CNIO - LILLY EPIGENETICS SECTION

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**Titulado Superior* (Advanced Degree)

SCOPE OF THE CNIO - ELI LILLY PARTNERSHIP

Eli Lilly and CNIO were collaborating on the identification and validation of novel targets in cancer epigenetics. Our Section was funded through a research contract with Eli Lilly and focuses on the identification of small molecular weight molecules able to modulate the epigenome of malignant cells and ultimately block the growth and spread of tumours. Potential targets were validated *in vitro* and *in vivo* using animal models developed at the CNIO. Furthermore, we set up biochemical and cell-based assays with the aim of understanding the mechanism of action of such targets at the molecular level (FIGURE).

SCIENTIFIC CONTEXT

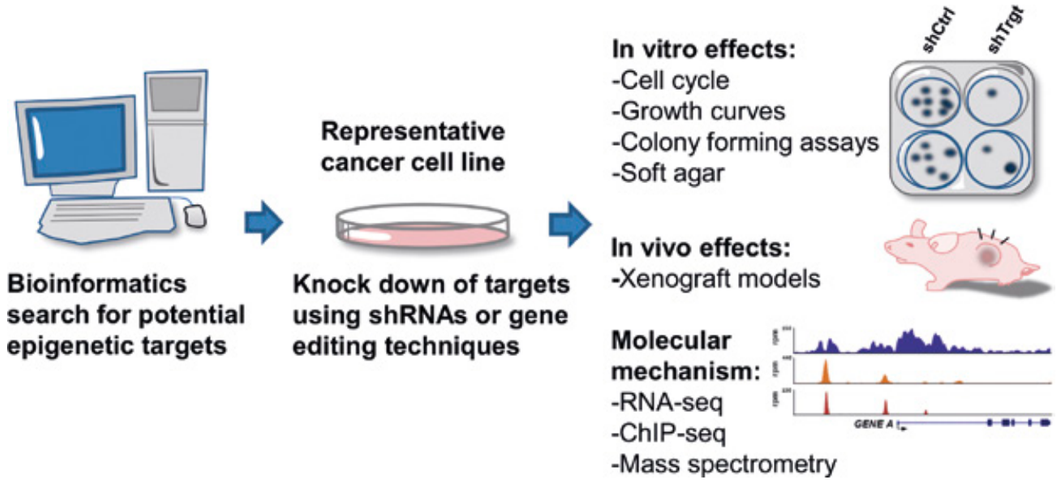

Figure *In vivo* and *in vitro* strategies for target validation.

Recent studies have shown that the alterations that take place in cancer cells not only occur at the DNA sequence but also at the level of the epigenome. Eukaryotic DNA is wrapped around histone proteins to constitute chromatin, which plays fundamental structural and regulatory roles. The epigenome consists of chemical changes in both DNA and histones that can be inherited through cell division and are controlled by the action of a large set of epigenetic regulators that possess enzymatic activity. Ultimately, DNA and histone modifications control the level of chromatin condensation, which in turn regulates the accessibility of transcription factors to the chromatin and, therefore, gene expression.

During the past few years several studies, including our own, have suggested that the deregulation of the chromatin-modifying machineries can lead to aberrant gene expression causing cancer and other human diseases. The epigenome is regulated in a highly dynamic fashion by the coordinated action of regulators able to write, erase and read histone and DNA modifications. Thus, contrary to genetic mutations, epigenetic aberrations can be reversed through the targeting of the appropriate epigenetic regulators. Indeed, drugs targeting DNA methyltransferases and histone deacetylases have successfully demonstrated anticancer properties and are currently used in the clinic. Therefore, identifying the molecular function of critical epigenetic regulators and their complex relationship with the cancer epigenome (FIGURE), as well as the development of small molecular inhibitors of their activities holds great promise for the therapeutics of cancer. ■

PUBLICATIONS

- Garcia-Carpizo v, Ruiz-Llorente S, Sarmentero J, Graña-Castro O, Pisano DG, Barrero MJ (2018). CREBBP/EP300 bromodomains are critical to sustain the GATA1/MYC regulatory axis in proliferation. *Epigenetics Chromatin* 11, 30.
- Garcia-Carpizo v, Ruiz-Llorente S, Sarmentero J, Barrero MJ (2018). Therapeutic potential of TAF1 bromodomains for cancer treatment. *bioRxiv*. doi: https://doi.org/10.1101/394254.