

## Epigenetic drugs: More than meets the eye

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The Epigenome constitutes the orthography and grammar of the cell abecedary, the Genome. From DNA methylation to histone modifications, from chromatin remodelling to noncoding RNAs, all these chemical marks and molecules facilitate the correct reading of our genetic material. The epigenetic setting sits between the genotype and the phenotype to originate cellular homeostasis. In addition, the plastic and dynamic nature of the epigenetic marks permits the adaptation of tissues, organs, and individuals to changes in the environment. The described belts of DNA, RNA, and protein regulation become almost unrecognizable in many human diseases, with cancer cells being the most studied pathology. There is margin for hope and, due to the reversible nature of the described chemical modifications, targeting of the proteins that write, erase, and read the epigenetic language have extremely great potential as therapeutic tools. The use of the so-called epigenetic drugs have changed the morbidity of diseases with unmet medical needs, such as myelodysplastic syndrome or cutaneous lymphoma. But beyond DNA demethylating agents and inhibitors of histone deacetylases, we have today an expanding portfolio of compounds that target the epigenetic machinery, including histone methyltransferase, histone demethylase, histone kinase, and bromodomain inhibitors. Some of these are central in ongoing clinical trials and high expectations are placed on them, particularly in the context of hematological malignancies and soft tissue tumors. However, other human disorders can follow this lead, and neurodegenerative and cardiovascular disease could eventually benefit from the results obtained in the oncology field. More importantly, additional effects beyond those classically ascribed to these drugs are now beginning to be reported,<sup>1,2</sup> some of them related to shifts in the immune recognition systems and the response to agents in the renewed area of immunotherapy. I am sure that we will witness many unexpected advances in now forgotten areas in the same way.

Herein, we have devoted a Special Focus Issue of *Epigenetics* to Epigenetic Drugs, touching the intimate mechanisms of their

effects,<sup>3</sup> the irruption of bromodomain inhibitors,<sup>4</sup> the next generation of lysine demethylase inhibitors,<sup>5</sup> the applications in pediatric brain tumors<sup>6</sup> and follicular lymphoma,<sup>7</sup> and their potential uses beyond oncology.<sup>8</sup> I hope that all of you enjoy reading these insightful review articles.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

### References

1. Liu M, Ohtani H, Zhou W, Ørskov AD, Charlet J, Zhang YW, Shen H, Baylin SB, Liang G, Grønbaek K, et al. Vitamin C increases viral mimicry induced by 5-aza-2'-deoxycytidine. *Proc Natl Acad Sci USA* 2016; 113:10238-44; <https://doi.org/10.1073/pnas.1612262113>
2. Chiappinelli KB, Strissel PL, Desrichard A, Li H, Henke C, Akman B, Hein A, Rote NS, Cope LM, Snyder A, et al. Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* 2017; 169:361; <https://doi.org/10.1016/j.cell.2017.03.036>
3. Hau M, Zenk F, Ganesan A, Iovino N, Jung M. Cellular analysis of the action of epigenetics drugs and probes. *Epigenetics* 2017; Jan 10:0; <https://doi.org/10.1080/15592294.2016.1274472>
4. Pérez-Salvia M, Esteller M. Bromodomain Inhibitors and Cancer Therapy: From Structures to Applications. *Epigenetics* 2016; Dec 2:0; <https://doi.org/10.1080/15592294.2016.1265710>
5. Niwa H, Umehara T. Structural insight into inhibitors of flavin adenine dinucleotide-dependent lysine demethylases. *Epigenetics* 2017; Feb 10:1-13; <https://doi.org/10.1080/15592294.2017.1290032>
6. Maury E, Hashizume R. Epigenetic modification in chromatin machinery and its deregulation in pediatric brain tumors: Insight into epigenetic therapies. *Epigenetics* 2017; Jan 6:1-17; <https://doi.org/10.1080/15592294.2016.1278095>
7. Korfi K, Ali S, Heward JA, Fitzgibbon J. Follicular Lymphoma, a B cell malignancy addicted to epigenetic mutations. *Epigenetics* 2017; Jan 20:0; <https://doi.org/10.1080/15592294.2017.1282587>
8. Ackloo S, Brown PJ, Müller S. Chemical probes targeting epigenetic proteins: Applications beyond oncology. *Epigenetics* 2017; Jan 12:1-23; <https://doi.org/10.1080/15592294.2017.1279371>