Editorial　　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

De-mystifying the Epigenetic Free for All: Pharmacophore Modeling for Epigenetic Cancer Therapy

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Abstract

Epigenetic regulators have quickly become one of the most widely studied therapeutic agents for a vast array of diseases, making histone deacetylase inhibitors (HDIs) and DNA methyl-transferase (DNMT) inhibitors commonly used molecules in pre-clinical and clinical anti-cancer studies. Their ability to regulate gene expression and to potentiate the effects of other chemotherapeutic drugs has put HDIs and DNMT inhibitors in the spotlight not only as single agents, but also as combined therapy. The plethora of HDIs and DNMT inhibitors available nowadays has led to promising results in Phase I, II and III clinical oncology studies. While it was first believed that these molecules would all have an additive or synergistic effect when combined with the classical chemotherapeutic drugs available, our group and others have shown that epigenetic regulators potentiate the effects of some, but not all, anti-cancer molecules. Pharmacophore modeling may therefore serve the purpose to optimize pre-clinical research and to develop more efficient and targeted therapies incorporating epigenetic regulators.

Epigenetic regulators have quickly become one of the most widely studied therapeutic agents for a vast array of diseases, making histone deacetylase inhibitors (HDIs) and DNA methyl-transferase (DNMT) inhibitors commonly used molecules in pre-clinical and clinical anti-cancer studies [1-4]. Their ability to regulate gene expression and to potentiate the effects of other pharmaceutical drugs has put HDIs and DNMT inhibitors in the spotlight not only as single agents, but also as combined therapy. The plethora of HDIs (Table 1 included as supplementary data) and DNMT inhibitors (Table 2 (included as supplementary data)) available nowadays have led to promising results in Phase I, II and III clinical oncology studies. Results not only show their potential as cytostatic and cytotoxic agents, but also as chosen agents for combined therapy because of their ability to potentiate classical drugs utilized to treat the disease, allowing for the same cytotoxic effect at lower doses [5,6].

While it was first believed that these molecules would all have an additive or synergistic effect when combined with the classical chemotherapeutic drugs available, our group and others have shown that epigenetic regulators potentiate the effects of some, but not all, anti-cancer molecules [6-8]. Since epigenetic regulators exert their effect mainly on the DNA conformation, allowing for otherwise silenced genes to be expressed, and vice-versa, it was first postulated that they would potentiate the effects of the classical chemotherapeutic drugs that interact directly with the DNA. This has proven not to be the case, making screening for additive or synergistic effects *in vitro* a necessity before designing any *in vivo* experiments or feasibility studies. Pharmacophore modeling may therefore serve the purpose to optimize pre-clinical research and to develop more efficient and targeted therapies incorporating epigenetic regulators.

Ehrlich first defined a pharmacophore as "a molecular framework that carries the essential features responsible for a drug's biological activity" [9]. This definition evolved twenty years to its current definition: "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger, or block, its biological response" [10]. Pharmacophore models can be established either as ligand-based or structure-based. Ligand-based models are usually utilized when a macromolecular target structure is not available, and therefore a set of active molecules are superposed and their common chemical features, essential for their bioactivity, are then extracted by a computer software. Structure-based pharmacophore models utilizes the three-dimensional structure of a macromolecular target or, at times, a target– ligand complex, and probes possible interaction points between target and ligand [11]. Both models present advantages and disadvantages that are best described Yang's review [12], the most prominent disadvantage being the high cost involved in developing and analyzing the algorithms necessary for the optimization of drug design. Nonetheless, as exemplified by Yoo and Medina-Franco [13], pharmacophore modeling has been used to predict the activity of DNMT inhibitors, elucidating the interactions that allow for their mechanism of action and allowing for a more efficient screening of novel inhibitors. Even though there are significant costs involved with pharmacophore modeling, the employment of this technique reduces significantly the time spent on experimental drug design, indirectly reducing costs as well [14]. Therefore, if a multi-disciplinary effort is made to optimize and shorten the time necessary for the drug design of these inhibitors, considerable clinical advances will also be achieved.

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Conflicts of Interest

The authors declare no conflicts of interest that may have influenced the discussion therein.

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