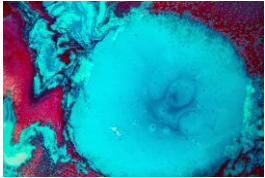




## Epigenetics

Since the sequencing of DNA in 1980, the concept of the genome as the basis of biology has reigned. But what of the epigenome?



### What is epigenetics?

Epigenetics can be defined most simply as the study of changes in the way genes are 'read' (expressed). A number of external

factors can switch genes on and off to modify expression, without actually making any changes in the sequence of DNA. These changes are called epigenetic modifications.

In cell nuclei the DNA is tightly packed and forms 23 pairs of chromosomes. To achieve this, the DNA is rolled up on protein complexes called histones, which provides compaction and prevents genes from being accessible.

The resulting structures, nucleosomes, are basic building blocks that further form a chromatin strand, which in turn is packed into dense chromosomes.

Epigenetic modifications cause changes in this spatial organisation, which leads to different genes becoming accessible for expression, or silenced. This process is part of the regulation of gene expression but, if it falters, can be the cause of a variety of diseases.

### What are epigenetic modifications?

There are three main types of epigenetic modification: DNA methylation occurs when a methyl group (a chemical tag) is added directly to a specific location on the DNA strand. This modification most commonly results in gene deactivation.

Histone modification occurs when different chemical tags, such as acetyl or methyl groups, are added to a histone tail within the nucleosome complex. This can either increase or decrease gene expression.

RNA-based mechanisms have also been shown to affect the spatial configuration of chromatin.

### Which diseases can be treated with epigenetic drugs?

Epigenetics is a relatively young field in terms of drug development and histone deacetylase (HDAC) inhibitors were among the first compounds with epigenetic modification capability to be brought to

market.

Merck's vorinostat (Zolinza) was the first HDAC inhibitor approved for cutaneous T-cell lymphoma and was marketed in 2006. Currently, the FDA has approved seven epigenetic drugs, including Celgene's azacitidine, Novartis's panobinostat and [Onxeo's belinostat](#).

Traditionally, cancer is thought to be a disease resulting from the accumulation of genetic mutations. More recently, however, epigenetic abnormalities have also been implicated in the development of many different forms of cancer.

One of the underlying mechanisms could be the fact that epigenetic dysregulation ultimately leads to changes in the pattern of gene expression, with tumour-promoting genes activated while tumour-suppressing genes are silenced.

Additional data in the field suggest that epigenetic mechanisms are dynamically regulated in various other chronic conditions that could potentially be treated with epigenetic compounds.

### How large is the market for epigenetic treatments?

The epigenetic market is still in its infancy. Most of the epigenetic drugs approved are for rare forms of cancer like cutaneous T-cell lymphoma or myelodysplastic syndromes. However, Novartis's panobinostat has been approved for

multiple myeloma, a more common form of cancer that Cancer Research UK estimates affects 39,000 patients in Europe alone.

Although there are no approved epigenetic drugs other than for oncology at the moment, the potential market for epigenetics could be vast, for example if epigenetic compounds in CNS diseases prove beneficial.

There are 44 million dementia sufferers worldwide, around 60% of whom have Alzheimer's disease. Theoretically, epigenetic treatments could also alleviate diseases like heart disease or diabetes

#### Edison's insight:

"The rise of research in epigenetics delivered a novel class of anticancer drugs a decade ago. Understanding the epigenetics of disease now transcends oncology and is a new data point in the potential for epigenetic treatments in a wide array of chronic diseases." Jonas Peciulis, healthcare analyst

with strong genetic links, although research is still nascent.

### **Which companies are developing epigenetic treatments?**

While the first generation of HDAC inhibitors faced some safety issues, a number of newer-generation, more selective HDACs ([eg domatinostat, an HDAC Class I inhibitor from 4SC](#)) and other novel epigenetic targets are in the R&D stage currently.

Novel epigenetic targets and drugs include histone demethylase inhibitors, histone methyltransferase inhibitors and bromodomain and extra-terminal (BET) inhibitors.

For example, Oryzon, Incyte and GSK have lysine-specific histone demethylase 1 (LSD1) inhibitors in Phase I-II trials.

Epizyme and Constellation Pharmaceuticals have histone methyltransferases (EZH2) inhibitors in Phase I-II trials.

The most advanced BET inhibitors are also in Phase I-II trials run by Constellation Pharmaceuticals, GSK and Incyte. Beyond oncology, [Oryzon is pioneering its dual LSD1/MAOB inhibitor vafidemstat in Phase II trials in various CNS indications.](#)