSTITUTE (300+ programs)
- THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History® (130+ programs)
- NIH National Institutes of Health (30+ programs)
- SOOCHOW UNIVERSITY (25+ programs)
- Groupe Francophone des Myélodysplasies (20+ programs)
- Washington University in St. Louis SCHOOL OF MEDICINE (25+ programs)
- MOFFITT CANCER CENTER (20+ programs)
- Memorial Sloan Kettering Cancer Center (20+ programs)

Big Pharma Players

- Celgene (200+ programs)
- MERCK (114 programs)
- gsk (26 programs)
- NOVARTIS (210 programs)
- Takeda (14 programs)
- Pfizer (76 programs)
- Abbott (11 programs)
- Roche (11 programs)

Key companies are evaluated based on the number of clinical trials with epigenetic drugs. These companies and R&D centres develop new epigenetic drugs, conduct the clinical trials of existing epigenetic medications for different conditions (various cancer types, cancers in special population groups, cancers with specific mutations, etc.), and conduct the clinical trials of existing epigenetic drugs in combination with other treatments.

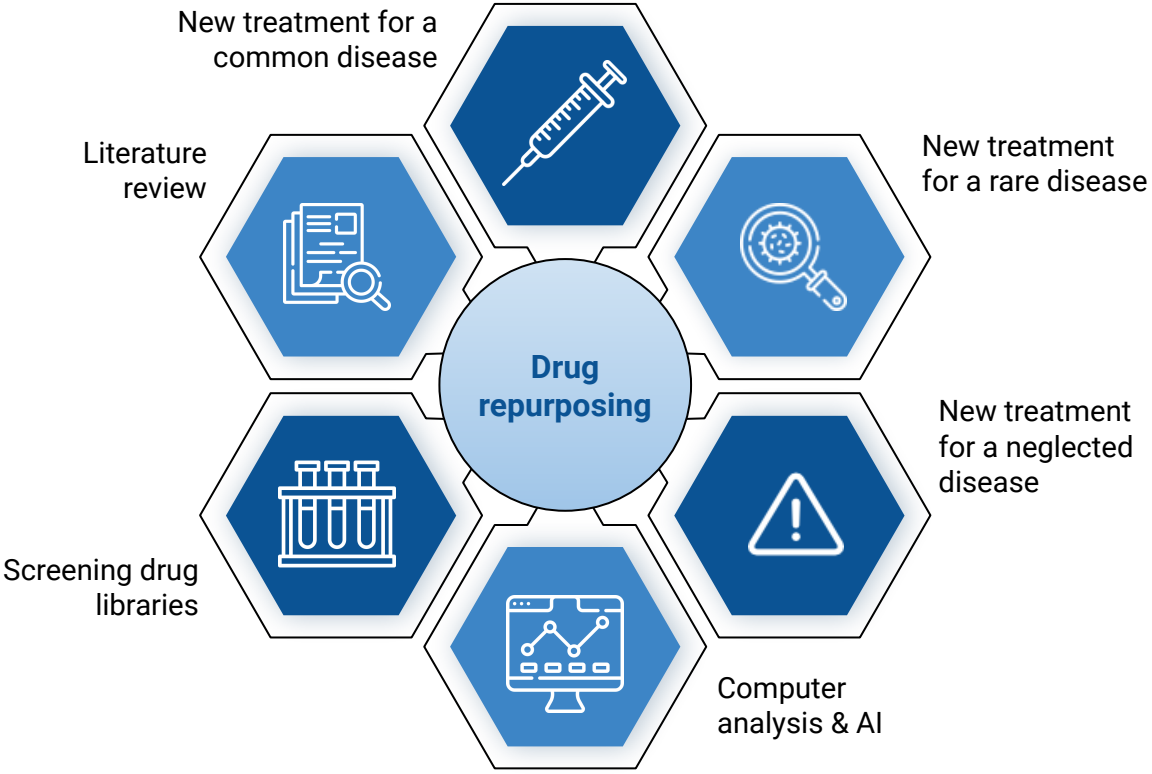
Selected Collaborations

Note: the central column defines the pharmaceutical corporations and side columns define companies and R&D centres that have collaborations with pharma companies from the central column.

EpiDrug Repurposing

The typical process for EpiDrug development is time-consuming and costly. As a result, **medication repositioning or repurposing**, a promising technique for EpiDrug development, is focused on tracing novel potential epi-targets in already authorized pharmaceuticals.

Due to a large number of repositioned candidate molecules that have previously undergone clinical and toxicity profiling studies, the medication repositioning technique is becoming more popular. The **increased availability of biomedical data**, particularly genomic data, which includes numerous elements of cellular systems, **has fueled this method**, allowing for a search that is not limited to biological components implicated in a disease.



Source: Montalvo-Casimiro M, González-Barrios R, Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy. *Front. Oncol.* (2020)

Examples of EpiDrug Repurposing

5-azacytidine and 5aza2'deoxycytidine (decitabine) were the first repurposed pharmaceuticals in the area as anticancer EpiDrugs. These medications were first authorized by the FDA to treat myelodysplastic syndromes because of their antimetabolic actions in cancer cells in vitro experiments. Azacytidine and decitabine were later discovered to prevent DNA methylation and were incorporated by tumor cells as well as in myelodysplastic syndromes.

Platycodi radix (*Platycodon grandiflorum*), often known as balloon flower, is used to cure a variety of obesity-related disorders in East Asia. **Ginseng and *platycodi*** have recently been shown to have **high HDACi action in lung cancer cell** lines, upregulating p21 gene expression and causing cell death.

Green tea (Camellia sinensis) contains a polyphenol called **EGCG**, which is an **anti-inflammatory substance**. It has recently been proposed as a **DNMT inhibitor** that interacts directly with the DNMT catalytic site.

Resveratrol, commonly used for **high cholesterol, cancer, and heart disease,** has been postulated as a dual DNMT and HDAC inhibitor. Resveratrol **suppresses both HDAC and DNMT1 activity in breast cancer** cell lines, as well as histone H3 lysine 27 methylation and acetylation.

Chlorogenic acid may be responsible for the beneficial effects of coffee on glucose regulation and the development of type 2 diabetes. Chlorogenic acid has been **proven in breast cancer cell lines to block DNMT1, lowering DNA methylation.**

Soybean, barley, wheat, and rye all contain lunasin, a 43-amino-acid peptide. **Lunasin** has been found in previous research to **inhibit cancer cell proliferation** and migration while having no effect on wild-type cells. HATs are inhibited by **Lunasin**, affecting the cell cycle and suppressing histone acetylation.

Source: Montalvo-Casimiro M, González-Barrios R, Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy. *Front. Oncol.* (2020)

Epigenetics and Cancer

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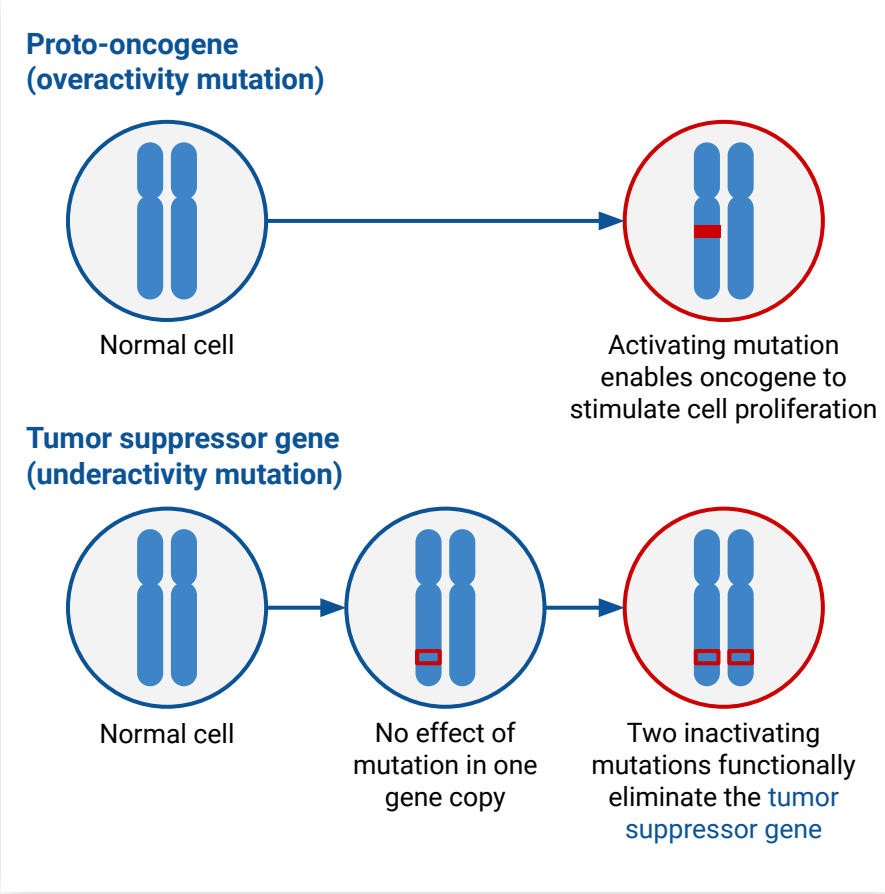
The Biological Basis of Cancer

Cancer is caused by the somatically heritable **dysregulation of genes controlling cell division, death, and movement** from one place of the body to another. During carcinogenesis, genes can become activated in a way that **promotes cell division or prevents cell death (oncogene)**. Genes can also become inactive, meaning they are **no longer able to put a stop to these activities (tumor-suppressor gene).** Cancer develops as a result of the interaction between these two types of genes.

Signalling gene (**oncogene**) mutations in many human cancers are **often dominant and drive the formation of cancers**. Most oncogenes begin as **proto-oncogenes,** which are normal genes involved in cell growth and proliferation or apoptosis inhibition. **Normal genes that promote cellular growth are up-regulated by mutation (gain-of-function mutation)** and predispose the cell to cancer.

Tumor-suppressor genes (TSGs) can be inactivated in at least 3 ways: (1) through **mutations**, which disable their functions; (2) a gene can be completely lost and thus not available to work properly (**loss of heterozygoity**); and (3) a gene can be switched off in a somatically heritable manner by **epigenetic changes**, rather than by mutation of the DNA sequence.



Source: Baylin, S. B., & Jones, P. A. Epigenetic Determinants of Cancer. *Cold Spring Harbor perspectives in biology*. (2016)

Hallmarks of Cancer

Genome Instability and Mutations

Cancer frequently results from damage to genes controlling cell division and tumor suppressors. The genome instability and mutations are highly connected with epigenetic changes.

Activating Invasion and Metastasis

One of the most prominent characteristics of cancer is its ability to invade and grow in distant tissues, which is dependent on changes in cancer cells' interactions with their environment.

Inducing Angiogenesis

The developing tumor tissue need more oxygen and nutrients, therefore it must release pro-angiogenic signals to encourage the development of new blood vessels.

Tumour-promoting Inflammation

Cancer cells hijack inflammatory mechanisms to promote their own growth and survival. It helps to promote and develop all stages of tumorgenesis.

Avoiding Immune Response

Some cancer cells develop mechanisms to avoid identification and killing by the immune system. One method cells do this is by using STING to hijack normal immunological regulation.

Sustaining proliferative signalling

Normal cells rely on external growth signals to proliferate, whereas cancer cells can produce most of their own growth signals, reducing or eliminating their dependency on external stimuli.

Evading Growth Suppressors

Cancer cells escape antiproliferative signals by manipulating cell cycle regulatory mechanisms, such as altering the pRb pathway.

Enabling Replicative Immortality

Malignant cells rely on the telomerase enzyme to keep the length of their telomeres above a key threshold that allows them to keep dividing in order to become immortal.

Resisting cell death

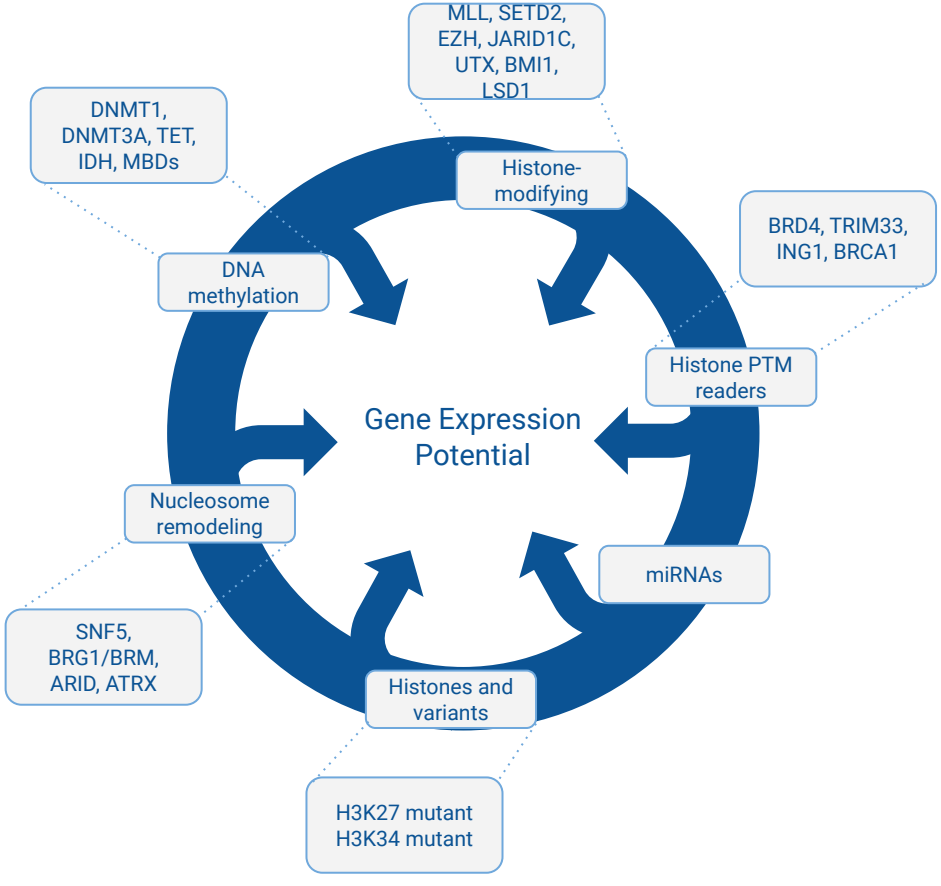
Apoptosis is a crucial anticancer barrier, as immortality is another mechanism for cancer cells to multiply.

Source: Douglas Hanahan and Robert A Weinberg (2011). Hallmarks of cancer: the next generation. Cell.

The Epigenetics of Cancer

One of the **ways to inactivate tumor-suppressor genes is by epigenetic changes,** rather than by mutation of the DNA sequence. Epigenetic silencing can occur by deregulation of the epigenetic machinery at several different levels; 1) it may **involve inappropriate methylation of cytosine** (C) residues in CpG sequence motifs that reside within control regions governing gene expression. 2) **changes to histone posttranslational modifications (PTMs)** or aberrations in the way histone-modifying enzymes function may occur, 3) **change in a protein's ability to read histone marks,** and hence bind to chromatin, or alterations in the way nucleosome-remodeling or histone exchange complexes function can result. Finally, changes in regulatory microRNA (miRNA) expression patterns have been noted.

There is constant research on how epigenetic silencing affects cancer prevention, detection, and treatment. The **FDA has recently approved medications to reverse epigenetic alterations and restore gene function in cancer cells.** Furthermore, because changes in DNA methylation can be identified with great sensitivity, there are numerous ways to detect cancer in its early stages just by looking for changes in DNA methylation. As a result, **the potential for epigenetics to be used in human cancer research, detection, prevention, and therapy is enormous.**

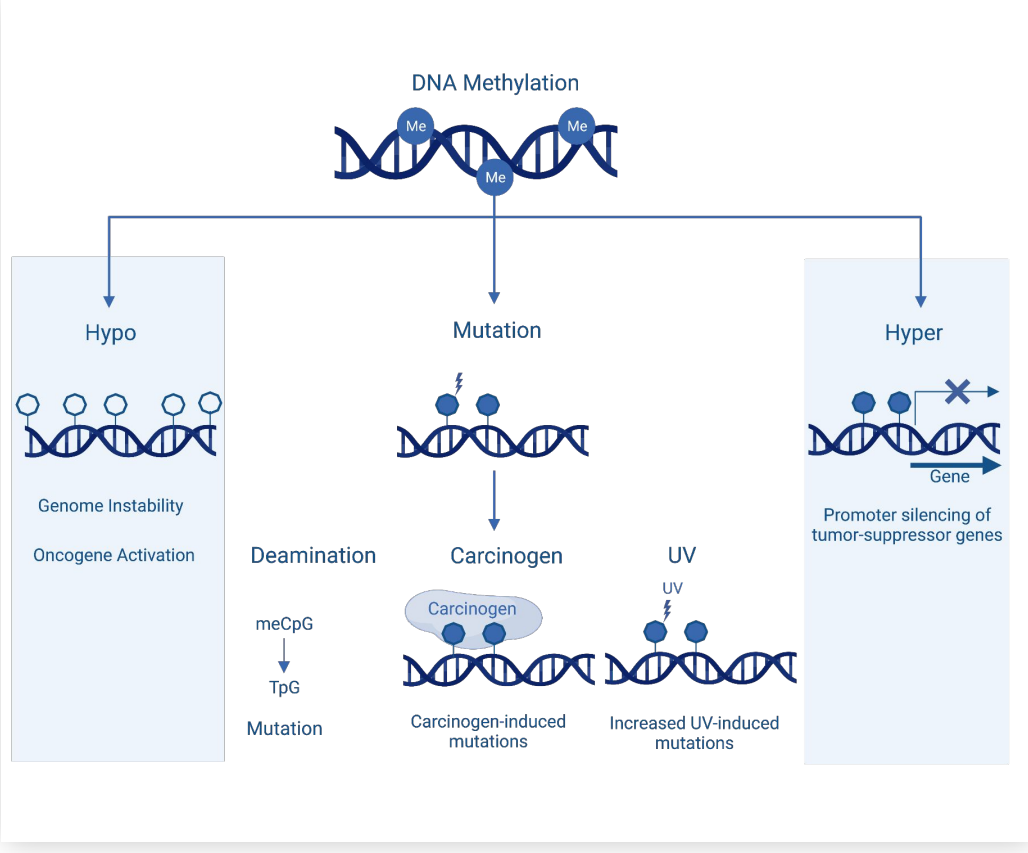


Source: Baylin, S. B., & Jones, P. A. Epigenetic Determinants of Cancer. *Cold Spring Harbor perspectives in biology*. (2016)

The Role of DNA Methylation in Cancer

Over the last 40 years, studies have shown that changes in the **distribution patterns of 5-methylcytosine (5mC), also known as the 5th base, can identify cancer cells from normal cells**. At least three key pathways for CpG methylation to contribute to the oncogenic phenotype have been identified. 1) by **general hypomethylation** of the genome. 2) TSG promoters may experience **localized hypermethylation**. 3) **Deamination, UV irradiation, or exposure to other carcinogens** can all be used to cause direct mutagenesis of 5mC-containing sequences. Notably, all three of these changes tend to happen at the same time and lead to cancer, implying that epigenetic homeostasis is crucial to the evolution of human cancer.

To fuel cancer growth, the link between **genetic disruptions and epigenetic abnormalities is mutually advantageous**, and it might be playing a **crucial role in individual variances in how patients respond to medicines** in terms of toxicity and treatment efficacy. *De novo* EpiDrugs and EpiDrug repurposing have been shown in several studies to resensitize cancer cells to chemotherapy by reversing epigenetic changes.



Source: Baylin, S. B., & Jones, P. A. Epigenetic Determinants of Cancer. *Cold Spring Harbor perspectives in biology*. (2016), Biorender.com

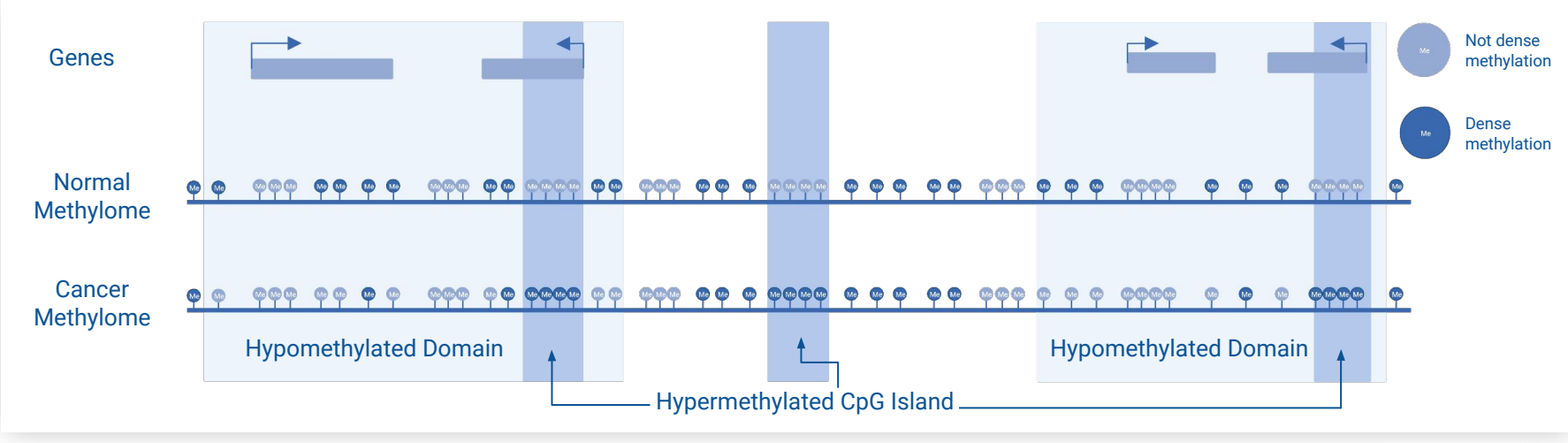
The Role of DNA Methylation in Cancer

DNA Hypomethylation

DNA demethylation has been linked to aneuploidy and genomic instability, both of which are cancer hallmarks. When the maintenance DNA methyltransferase, Dnmt1, is deleted or decreased, increased mutation rates, aneuploidies, and tumor formation are seen, demonstrating that DNA hypomethylation plays a role in promoting chromosomal fragility.

DNA Hypermethylation

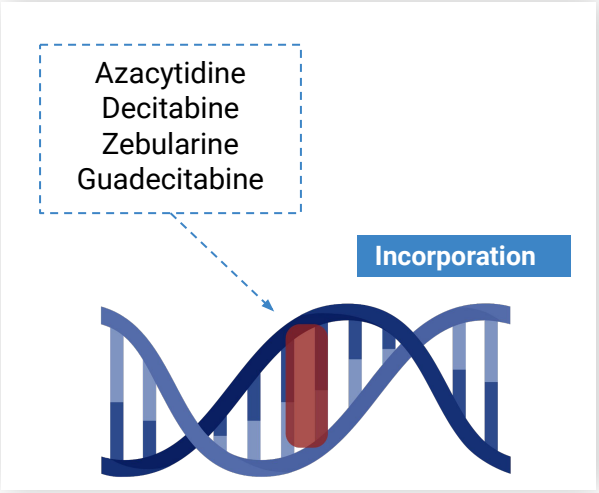
The aberrant hypermethylation of CpG islands in the 5' regions of cancer-related genes is a well-known DNA methylation alteration in cancer. This alteration may be linked to transcriptional silence, giving an alternative to mutation for inactivating tumor-suppressor genes, which usually prevents cells from stopping the cancerous growth.



Source: Baylin, S. B., & Jones, P. A. Epigenetic Determinants of Cancer. *Cold Spring Harbor perspectives in biology*. (2016), Biorender.com

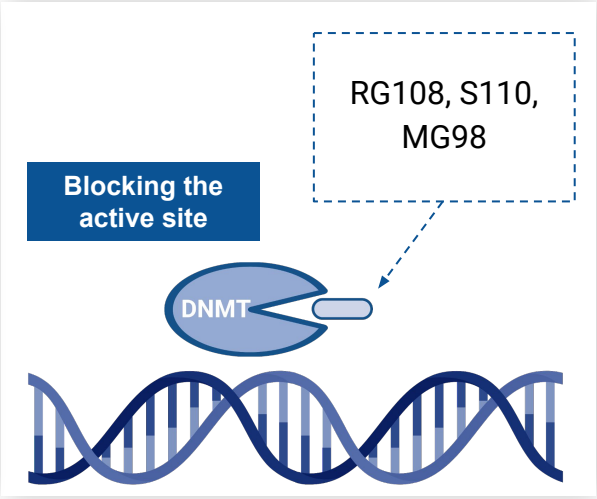
DNMTs Inhibitors

Inhibiting DNMTs with demethylating drugs can efficiently reactivate previously epigenetically repressed genes. In general, there are three types of DNA methylation inhibitors: **nucleoside inhibitors**, **non-nucleoside inhibitors**, and **rationally designed inhibitors**.



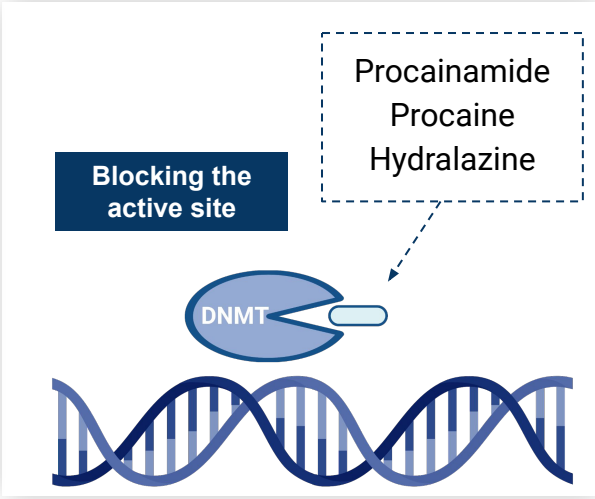
Nucleoside inhibitors

Metabolized and phosphorylated to deoxynucleotide triphosphates and incorporated into DNA. DNMT recognizes the modified bases as natural substrate, the enzyme becomes trapped and subsequently is been degraded.



Non-nucleoside inhibitors

Non-nucleoside inhibitors either block the DNMTs enzyme catalytic site or interact with enzyme recognition of target sequences. Although several non-nucleoside agents also possess DNA-demethylating activity.



Rationally designed inhibitors

The popularity of rationally designed inhibitors, a new strategy for inhibiting DNMTs based on small compounds, is growing. They can directly and specifically blocks the active site of DNMTs.

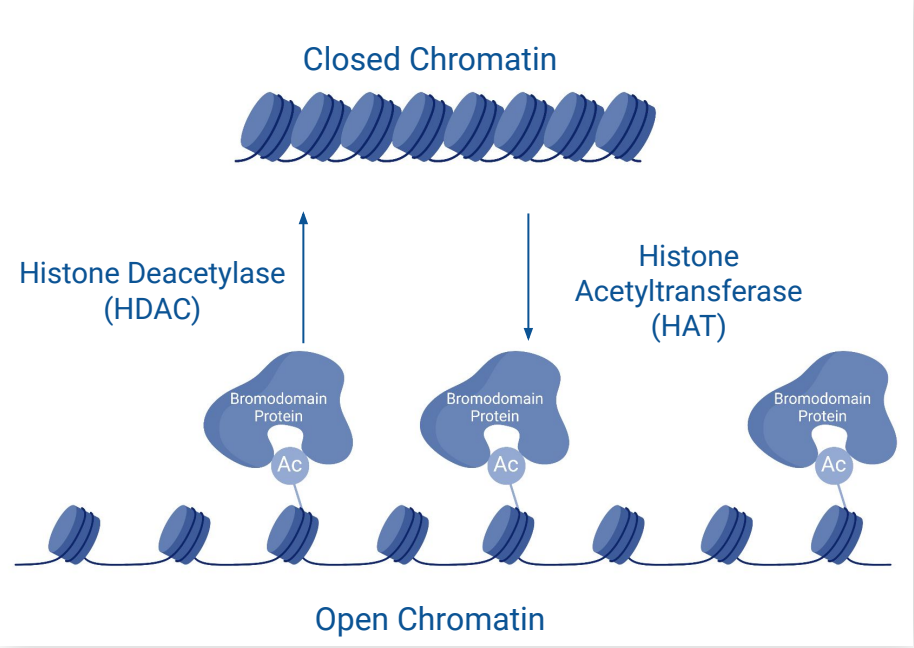
Source: Magic et al (2009). Journal of B.U.ON

The Importance of Chromatin to Cancer

From the recent research, it's clear that **epigenetic regulation affects** not only canonical coding genes, but also **noncoding RNA (ncRNA), microRNAs (miRNAs), and other genome regulatory areas**. Thousands of tumors have been examined, revealing, an unexpected abundance of mutations in genes that affect epigenome activity. Several of these **mutations occur often enough in tumors to support their roles as "driver" mutations**—that is, the findings suggest that mutations disrupting the **epigenome may contribute to cancer start and development.**

Recent genomic alterations on epigenetic modulators were revealed by the mutational fingerprints of human malignancies. A wide range of cellular activities essential for carcinogenesis and **tumor growth is orchestrated by cancer's dependence on the epigenome**, potentially facilitating escape mechanisms that result in treatment resistance.

Epigenetic changes in cancer can occur independently of chromatin-modifying factor mutations; the epigenome is also vulnerable to damage and heritable alterations brought on by physiological or environmental events that are part of cancer risk states and steps in the progression of cancer.



Chromatin remodeling factors control how cellular factors interact with target DNA, any disruption or dysregulation of these special machinery is anticipated to alter the transcriptome status to a malignant state.

Source: Baylin, S. B., & Jones, P. A. Epigenetic Determinants of Cancer. *Cold Spring Harbor perspectives in biology*. (2016), Biorender.com

HDACs Inhibitors

The acetylation level of histones in chromatin and a variety of non-histone substrates, such as several proteins implicated in **tumor development**, **cell cycle regulation**, **apoptosis**, **angiogenesis**, and **cell invasion**, are regulated by the **HDAC family of enzymes (histone deacetylases)**. There are 18 genes in the HDAC family, which are divided into **classes I**, **II**, **III**, and **IV.**
HDAC inhibitors primarily target classes **I, II**, and **IV HDACs**, which are considered to be **"classical" HDACs** since they have a Zn2+ catalytic ion in their active site rather than class III HDACs, which have NAD+ as a necessary cofactor.

Specificity to Class I

- Valproic acid
- Entinostat
- Mocetinostat
- Romidepsin
- Panobinostat

Specificity to Class II

- Abexinostat
- Belinostat
- Panobinostat
- Vorinostat

Specificity to Class IV

- Mocetinostat
- Quisinostat
- Belinostat
- Panobinostat

Note: Selected EpiDrugs that are related to HDACi and are in development or are currently on the market. Here you can see also companies that are mainly involved in their development, but there are several others. Diverse drugs can target two or three classes of HDACs at the same time.

Other Epigenetics Targets

Target	Description	# of Drugs	Companies
Isocitrate dehydrogenase (IDH)	IDH is involved in the conversion of isocitrate to α-ketoglutarate (α-KG). IDH mutation produces a neomorphic enzyme, which inhibits histone and DNA demethylases, resulting in hypermethylated histones and DNA, altering gene expression and driving cancer progression.	Approved: 2 In clinical trials: 2	forma THERAPEUTICS agios Bristol Myers Squibb
Histone methyltransferase (HMT)	HMTs are a class of enzymes that mediate the methylation of lysine or arginine residues of histones. Some enzymes tend to have a mutation in cancers, which enhances their activity. Inhibitors target both mutant and wild-type forms of the protein to induce cell cycle arrest and apoptosis of lymphoma cells in preclinical models.	Approved: 1 In clinical trials: 9	gsk Epizyme morphosys
Poly(ADP-ribose) polymerase (PARP)	PARP is a family of proteins involved in several cellular processes such as DNA repair, genomic stability, and programmed cell death. PARPs catalyze the addition of ADP ribose units from “nicotinamide adenine dinucleotide-donor molecules” to their target substrates. This reaction is essential for DNA methylation.	In clinical trials: 2	Pfizer abbvie Abbott

Other Epigenetics Targets

Target	Description	# of Drugs	Companies
Histone demethylases	Aberrant expression of histone lysine demethylases has been documented in many types of blood and solid tumors, and thus demethylases represent promising therapeutic targets. Additionally, aberrant histone methylation helps oncogenic drivers accelerate cancer progression, metastasis, and therapy resistance.	In clinical trials: 4	OnKure® THERAPEUTICS, VANDA PHARMACEUTICALS INC., Sbio®
Bromodomain and extraterminal (BET)	Epigenetic reader proteins BET are known to drive stem cell development, cellular identity, and transitions between mature cell states. In cancer BET regulate the expression of multiple genes involved in carcinogenesis. BET inhibitors exhibit selectivity for tumor cells by preferentially binding to superenhancers.	In clinical trials: 10	AstraZeneca, RESVERLOGIX, gsk, Roche
Histone kinase	Histone phosphorylation and dephosphorylation by kinases and phosphatases has emerged as an important mechanism for the regulation of diverse events involving chromatin, including transcription, DNA replication, chromosome segregation, DNA damage, and apoptotic responses.	In clinical trials: 1	Incyte

Main Developers of Epigenetics Targets

HDACi

- HDAC class I
- HDAC class II
- HDAC class IV

Treatment products

VANDA PHARMACEUTICALS INC., OnKure THERAPEUTICS, abbvie, Chroma THERAPEUTICS, TITAN PHARMACEUTICALS, MIRATI THERAPEUTICS, AXIS CLINICALS, BAYER, SAMSUNG, Pharma Mar, CURIS, ACROTECH BIOPHARMA, XYNOMIC Pharma, ONXEO THE ORPHAN ONCOLOGY INNOVATOR, 微芯生物 CHIPSCREEN, HELSINN Building quality cancer care together, NOVARTIS, EOC, Celldex therapeutics, 4SC EpiScience for Life, gsk, janssen, MSD, Bristol Myers Squibb

DNMTi

- DNMT1
- DNMT3A
- DNMT3

Treatment products

NYU Langone Health, Eisai, BAYER, Bristol Myers Squibb, CANTEX, SAMSUNG, 亚盛医药 Ascentage Pharma, janssen, aprea therapeutics, GILEAD, Pfizer, Takeda, Otsuka, AMGEN, innovent, cti BIOPHARMA, Salarius PHARMACEUTICALS

IDHi

- IDH1
- IDH2

Treatment products

forma THERAPEUTICS, agios, Bristol Myers Squibb

PARPi

- PARP1
- PARP2

Treatment products

abbvie, Pfizer, Abbott

HDMi

- KDM1
- KDM2
- KDM4
- KDM15

Treatment products

gsk, ORYZON

HMTi

- EZH2
- PRMT1
- PRMT5

Treatment products

gsk, morphosys, janssen, Epizyme

BETi

- BRD2
- BRD3
- BRD4
- BRDT

Treatment products

AstraZeneca, RESVERLOGIX, Roche, gsk, morphosys

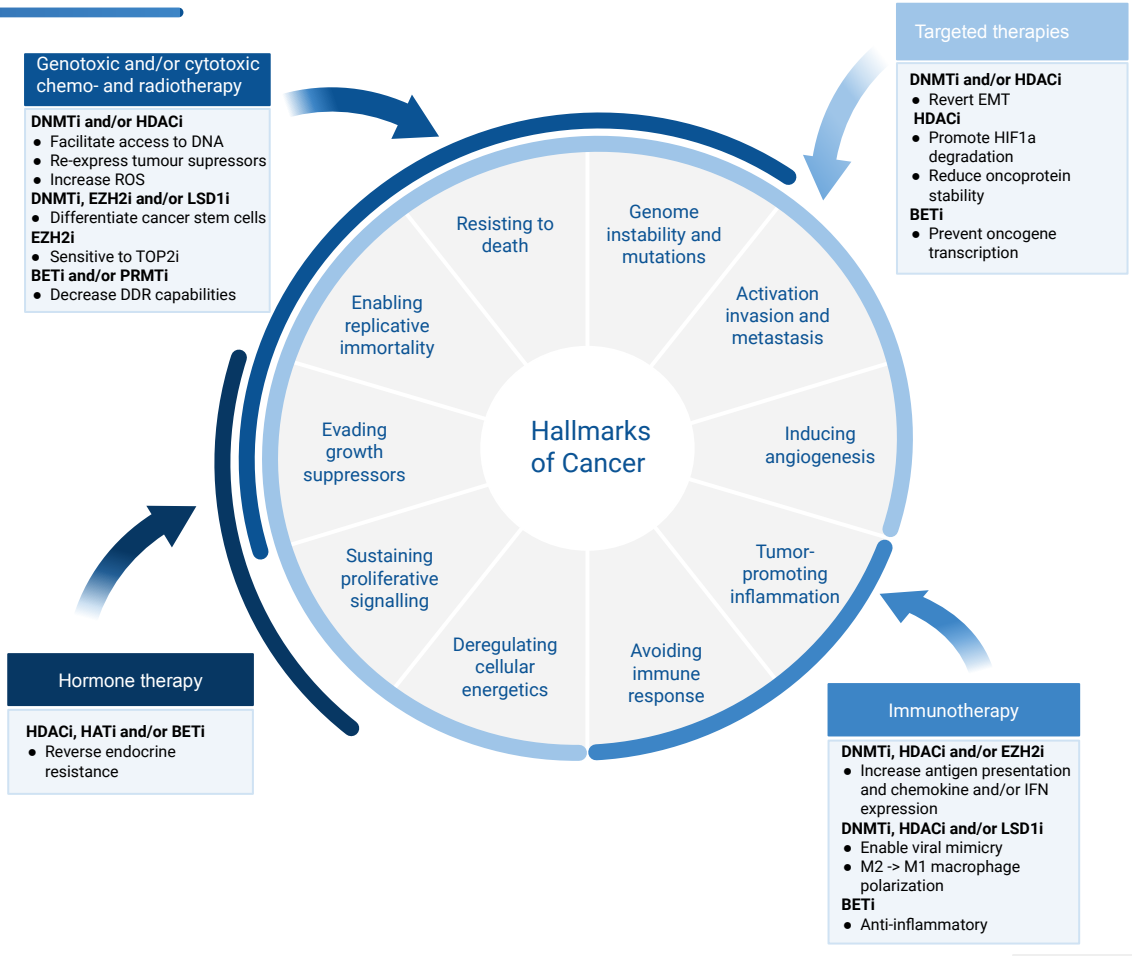
Data based according to reported clinical trials

Note: Therapeutic target medicines that are in development or are currently on the market are presented here. It is evident that HDACi are the primary focus of study and development. Other fields are actively growing, but because of the high complexity, most of them are not yet marketed.

Combination Therapy

All of the identified hallmarks of cancer are influenced by epigenetic regulation, which can be addressed utilizing various treatment techniques. According to Hanahan and Weinberg, these hallmarks are ten biological qualities gained during oncogenesis that drive and/or enable the development of cancer. **Various epi-drugs have the potential to improve the efficacy of four primary anticancer treatment pillars: genotoxic and/or cytotoxic treatments (including chemotherapy and radiotherapy), hormone therapy, molecularly targeted therapy, and immunotherapy.**

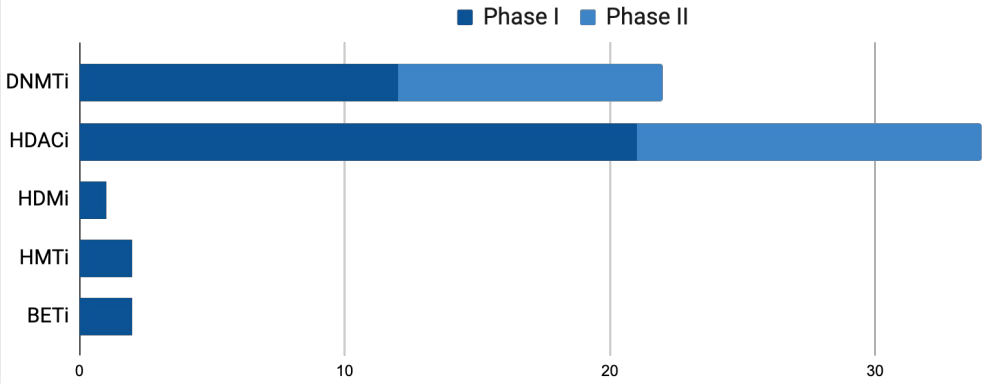
Cancers change over time, in part due to fitness-enhancing dynamic and reversible epigenetic modifications.. **Epi-drugs may thus be most successful when combined with other treatments**, and they present particularly interesting ways for sensitizing cancer cells to specific therapy and dynamically overcoming accumulated resistance mechanisms.



Sources: Morel et al (2020). Nature Reviews Clinical Oncology

Combination of EpiDrugs with Immunotherapy to Treat Cancer

Clinical Trials of EpiDrugs in Combination with Immunotherapy



Antitumor immunity is the result of a complicated interaction of immune, cancer, and stromal cells. Specific DNA-modifying or histone-modifying enzymes, such as DNMTs and HDACs and chromatin assembly factors have a role in cancer cell immunogenicity as well as immune cell lineage commitment and maturation. In preclinical models, epigenetic alterations can reverse several pathways of resistance to immune-checkpoint inhibitors (ICIs). As a result, epi-drugs could be employed to modify antitumor immunity.

Some recent clinical studies highlight the potential of combining epi-drugs with ICIs, particularly in tumors resistant or refractory to ICIs.

- ➔ **DNMTi, HDACi** and/or **EZH2i:** Increase antigen presentation and chemokine and/or IFN expression
- ➔ **DNMTi**, **HDACi** and/or **LSDi:** Enable viral mimicry
- ➔ **BETi:** Anti-inflammatory.

Advanced Study

Pembrolizumab (anti-PD-1antibody) + Entinostat (HDACi)

Results of phase Ib/II trial

Partial response:

- 1 patient with microsatellite-stable Colorectal cancer
- 9 patients with ICI-resistant melanoma
- 7 patients with ICI-resistant Non-small cell lung cancer

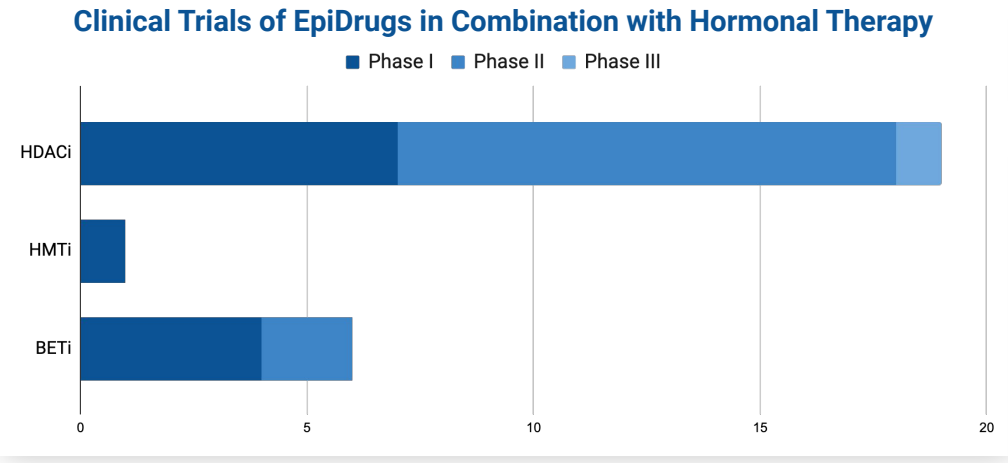
Complete response:

- 1 patient with ICI-resistant melanoma

MSD Syndax

Sources: ClinicalTrials.gov

Combination of EpiDrugs with Hormone Therapy to Treat Cancer



Invasive **breast cancer** has been on the rise since 2004, with over two million cases recorded worldwide in 2018, and over **270,000** cases expected in the United States in 2020. Small drugs targeting chromatin regulators may re-sensitize resistant cells to endocrine therapy or boost sensitivity to novel treatments by remodeling the cancer epigenome.

The key oncogenic driver of 70% of breast cancers is the **oestrogen receptor** (**ER**).

HDAC inhibitors have been proven in preclinical studies to improve the antitumor efficacy of hormone treatments or reverse resistance to them in ER-positive breast cancer living creatures. In combination with the anti-oestrogen fulvestrant, **BETi** inhibits the growth of tamoxifen-resistant tumor cells and xenografts.

→ **HDACi, HMTi** and/or **BETi:** reverse endocrine resistance

Advanced Study

Exemestane + Entinostat (HDACi)

→ **Exemestane** may help to prevent **Breast Cancer** by reducing the amount of estrogen produced by tissue aromatase.

→ **Entinostat** may assist overcome tumor resistance via epigenetic alterations, enhancing the anti-tumor efficacy of exemestane in **Breast Cancer**.

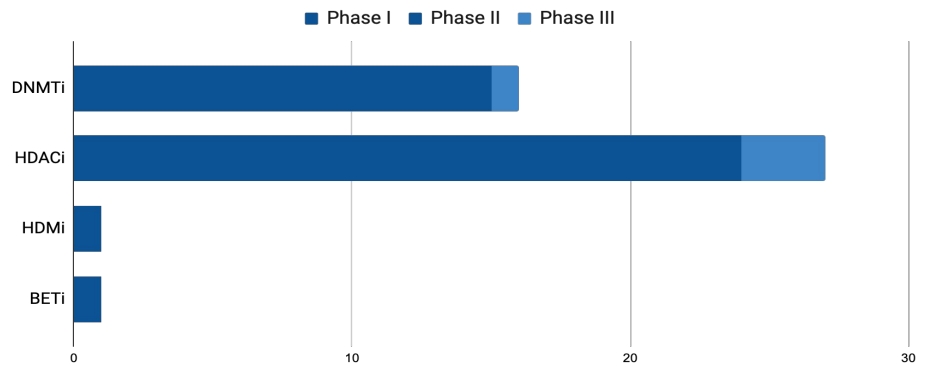
→ A previous **Phase II** trial in US Breast **Cancer patients** found that combination therapy had a substantial effect on reducing disease progression and improving patient survival.

→ **Phase III trial** is ongoing

Sources: ClinicalTrials.gov

Combination of EpiDrugs with Chemotherapy to Treat Cancer

Clinical Trials of EpiDrugs in Combination with Chemotherapy



Synergy has generally been observed with **DNA-damaging compounds** in preclinical investigations evaluating the effects of epi-drugs in conjunction with chemotherapy. **HDAC inhibitors** and **DNMT inhibitors** cause global chromatin relaxation, which allows genotoxic chemicals to damage DNA more easily and interferes with DNA repair.

In addition, low-dose combinations of HDAC inhibitors and DNMT inhibitors may revert cytotoxic drug resistance, in part by removing accumulated epigenetic changes that underlie the resistance phenotype.

Other third-generation epi-drugs, such as **BET inhibitors**, interfere with DNA repair processes as well, boosting the risk of cytotoxic therapeutic synergy.

- **DNMTi** and/or **HDACi**: Facilitate access to DNA, re-expression of epigenetically silenced genes
- **BETi:** Decrease DNA repair capabilities

Advanced Study

Temozolomide or Bevacizumab + Vorinostat (HDACi)

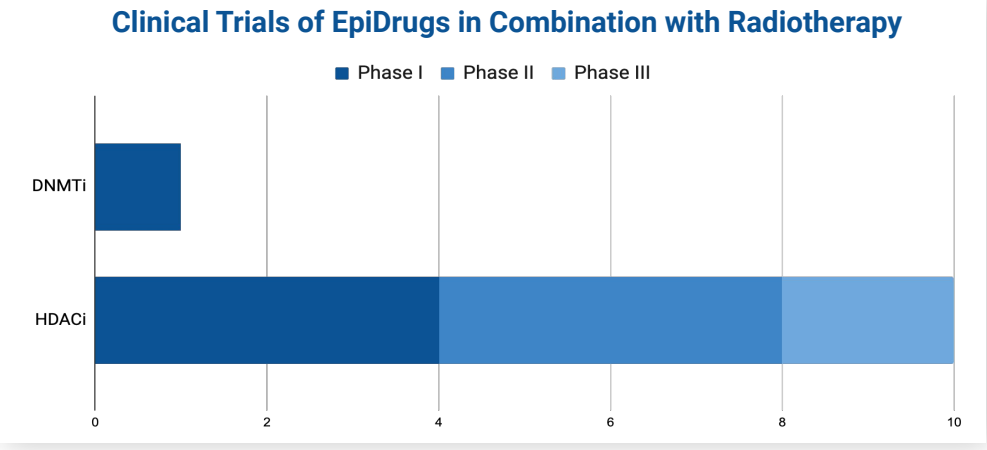
Radiotherapy

- A randomized **phase II/III trial** is studying **Vorinostat**, **Temozolomide**, or **Bevacizumab** to see how well they work compared with each other when given together with **Radiation therapy** followed by **Bevacizumab** and **Temozolomide** in treating young patients with newly diagnosed **High-Grade Glioma.**
- It is not yet known whether giving **Vorinostat** is more effective than **Temozolomide** or **Bevacizumab** when given together with Radiation Therapy in treating glioma.

NIH NATIONAL CANCER INSTITUTE

Sources: ClinicalTrials.gov

Combination of EpiDrugs with Radiotherapy to Treat Cancer



HDAC, **DNMT**, **EZH2**, or **BET** inhibition force the antitumor effect of radiation in preclinical trials by **interrupting the cell cycle**, as well as **increasing oxidative stress**. In mouse models, **BET** inhibition reduces the risk of radiation-induced lung fibrosis and has a radioprotective impact on irradiated non-malignant lung tissue *in vitro*. However, combining **HDAC** inhibitors with radiation has mostly resulted in **higher toxicity and minimal patient benefit** in clinical trials.

Certain **DNMT inhibitors,** such as **5-azacytidine**, can be integrated into DNA and/or RNA, making them particularly potent **radiosensitizers** in all tissues. Therefore, using these epi-drugs with radiotherapy is not suggested due to **toxicity concerns**.

- **DNMTi** and/or **HDACi**:Facilitate access to DNA, Increase ROS
- **BETi**: Decrease DNA repair capabilities
- **EZH2i**: Sensitive to TOP2i

Advanced Study

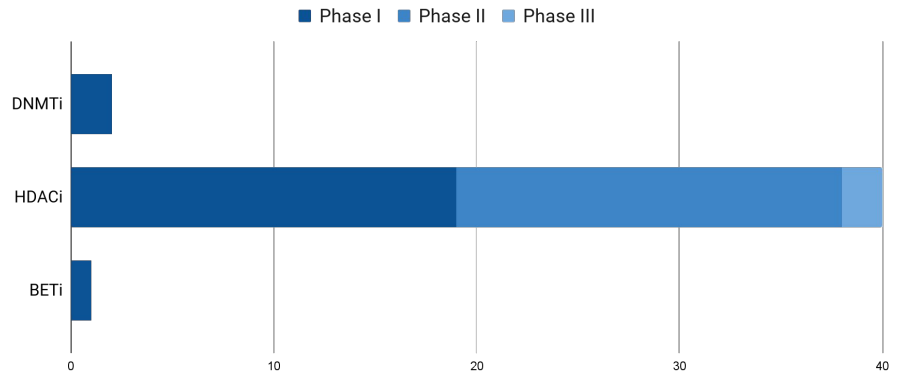
^{131}I-MIBG + Vorinostat (HDACi)

- This combination in children with **Relapsed and/or Refractory High-risk Neuroblastoma** led to an ORR of **12%** at all dose levels and **17%** at the recommended **phase II** dose.
- The results of phase II trial show that **Vorinostat** and **MIBG** is likely the arm with the highest true response rate, with **manageable toxicity.**

Sources: ClinicalTrials.gov

Combination of EpiDrugs with Targeted Therapies to Treat Cancer

Clinical Trials of EpiDrugs in Combination with Targeted Therapies



Resistance to medicines targeting **HER family** receptor tyrosine kinases can be epigenetically induced and consequently reverted by **EpiDrugs**, according to **preclinical** research.

Several **early-stage clinical trials** have been done to assess the safety of **HDAC inhibitors** and **anti-angiogenic** medicines in combination.

Combinations of **HDAC inhibitors** and **inhibitors of the PI3K–AKT–mTOR pathway** have shown promise in preclinical investigations.

- **DNMTi** and/or **HDACi:** Revert epithelial-mesenchymal transition
- **HDACi**: Promote HIF1a degradation, Reduce oncoprotein stability
- **BETi:** Prevent oncogene transcription

Advanced Study

Pazopanib + Abexinostat (HDACi)

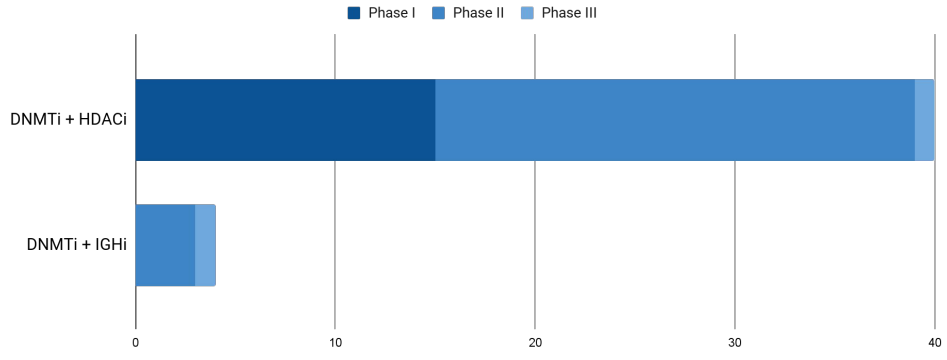
- This is a randomized, **Phase 3**, placebo-controlled study in patients with locally Advanced Unresectable or Metastatic **Renal Cell Carcinoma** (RCC).
- A **phase 1b** study demonstrated strikingly durable responses in patients with RCC. Induction of **histone acetylation** in peripheral blood mononuclear cells was associated with a durable treatment response.
- The addition of **Abexinostat** to **Pazopanib** could significantly improve outcomes in patients with clear cell RCC.

XYNOMIC Pharma

Sources: ClinicalTrials.gov

Combination of Different EpiDrugs to Treat Cancer

Clinical Trials of Different EpiDrugs Combination



Many studies investigate the **combination of different epigenetic drugs** to treat cancer. Additionally, the cooperation of varying types of epigenetic medicines and other treatments (for example, immunotherapy, chemotherapy, cell transplantation, etc.) are also actively studied.

The most actively are studying the combination of **DNMT inhibitors with HDAC inhibitors**. Mainly this combination is used for the treatment of blood cancers. Clinical trials look at the effectiveness of this combination in different age groups, patients with specific mutations and special disease conditions (for example, recurrent disease).

- **DNMTi:** causes hypomethylation of DNA
- **IGHi**: Inhibits mutant IDH to stop the reduction of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG)

Advanced Study

Azacitidine (DNMTi) + Ivosidenib (IGHi)

- This is a placebo-controlled clinical trial (**Phase III**) to evaluate the efficacy and safety of **Ivosidenib + Azacitidine vs placebo + Azacitidine** in adult participants with previously untreated **Acute Myeloid Leukemia**.

- Preliminary data shows that **median overall survival** was **24.0 months** with ivosidenib and azacitidine and **7.9 months** with placebo and azacitidine and estimated **probability that a patient would remain event-free** at 12 months was **37%** in the ivosidenib-and-azacitidine group and **12%** in the placebo-and-azacitidine group.

SERVIER

Sources: ClinicalTrials.gov

Epigenetics and Aging

DEEP
PHARMA
INTELLIGENCE

Hallmarks of Aging

Genomic Instability

Ageing can be the consequence of increased DNA damage accumulation. This is due to physical, chemical, and biological agents, as well as DNA replication errors, spontaneous hydrolytic reactions, and reactive oxygen species (ROS).

Telomere Attrition

Telomeres are the chromosomal regions located on the ends of chromosomes. They tend to become increasingly shorter after each DNA replication. When this sequence ends, the cell dies. Telomerase deficiency in humans is associated with age-related diseases.

Epigenetic Alteration

Epigenetic changes involve alterations in DNA methylation, post-translational modification of histones, and chromatin remodeling.

Loss of Proteostasis

Proteostasis involves mechanisms for the stabilization of correctly folded proteins, and the heat-shock family of proteins, as well as mechanisms for the degradation of proteins. These processes tend to change during ageing.

Deregulated Nutrient Sensing

Nutrient sensing includes trophic and bioenergetic pathways, such as insulin and IGF-1, signaling pathways, and other systems (mTOR, AMPK, and sirtuins).

Mitochondrial Dysfunction

There is a noticeable reduction in ATP generation and increased electron leakage in the respiratory chain caused by ageing.

Cellular Senescence

Cellular senescence can be defined as a stable arrest of the cell cycle. The accumulation of senescent cells in aged tissues can lead to age-related disease progression.

Stem Cell Exhaustion

Stem cells are cells from which all other cells with specialized functions are generated. There is a substantial decrease in the number of stem cells during life. Recent studies suggest that stem-cell rejuvenation may reverse the ageing phenotype.

Altered Intercellular Communication

Neurohormonal signaling tends to be deregulated in ageing as inflammatory reactions increase, while immunosurveillance against pathogens and premalignant cells declines.

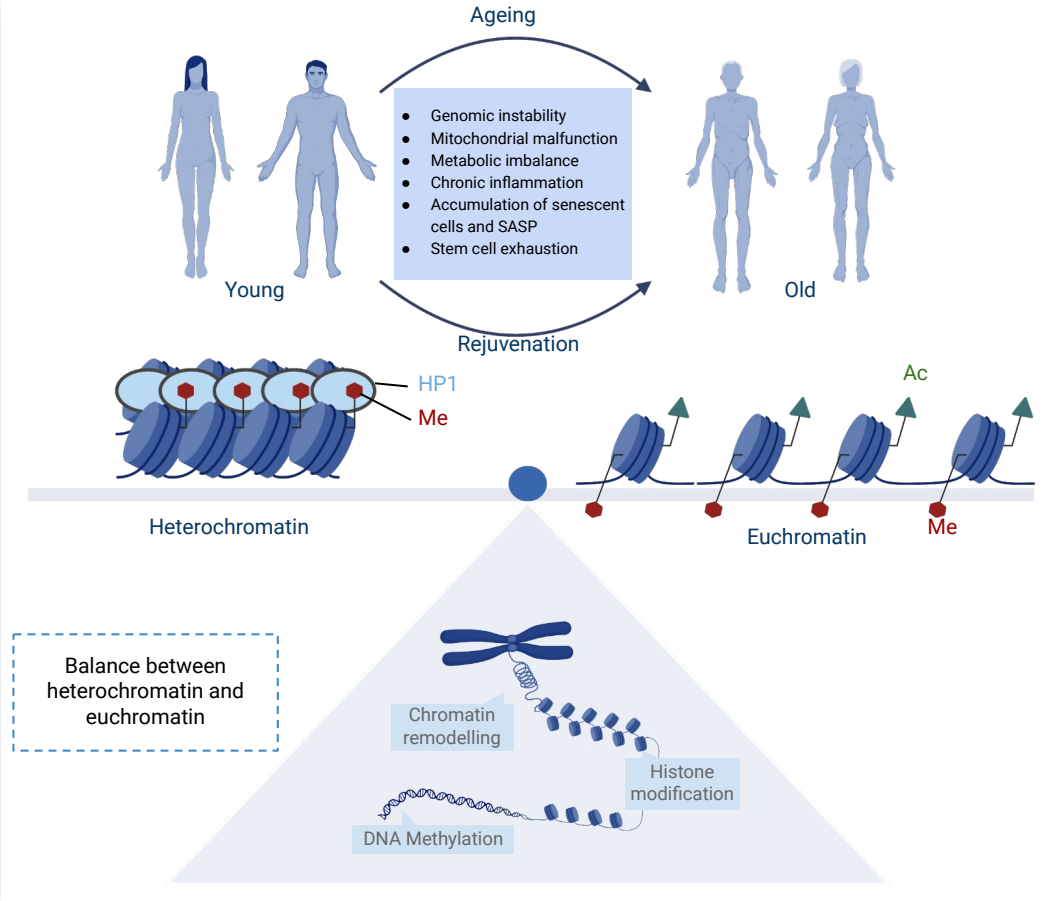
Sources: López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013

The Aging Epigenome

Ageing is associated with functional **decline in tissues and organs** as well as increased risk of developing age-related disorders.

The interventions **delaying ageing include metabolic manipulation, partial reprogramming, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation**. Changes in DNA methylation, histone post-translational modification, and chromatin architecture and remodeling impact healthspan and longevity, according to recent animal research.

Since the ageing process is associated with altered epigenetic mechanisms of gene regulation, such as DNA methylation, histone modification and chromatin remodeling, and non-coding RNAs, the **manipulation of these mechanisms is central to the effectiveness of age-delaying interventions.**



Source: Zhang, W., Qu, J., Liu, GH. *et al.* The ageing epigenome and its rejuvenation. *Nat Rev Mol Cell Biol* 21, 137–150 (2020)

Epigenetic Biomarkers for Aging

Finding **accurate aging biomarkers** is a fundamental goal in modern geroscience. As the aging process is closely associated with altered epigenetic mechanisms, **epigenetics biomarkers have become an interesting research object.** The hypo- and hyper-methylation changes in many regions across the genome have the potential to predict biological age. **Epigenetic clocks** are age-related indicators based on DNA methylation levels at a subset of CpG sites. The difference between age indicated by these clocks and chronological age, termed "epigenetic age acceleration", has been shown to predict age-related disease and mortality.

The **first generation** of the epigenetic aging clocks was developed using chronological age as a surrogate for biological age. The **new generation** of epigenetic clocks, DNAm PhenoAge, incorporated composite clinical measures of phenotypic age that capture differences in lifespan and healthspan and, besides **biological age prediction**, can also predict **forecasts for a variety of aging outcomes**, including all-cause mortality, cancers, healthspan, physical functioning, and Alzheimer's disease. This set of biomarkers is able to capture risks for an array of diverse outcomes across multiple tissues and cells and provide insight into essential pathways in aging.

Many companies are trying to create reliable epigenetic clocks because it enables the evaluation of interventions to **promote healthier aging**.

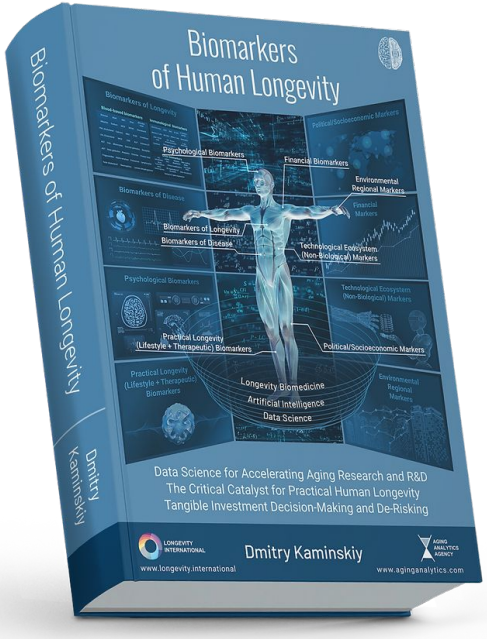
Key Companies

genknowme Personalized prevention solutions
MUHDO YOUR HEALTH MATTERS
St.Mary's General Hospital
ACTIVE MOTIF
VitaLife MD Add Vitality to Your Life
RGCC
MDxHealth
adela
Inherent Biosciences
AGELESSLX
TECAN.
ELYSIUM
BioViva
TWIST BIOSCIENCE
GRAIL
LIFE EXTENSION
ZYMO RESEARCH
Capsulomics
Chronomics
MODERN WELLNESS DIAGNOSTIC SERVICES
MAYO CLINIC LABORATORIES
EarlyDx
NUCLEIX
myDNAge
EPIGENDX
Extended Longevity
CC DIAGNOSTICS
EPIFY
FMI Friedrich Miescher Institute for Biomedical Research
FOXO
US-EPI

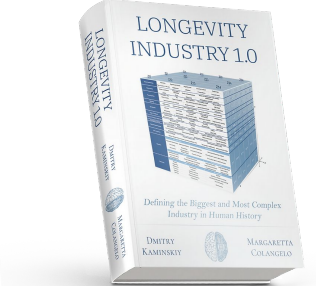
Source: Clinical Epigenetics

Biomarkers of Human Longevity

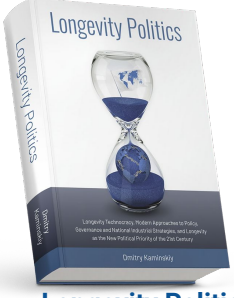
Dmitry Kaminskiy, co-founder and managing partner of Deep Knowledge Group, published a **series of books dedicated to the topic of Human Longevity**. One of the most intriguing is **"Biomarkers of Human Longevity"**. That book placed particular emphasis on the power that Biomarkers of Human Longevity have to serve as a major catalyst and accelerator of short-term practical applications, the translation of theory into practice.



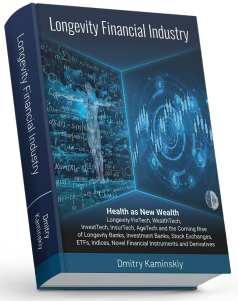
Biomarkers of Human Longevity



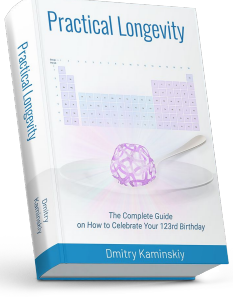
Longevity Industry 1.0



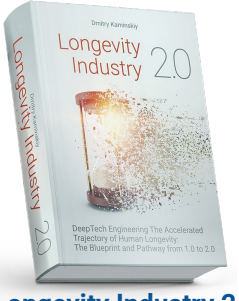
Longevity Politics



Longevity Financial Industry



Practical Longevity



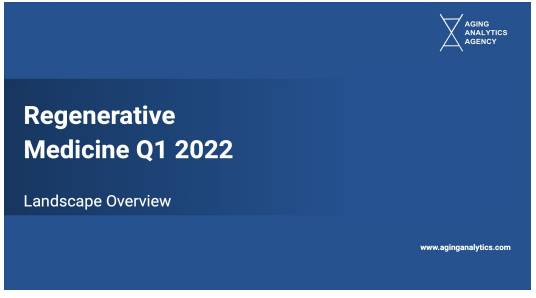
Longevity Industry 2.0

To learn more about the books: **https://www.longevity-book.com/**

Longevity Reports

Aging Analytics Agency is the world's premier provider of industry analytics on the topics of **Longevity**, **Precision Preventive Medicine** and **Economics of Aging**, and the convergence of technologies such as AI, Blockchain, Digital Health and their impact on the healthcare industry. Aging Analytics Agency published a series of reports dedicated to longevity industry in in various manifestations.

Longevity Biomarkers Landscape Overview, Q1 2022



Regenerative medicine, Q1 2022

VR in Medical Practice, Q1 2022

Mitochondria in Longevity and Space Medicine, Q3 2021

Longevity Industry in Switzerland

Longevity Clinical Trials, Q3 2021

To learn more about the reports: **https://www.aginganalytics.com/**

Epigenetics in Neurodegenerative Diseases

Environmental variables have a significant impact on neurodegenerative disorders including **Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Prion disease,** and others; thus, modifications in the epigenome are implicated. **Neuroepigenetics** refers to the study of epigenetics in neurons.

	Alzheimer's disease	Parkinson's disease
Methylation	**Limited 5mC, 5Fc, 5hmC, and 5caC** signatures in AD lead to **neuronal degeneration**. With age, methylated cytosines in 207–182 area get demethylated resulting in the deposition of Aβ in the brain.	**Reduction of DNA methylation** in intron 1 of SNCA was observed **in PD patients.** Increased level of SNCA expression is seen if DNA methylation is inhibited
Histone Modifications	Memory-related brain regions show greater concentrations of HDAC2 & HDAC3. **HDAC2 reduces the histone acetylation of the memory and learning-related genes**. Increased HDAC6 was also found in AD patients with cognitive impairment	Response to treatment with HDACi in disease models A-synuclein reduction in histone acetylation and histone gene expression.
Micro RNA regulation	**miRNAs aid in neurogenesis and amyloid processing during the development of AD**. Brain-derived neuropathic factor, controlled by miR-206, may influence both synaptic plasticity and memory in a human AD brain.	**miR-7 and miR-153**, found in the PD patients, together **regulate the concentration of α-synuclein,** required for synaptic vesicle trafficking and subsequent neurotransmitter release.

Source: P. Ghosh, A. Saadat, Neurodegeneration and epigenetics: A review, Neurología, (2021)

Clinical Trials on Epigenetics Drugs for Neurodegenerative Diseases

Vafidemstat (ORY-2001), a CNS optimized covalent **LSD1 inhibitor** for **neurological disorders**.

Vafidemstat restores memory to normal levels and reduces the exacerbated aggressiveness in a model for **accelerated aging** and **Alzheimer's disease** (AD) as well as reduces neuroinflammation in **multiple sclerosis** (MS).

- ➔ Lysine-specific demethylase **LSD1** plays a fundamental role in neurogenesis, neuronal differentiation and axonal navigation.
- ➔ **LSD1** is the most abundant Lysine Demethylase in the prefrontal cortex.

Clinical trials of Vafidemstat

Currently in Phase IIa for:

1. Assessment of Vafidemstat'seffect on agitation-aggression in patients with **different psychiatric disorders** (REIMAGINE study)
2. Testing aggressive/agitated patients with moderate or severe **Alzheimer's disease** (REIMAGINE-AD study)
3. ETHERAL and ETHERAL-US studies in patients with **mild to moderate Alzheimer's disease**

Currently in Phase IIb:

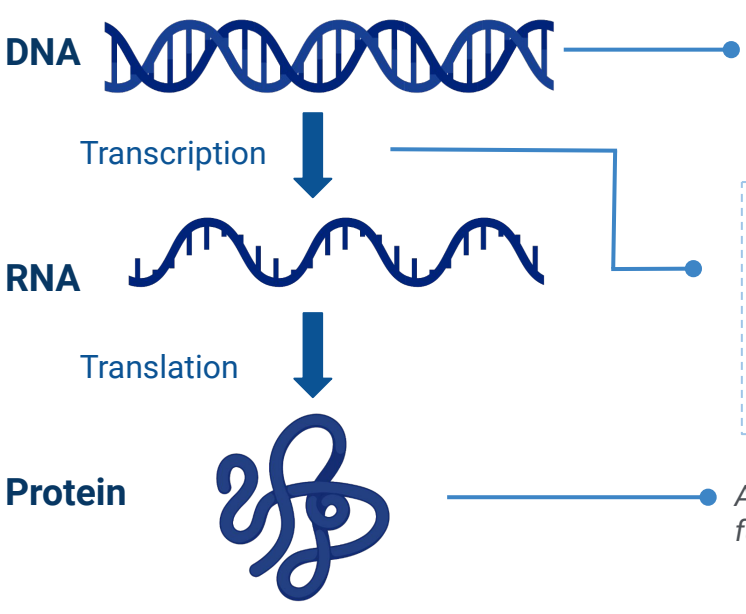
1. Ongoing study of vafidemstat in **Borderline Personality Disorder** patients (PORTICO study)
2. Evaluation of vafidemstat's efficacy on negative symptoms and cognition in **schizophrenia** patients
3. Vafidemstat is also being evaluated in severely ill COVID-19 patients (ESCAPE study), assessing the capability of the drug to prevent Acute Respiratory Distress Syndrome **(ARDS),** (the most severe complications of the viral infection).

ORYZON

Source: Oryzon.com

Epigenetics in Cardiovascular Diseases

The first **Phase 3 BET inhibitor clinical trial** conducted outside of oncology is called **BETonMACE**. The trial, which was completed in September 2019, was created to assess the safety and effectiveness of apabetalone in reducing **Major Adverse Cardiac Events** (MACE) in high-risk patients with **type 2 diabetes mellitus** who had **cardiovascular disease**.



Genome editing

*There are currently no **FDA-approved** therapies based on gene editing.*

Transcriptional regulation

***Apabetalone,** acting upstream of traditional pharmaceuticals, represents a **paradigm shift** in the treatment of chronic disease.*

Protein inhibition

*Almost **all current therapeutics** function via protein inhibition.*

Apabetalone is an epigenetic drug that treats **vascular diseases** by reducing the expression of genes associated with the ailment.

Patients with **diabetes** and **vascular disease** who express these genes have a faster progression of their conditions, which **damages their arteries** and raises their risk of **heart attacks and strokes**.

Apabetalone **normalizes expression towards a healthier state** by preventing specialized proteins known as **bromodomain and extraterminal domain (BET) proteins** from activating the expression of disease-associated genes.

RESVERLOGIX

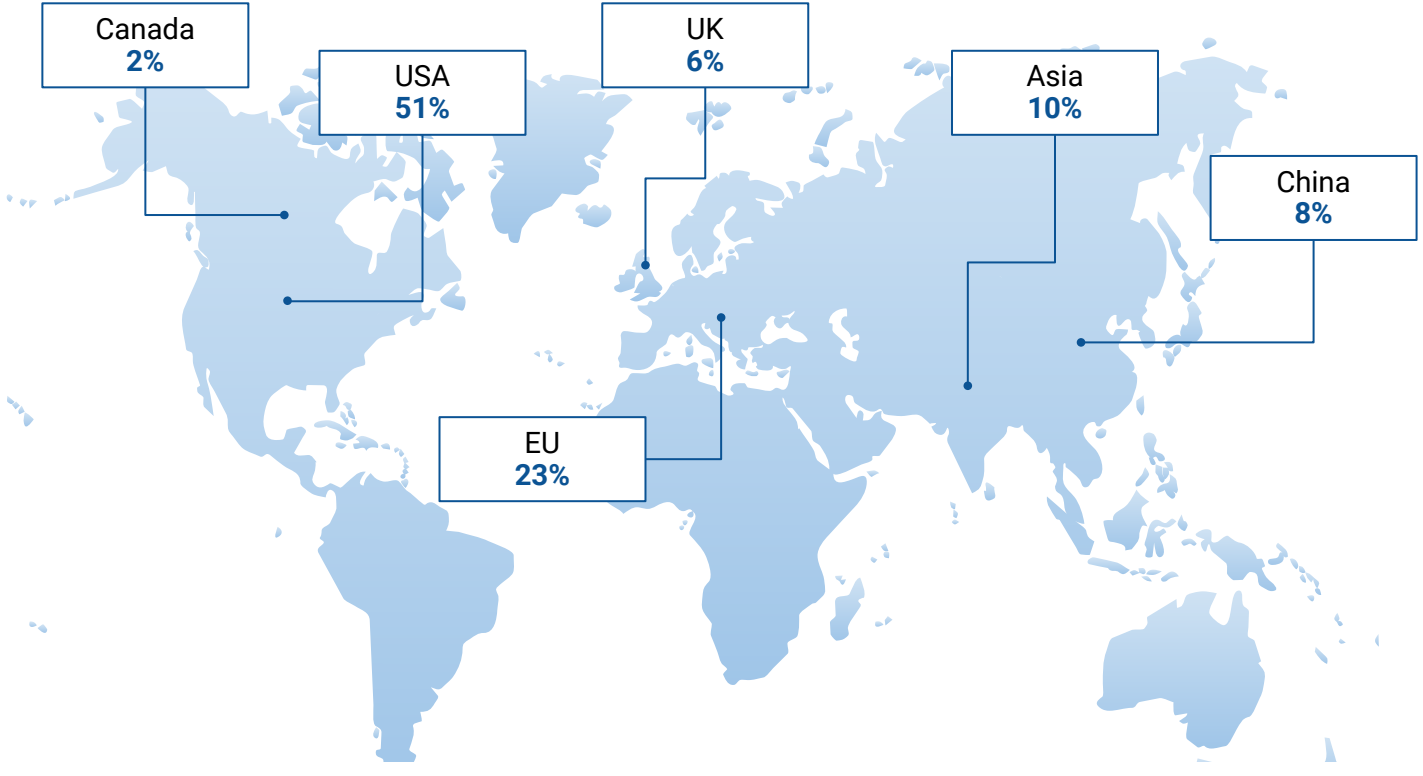
BETonMACE
A CARDIOVASCULAR STUDY FOR PEOPLE WITH TYPE 2 DIABETES

Sources: Reverselogix

Market Overview

DEEP
PHARMA
INTELLIGENCE

Regional Distribution



Most companies conducting research and development of epigenetics drugs are located in the **United States (51%)**. The second place is **Europe (23%)**, where the most active countries are Germany and Switzerland. The **Asian region** also has many developments in this direction: overall, Asia has **18%** of companies developing the epigenetic drugs, and **8%** of them are in **China**.

Categorical Distribution

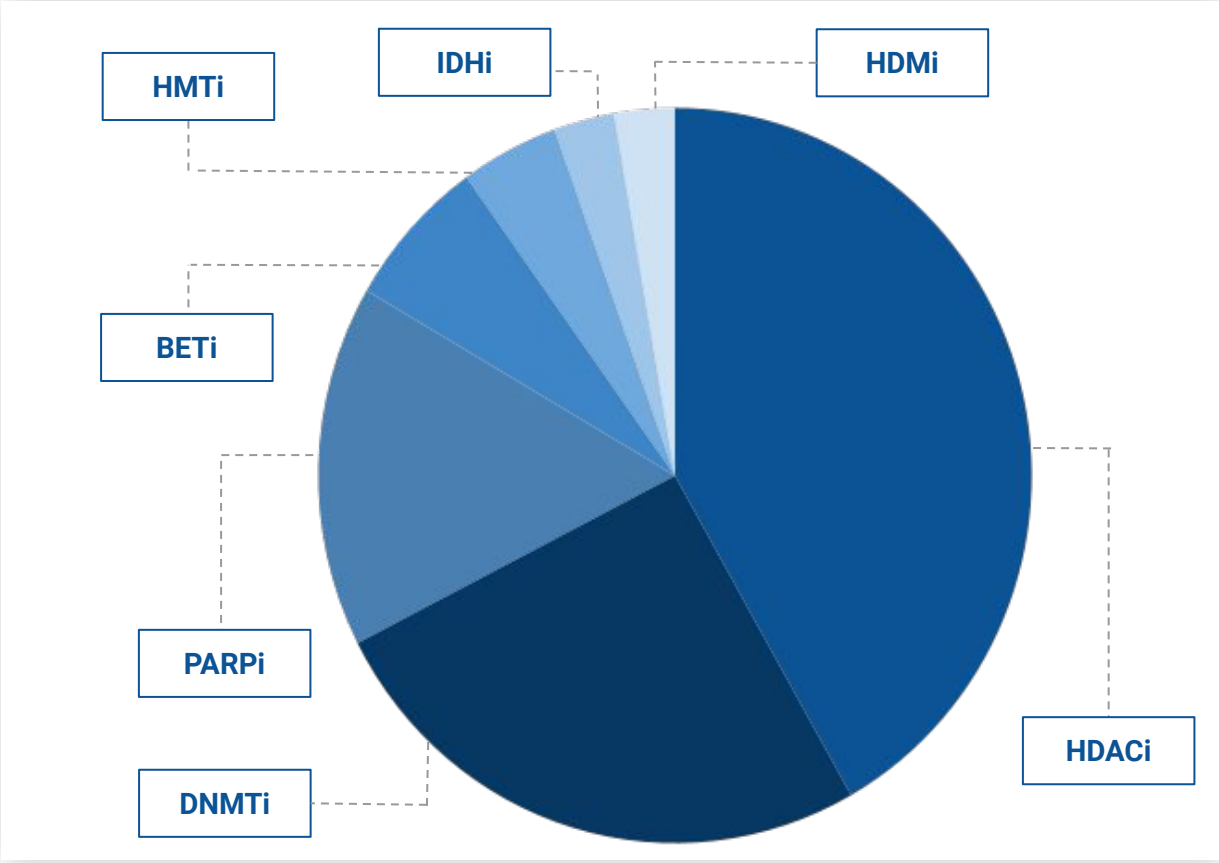
The **epigenetic drug** discovery field has evidenced significant advancement in recent times.

The **majority** of companies conducting EpiDrug development are focused on **HDACi**, which accounts for **42%** of the clinical trials analysed companies.

DNMTi is in second place, and **26%** of clinical trials presented here aim to develop drugs which will target this class of enzymes.

Surprisingly, **16%** of calculated clinical trials are tested **PARPi,** which are very popular among a few advanced companies.

Other drugs that have fewer than **10%** of clinical trials are **HMTi**, **IDHi** and **HDMi**.

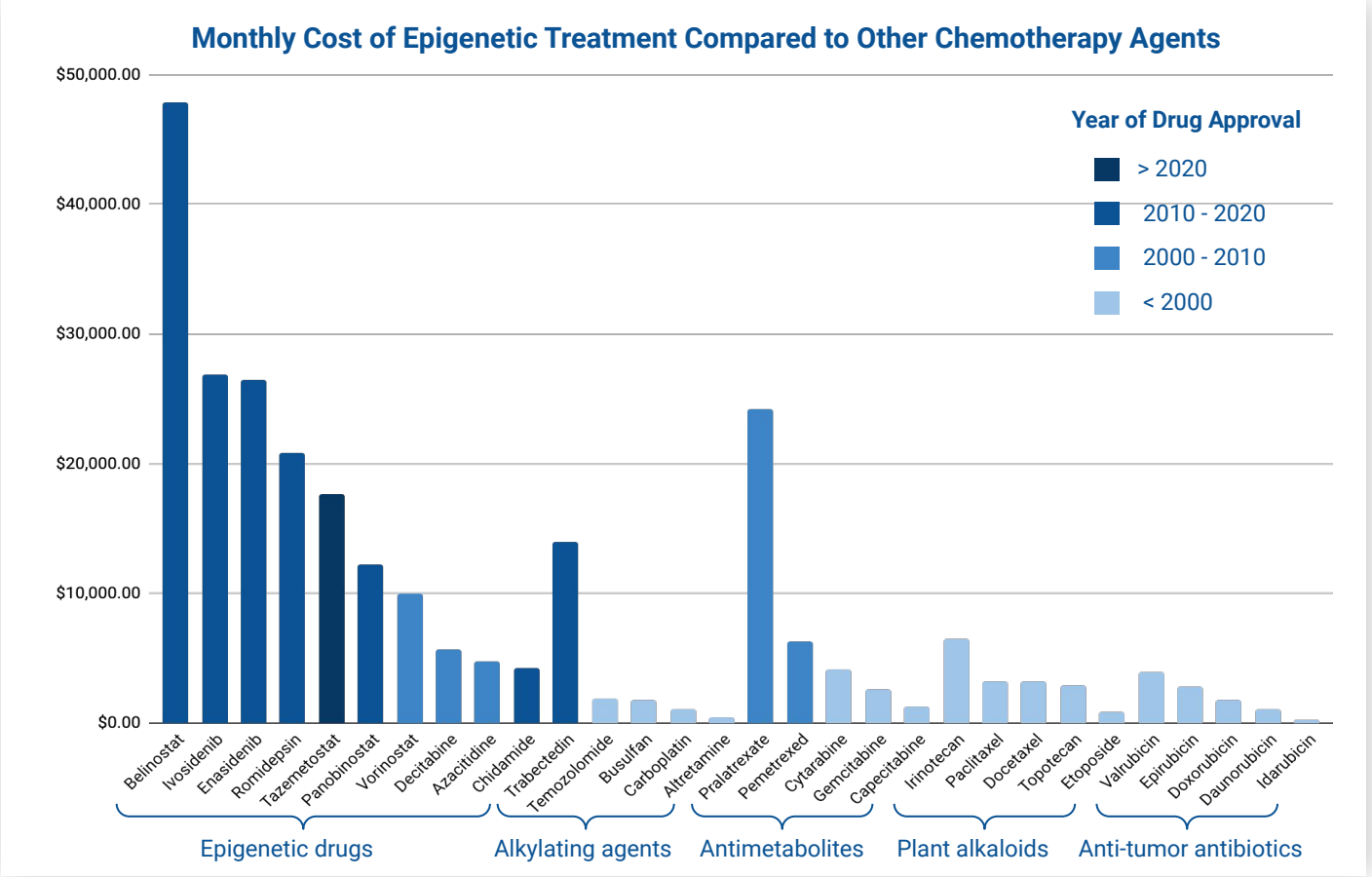


Sources: ClinicalTrials.gov

Epigenetic Drugs' Costs

The comparison of the **monthly cost of epigenetic drugs** with **other common chemotherapy agents** showed that epigenetic drugs' prices are, on averagely, four times higher. Most costs were taken for 2015 and adjusted by the inflation rate.

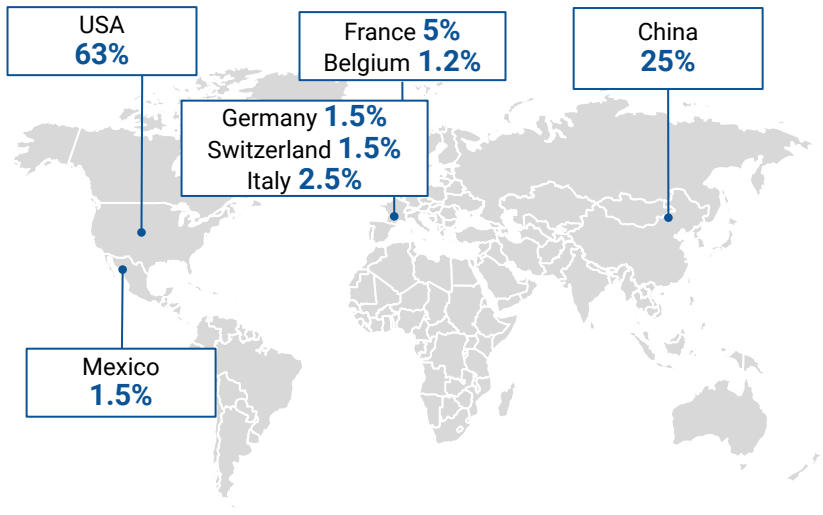
There are a few reasons for the high prices of epigenetic drugs. One of the most significant is the **high cost of the research and development** of such drugs. Additionally, epigenetic drugs are relatively new; most of them were approved after 2010, when some other chemotherapy agents were more than 50 years on the market. That may note that companies had less time for manufacturer process adjusting to make it more cost-efficient.



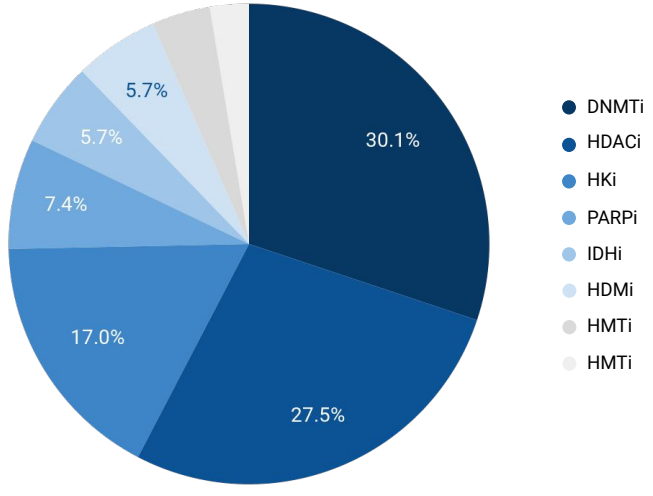
Sources: Medical News Today, Memorial Sloan Kettering Cancer Center

R&D Centres

Distribution of R&D Centres by Country, %



Distribution of R&D Centres by Category, %



The **vast majority of R&D Centres** that conduct mitochondria research are located in the **United States**, where **63%** of the whole range of analysed R&D Centres are located. The United States is distantly followed by **China** and **France** which together make up **30%** of all R&D Centers.

The major domain in which epigenetics research are being conducted is DNMT inhibitors and HDAC inhibitors. More than half of main R&D centers conduct research in this field.

Challenges and Opportunities for Epigenetic Drug Discovery

TARGET SELECTION	• Enzyme isoform selectivity • PTM modifications of histones vs non-histone substrates • Functional effect of inhibiting specific epigenetic modifiers • Off-target effects on additional complex members • Effects on high-order chromatin structure	• Isoform selective inhibitors • Genetic-engineering tools (CRISPR-Cas9, siRNAs) • Multitarget compounds
CHEMICAL DESIGN, DRUG PRODUCTION, ENZYMATIC ASSAYS	• Development of reference compounds • Development of isoform-selective inhibitors • Development of dual inhibitors • Production of active enzymes and specific substrates	• Development of new *in vitro* models • Development of robust throughput in vitro and cellular/phenotypic assays • Design of focused chemical libraries • Improved *in silico* ADME prediction tools
***IN VIVO* BIOLOGY**	• In vitro assays based on nucleosome substrates may not fully recapitulate the effect of the drug • Production of active enzymes and specific substrates • Dose-limiting toxicities • Kinetics of the drug response • Improving the long-lasting effects of the drug	• Development of *in vitro* models closer to physiological context • Development of new models (inducible knockout animals, organoids, humanized murine models)
CLINICAL TRIALS	• Patient selection • EpiDrugs for solid tumors/non-tumoral diseases/ • EpiDrugs in combination to improve immunotherapy/chemotherapy/radiotherapy/hormone therapy/target therapy treatments • Reduction of off-target effects	• Biomarkers for prediction of drugs response • Combinatory therapy to minimize chemoresistance • Activating mutations as more targeted therapy • Synthetic lethal approaches

Sources: Ganesan et al (2019). Clinical Epigenecis.

Key Takeaways

Epigenetic dysregulation has been acknowledged as a significant cause of human diseases for the recent decades. This is encouraged more research into the area of finding drugs for epigenetic disorders that are called **EpiDrugs**. EpiDrugs usually are **small-molecule inhibitors** that either target the epigenome or enzymes with epigenetic activity. The three categories of epigenetic regulators are targeted by EpiDrugs: **writers**, **readers** and **erasers**. Nevertheless, the implementation of EpiDrugs in clinical practice is very scarce.

The biggest part of approved or tested in clinical trials EpiDrugs now are almost exclusively **DNA methyltransferase (DNMT) inhibitors** or **histone deacetylase (HDAC) inhibitors**. Nowadays, there are **11 EpiDrugs approved by FDA**. Both pharmaceutical companies and R&D centres are involved in EpiDrug development, but most of the clinical trials registered to date are owned by pharmaceutical companies.

Despite their promise, there are still many issues that need to be resolved before EpiDrugs can be effectively used to treat human cancer. These issues include the lack of specificity of EpiDrugs, their lackluster effectiveness in treating solid tumors, and their development of drug chemoresistance, which increases the risk of tumor relapse. Recent advancements highlight the significance of **integrating EpiDrugs with non-epigenetic therapeutic agents** to design better policies for the treatment of cancer and non-cancer disorders.

List of EpiDrugs

Number	Drug	Phase of development	Company
1	Azacitidine	Approved (2004)	Bristol-Myers Squibb
2	Decitabine	Approved (2006)	Otsuka America Pharmaceutical
3	Vorinostat	Approved (2006)	Merck
4	Romidepsin	Approved (2009)	Bristol-Myers Squibb
5	Belinostat	Approved (2014)	Celldex Therapeutics
6	Hydralazine	Approved (2014)	NYU Langone Health
7	Panobinostat	Approved (2015)	Novartis
8	Chidamide	Approved (2015)	Chipscreen Biosciences'
9	Enasidenib	Approved (2017)	Bristol-Myers Squibb
10	Ivosidenib	Approved (2018)	Agios Pharmaceuticals

List of EpiDrugs

Number	Drug	Phase of development	Company
11	Tazemetostat	Approved (2020)	Epizyme, Inc.
12	Abexinostat	Phase III	Xynomic Pharmaceuticals
13	ASTX727	Phase III	Otsuka America Pharmaceutical
14	CPI-0610	Phase III	MorphoSys
15	Entinostat	Phase III	Taizhou EOC Pharma Co., Ltd
16	Givinostat	Phase III	GlaxoSmithKline
17	Guadecitabine	Phase III	Otsuka America Pharmaceutical
18	Pracinostat	Phase III	Helsinn Healthcare
19	RVX-208	Phase III	Resverlogix
20	Talazoparib	Phase III	Pfizer

List of EpiDrugs

Number	Drug	Phase of development	Company
21	Tasquinimod	Phase III	Active Biotech
22	4SC-202	Phase II	4SC
23	ACY-1215	Phase II	Bristol-Myers Squibb
24	BMS-986158	Phase II	Bristol-Myers Squibb
25	Disulfiram	Phase II	Cantex Pharmaceuticals
26	EPZ-5676	Phase II	Epizyme
27	EPZ-6438	Phase II	Epizyme
28	GSK3326595	Phase II	GlaxoSmithKline
29	GSK525762A	Phase II	GlaxoSmithKline
30	INCB054329	Phase II	Incyte Corporation

List of EpiDrugs

Number	Drug	Phase of development	Company
31	INCB057643	Phase II	Incyte Corporation
32	Mocetinostat	Phase II	Mirati Therapeutics
33	ORY-2001	Phase II	Oryzon Genomics
34	Pinometostat	Phase II	National Cancer Institute
35	Pivanex	Phase II	Titan Pharmaceuticals
36	Plitidepsin	Phase II	PharmaMar
37	Quisinostat	Phase II	Janssen Research & Development
38	Resminostat	Phase II	4SC
39	Resveratrol	Phase II	GlaxoSmithKline
40	Ruxolitinib	Phase II	Incyte Corporation

List of EpiDrugs

Number	Drug	Phase of development	Company
41	SB939	Phase II	S*BIO
42	Valproic acid	Phase II	Pfizer
43	Veliparib	Phase II	Abbott
44	INCB059872	Phase I/II	Incyte Corporation
45	Olutasidenib	Phase I/II	Forma Therapeutics
46	PLX51107	Phase I/II	Plexxikon
47	Seclidemstat	Phase I/II	Salarius Pharmaceuticals
48	AZD5153	Phase I	Astrazeneca
49	CHR-2845	Phase I	Chroma Therapeutics
50	CHR-3996	Phase I	Chroma Therapeutics

List of EpiDrugs

Number	Drug	Phase of development	Company
51	CUDC-101	Phase I	Curis
52	Equol	Phase I	Ausio Pharmaceuticals
53	GSK2816126	Phase I	GlaxoSmithKline
54	GSK2879552	Phase I	GlaxoSmithKline
55	GSK3368715	Phase I	GlaxoSmithKline
56	JNJ-64619178	Phase I	Janssen Research & Developmen
57	MG98	Phase I	NCIC Clinical Trials Group
58	OKI-179	Phase I	OnKure
59	ORY-1001	Phase I	Oryzon Genomics
60	OTX015	Phase I	Merck

List of EpiDrugs

Number	Drug	Phase of development	Company
61	RO6870810	Phase I	Hoffmann-La Roche
62	Tranylcypromine	Phase I	University of Miami
63	Trichostatin A	Phase I	Vanda Pharmaceuticals
64	Vorasidenib	Phase I	Agios Pharmaceuticals
65	GSK343	Preclinical	GlaxoSmithKline

Overview of Proprietary Analytics by Deep Pharma Intelligence

Deep Pharma Intelligence (DPI) is a strategic partner to the leading Life Science organizations, investment institutions (VC funds, investment banks), and governments across the globe — in matters related to investments, strategic positioning, and policy development in the areas of pharmaceutical and biotech research, and healthcare tech.

While Deep Pharma Intelligence is regularly producing open industry reports covering high-growth sectors in the Life Sciences, including artificial intelligence (AI), digital health, and new therapies, some of the more in-depth research is only available to our clients and strategic partners under the "**Proprietary Analytics**" category.

Our range of proprietary services includes custom consulting projects, based on the specific customer needs, as well as a collection of pre-produced "ready-to-use" proprietary reports, produced by our research team, covering general trends and specific action ideas and strategy insights related to the most promising investment prospects (e.g. new technologies, biotech startups), M&A prospects (e.g. pipeline development targets), and strategic growth ideas (trends profiling, industry overviews etc).

Services:

- Investment landscape profiling, identifying investment ideas in the biotech/healthcare tech space
- Preliminary due-diligence (business, science and technology, intellectual property (IP) profiling, freedom of operation assessment, legal assessment etc)
- Comprehensive due-diligence (deep business, science and technology assessment, IP and legal assessment, growth potential assessment etc)
- Infringement analysis of technology (i.e. If you plan to partner or invest in a data-analytics biotechs, or AI-development vendors, it is essential to understand their technological assets, both in terms of innovation potential and in terms of legal protection and non-infringement risk management)
- SWOT analysis of companies and technological sectors, competitive profiling
- Industry profiling and growth strategy development for top-tier companies and governments.

Overview of Proprietary Analytics by Deep Pharma Intelligence

Proprietary Reports

There are a few 40+ page reports delivering practical answers to these specific questions in order to optimize the short and long-term strategies of biopharma corporations and other institutions related to the industry, with a newly updated edition being released each quarter, incrementally increasing the precision, practicality and actionability of its technological and financial analysis.

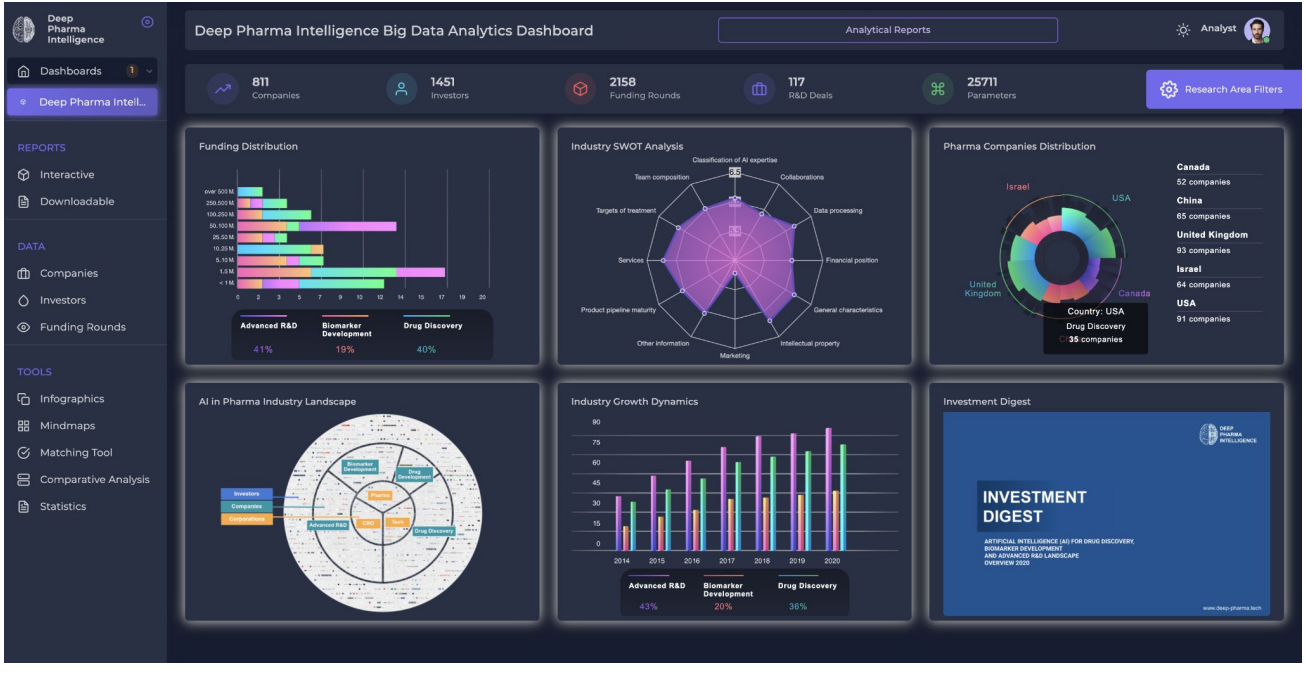
Our reports are supported by our rapidly developing data mining engine, data visualization platform and analytics dashboards.

The value our reports can deliver:

- Deep analysis of the deal-making prospects in the biotech and healthcare tech space, identification of top mini-trends and larger tendencies in innovations and technology adoption (e.g. AI, blockchain, eHealth tech, longevity biomarkers, new therapeutics and therapies etc.)
- Tangible forecasts on the 3-5 years horizon, providing an overview of future scenarios of the development of various technologies in the pharma industry
- Practical guides for adopting various technological solutions and best practises, vendor profiling and contract research strategy building
- Analysis of key market players in the emerging and high-growth areas of the pharmaceutical and biotech industries.

The parties who gain early access to these reports will have deep expertise on how their strategic agendas can be optimized in order to leverage novel research, new technologies, and emerging market opportunities, and stay competitive in a rapidly-changing technological environment, and taking into account shifting global priorities and trends.

Deep Pharma Intelligence: Analytical Dashboard



Our company is building a sophisticated cloud-based engine for advanced market and business intelligence in the pharmaceutical and healthcare industries. It includes data mining engine, infrastructure for expert data curation, and advanced visualization dashboards, including mindmaps, knowledge graphs, and 3-dimensional visualizations.

Visit our dashboard to learn more: **www.platform.dkv.global/dashboards/ai-for-drug-discovery**

Deep Pharma Intelligence: Analytical Dashboard

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The project generates **data-driven insights about emerging areas in the fields of medical research and technology**, including pharmaceuticals, BioTech, medical devices, and Healthcare Tech industries. The Dashboard is a well-suited tool for both private and institutional investors looking for an additional enhancement to their market analytics, providing sufficient means for the development of competitive advantages.

The Dashboard is a powerful tool for **strategic insights, opportunity evaluation, competitor profiling**, and other goals, relevant to pharma and biotech decision-makers, Life Science investors, consulting companies, and regulatory agencies.

Our Database:

- **490+** AI in DD Companies
- **1100+** Investors
- **1060+** Funding Rounds
- **290+** R&D Collaborations
- **120+** Clinical trials (constantly updated based on clinicaltrials.gov)

Our Capabilities:

- **Investment analytics** and actionable insights about primary and secondary markets.
- **SWOT analysis** of the most promising entities and technologies, providing a clear view of opportunities and risks.
- **Identification of growth opportunities,** including partnerships, technology deals, and transaction prospects.
- **Competitive analysis,** based on the analytical classification of companies and investors.

Visit our dashboard to learn more: **www.platform.dkv.global/dashboards/ai-for-drug-discovery**

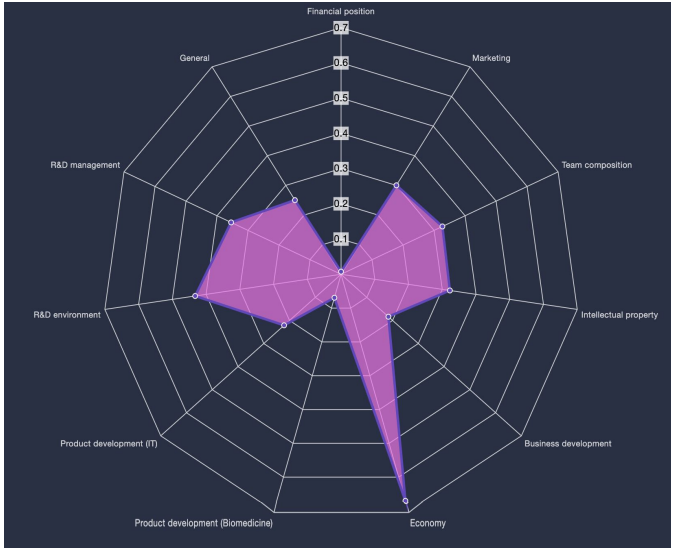
Deep Pharma Intelligence Analytical Dashboard: SWOT Analysis

Automated SWOT analysis and benchmarking system of Deep Knowledge Group allows to replace long, resource-requiring, manual, and unsystematic process of due diligence, investment analytics, analytics insights generation and investment targeting by a real-time available product extracting insights from the **largest in the world deep tech industry database** with the help of **deep learning algorithms and multidimensional polynomial formulas** calibrated by combining **expert opinions with big data analysis.**

This enables to conduct an investment analysis which is **faster, more precise, and cheaper** at the same time, since it is being done automatically, permanently, without essential human interaction, and using more data points.

Database, AI and ML algorithms overview

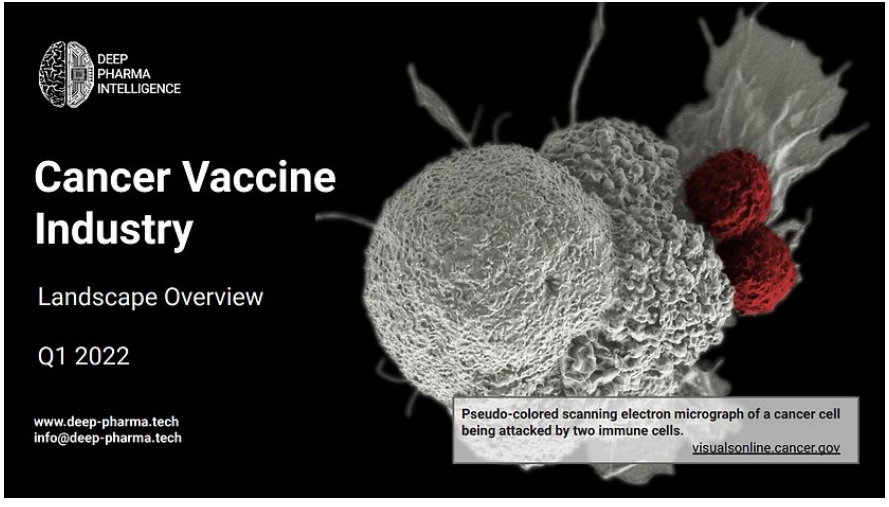
Data points	6 000 000 data points which are being updated permanently
Algorithms	Deep neural networks, polynomial formulas with mathematical transformations, regression models
Data aggregation	Automatized parsing, extrapolation using machine learning, feedback from companies



Example of the SWOT Analysis

Visit our dashboard to learn more: **www.platform.dkv.global/dashboards/ai-for-drug-discovery**

Deep Pharma Intelligence: Analytical Reports



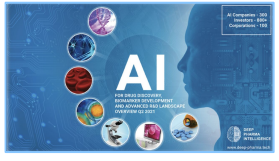
Cancer Vaccine Industry Landscape Overview, Q1 2022 is an analytical report created by Deep Pharma Intelligence company that focuses on a segment of cancer vaccine companies. It delivers advanced market profiling, interactive mindmaps, information about companies and investors, technology application use cases and other actionable information.

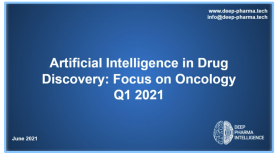
Learn more:
https://www.deep-pharma.tech/cancer-vaccines-q1-2022

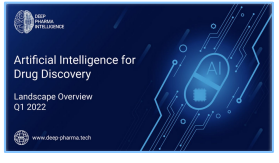
Artificial Intelligence for Drug Discovery Landscape Overview, Q1 2022 is an analytical report created by Deep Pharma Intelligence company that aims to provide a comprehensive overview of the industry landscape in what pertains adoption of AI in drug discovery, clinical research and other aspects of pharmaceutical R&D.

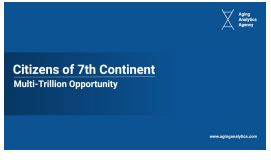
Learn more:
www.deep-pharma.tech/ai-in-drug-discovery-2022-q1

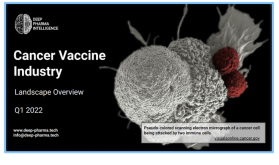
Deep Pharma Intelligence: Analytical Reports







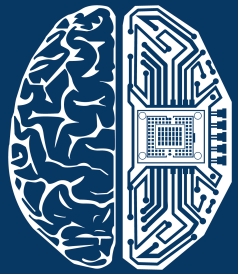




2020

2021

2022



Link to the Report: www.deep-pharma.tech/epigenetic-drugs-q2-2022

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