Issue 2/2023 February, 2023

PRESCRIPTION

Latest news and updates from the Faculty of Pharmacy

In This Issue:

EPIDRUGS IN PRECISION MEDICINE, THE PLAUSIBLE WAY FORWARD

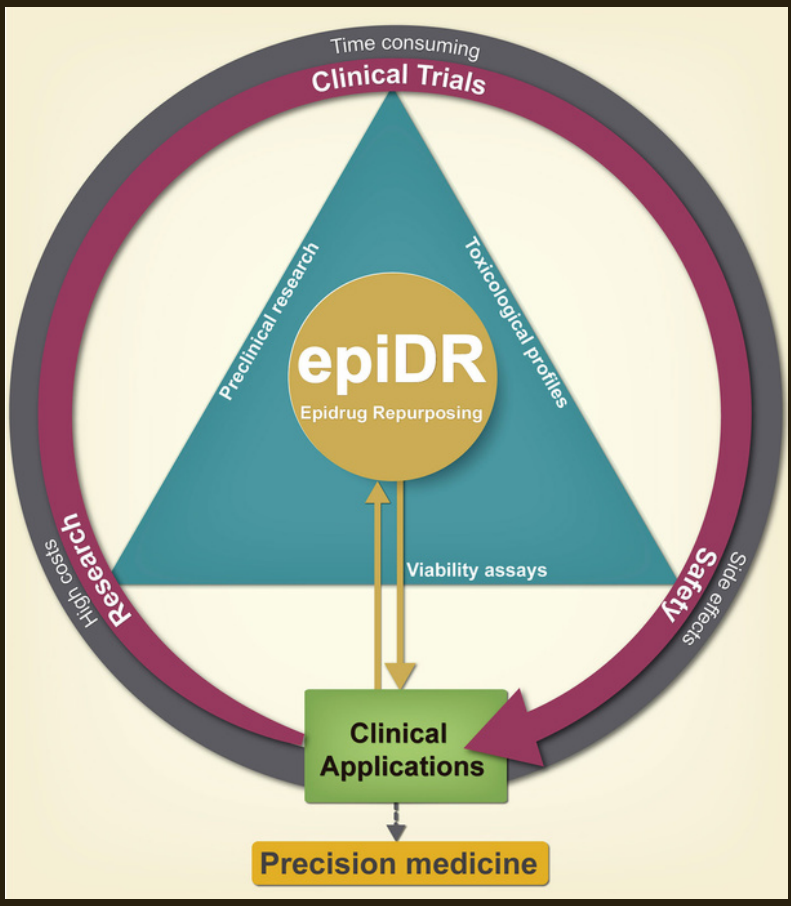
It is not only our genes that control how our bodies respond to drugs and cope with disease states, but also by identifying the modifications to our histone proteins that regulate gene expression, we can discover a whole new direction for diagnostic and therapeutic biomarkers and drug targets as well.

In the last two decades, epidrugs have been developed to target the histone-modifying enzymes. It could be defined as small-molecular entities that inhibit epigenome and/or enzymes with epigenetic activity. Many preclinical evidence suggested that targeting epigenetic deregulation is an effective strategy to combat human diseases. However, implementing epidrugs in clinical practice is mainly limited to haematological malignancies.

Epigenetics is the study of how cells control gene activity without affecting the DNA sequence. Several lifestyle factors have been identified that might modify epigenetic patterns, such as physical activity, tobacco smoking, diet, alcohol consumption, obesity, exposure to environmental pollutants, psychological stress, and working on night shifts.

The role of epigenetic modifications in individual drug response is generally less well studied than the role of genetic variations, but epigenetics has a big role to play in the expression of the genes that relate to drug metabolism, transport and receptors, which contribute to drug efficacy and safety.

Epidrugs were originally developed for the three common categories of epigenetic regulators (writers, readers and erasers) where they selectively target marks responsible for epigenetic alterations, consequently improving, treating, or preventing the associated disease state.



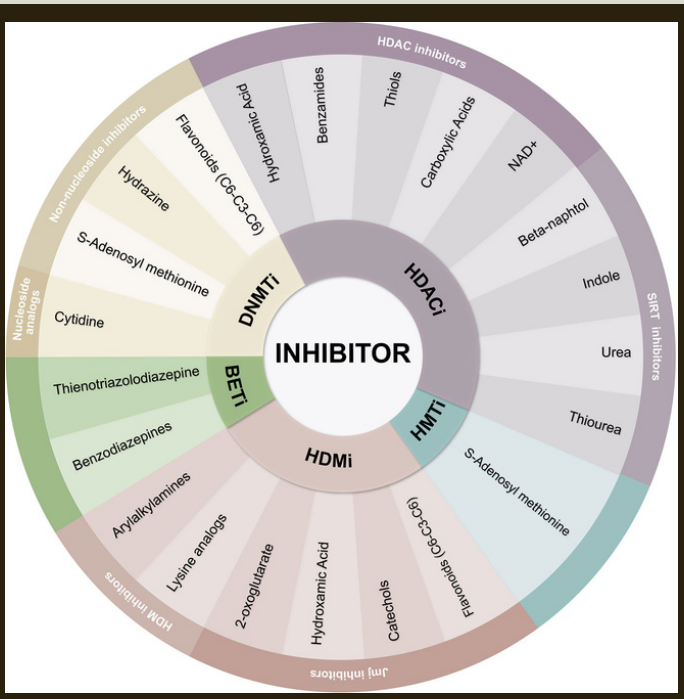
Epidrug Repurposing for Precision Medicine

Source: Montalvo-Casimiro M, González-Barrios R, Meraz-Rodriguez MA, Juárez-González VT, Arriaga-Canon C and Herrera LA (2020) Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy. Front. Oncol. 10:605386. doi: 10.3389/fonc.2020.605386

While writers are responsible for adding chemical groups to the target protein by transferases; erasers remove them. In addition, epigenetic modifications are recognized by a set of reader domains that are recruited to specific epigenetic marks and act as an effector protein. At present, vorinostat and romidepsin were the first drugs to be approved that influence epigenetic post-translational modification of histone proteins, for refractory cutaneous T-cell lymphoma. Belinostat targets HDAC (histone deacetylase) enzymes, thereby inhibiting tumour cell proliferation, inducing apoptosis, promoting cellular differentiation, and inhibiting angiogenesis. Panobinostat for multiple myeloma based on their HD inhibition.

Also, decitabine, the DNMTs (DNA methyltransferase) inhibitor was approved due to its positive results in patients with haematological malignancies, e.g myelodysplastic syndromes, acute myeloid leukaemia, and chronic myelomonocytic leukaemia. Currently, epidrug development in erasers is undergoing clinical evaluation for efficacy in different cancer settings.

In spite of their potential, there are many obstacles to be addressed for efficient application of epidrugs to treat a range of human cancers. Not only the lack of specificity, failure in solid tumours but also the likely chemoresistance leading to tumour relapse.



Epidrugs' Classification

Source: Montalvo-Casimiro M, González-Barrios R, Meraz-Rodriguez MA, Juárez-González VT, Arriaga-Canon C and Herrera LA (2020) Epidrug Repurposing: Discovering New Faces of Old Acquaintances in Cancer Therapy. Front. Oncol. 10:605386. doi: 10.3389/fonc.2020.605386

However, there are cutting edge approaches in the field of chemical and molecular biology that are running currently to help translate epidrug therapy to clinical practice. Although still in its early stages, the epidrug multitargeting interesting concept, the epigenetic-based synthetic lethality strategies and the use of epidrugs in combination with other therapies are introduced as alternatives for optimising the clinical translation of epigenetic therapy.

Finally, precision medicine, in general, suffers high cost, misinterpretation of genetic and health data, risk of genetic discrimination, access and availability of genetic testing, and a relatively unprepared primary care workforce. If these pitfalls are joined with the epidrugs challenges' such as persistent (or perhaps slowly-reversing) gene expression changes and epigenetic effects, then the situation becomes worse.

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