Epigenetic therapy in a new era of medicine: creating and integrating molecular profiles of patients

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In the 17th century, Antonie von Leeuwenhoek revolutionized microbiology with the advent of the microscope. Today we are in a similar revolution for cancer and genetics with the development of sequencing technology as "molecular microscopes" to peer into cells and catalog their genetic and epigenetic changes. We now have the capabilities to study diseases like cancer and how tumors evolve via single-cell sequencing and dynamics (1,2). Sequencing has gone far to transform the way we understand and view the central dogma of biology (3). While the central dogma of molecular biology is still a guiding framework for understanding disease (DNA to RNA to protein), we are beginning to understand the panoply of regulatory levers and mechanisms that guide—and even deviate—from such an orderly progression of molecular relationships, especially in the context of diseases like cancer.

Epigenetics, the modification of gene expression and genomic elements, may hold a key to current challenges in cancer therapies. The initiation, progression, and even relapse of cancers are linked both to genetic and epigenetic events (4), and epigenetic-based risk assessment has recently been demonstrated to stratify high- and low-risk leukemia patients and demonstrate independent evolution of genetic and epigenetic events (5). While genetic aberrations are irreversible, epigenetics changes may be reversible and quite labile, allowing malignant cell populations to be converted back to their normal state. Scores of studies in the past decade have explored epigenetic drugs and the role they can play in cancer treatment (4). Indeed, cancers now can be targeted and understood from either the genetic or epigenetic angles, or potentially both.

Demonstrating this, a paper recently published in *Science Translational Medicine* by Hasanali *et al*. demonstrated the effectiveness of epigenetic therapy in the treatment of T cell prolymphocytic leukemia (T-PLL) (6). T-PLL is an aggressive and rare disease that is considered incurable and difficult to treat. The current first-line therapy for T-PLL is the monoclonal antibody alemtuzumab, although the mechanism of action of the drug remains poorly characterized and it is not a curative approach for T-PLL due to resistance. Hasanali *et al*. presented a case series of eight T-PLL patients who were treated with cladribine, vorinostat/romidepsin/valproic acid, and alemtuzumab. Three of the eight patients survived, one in remission after allogenic transplant and two in early relapse. They also found cladribine inducing expression of CD30 in four of the patients. The authors appropriately addressed the limitations of their study (small sample size, sample collection limitations, varying epigenetic therapies, etc.) and suggested that cancer therapeutic platforms should include a regimen of cladribine (with or without HDACi) and the appropriate tumor-specific monoclonal antibody.

Nonetheless, the Hasanali *et al*., study is one of the first to show that an effective epigenetic combination drug therapy can transform the current treatment regimen and approach for T-PLL patients. Such a framework gives new methods and approaches for targeting cancer and can potentially improve patient outcomes, or at the very least options for care. As such, their work should drive researchers and clinicians to conduct more studies not only on T-PLL patients but all different kinds of cancers and

explore how we can utilize epigenetics and our molecular machinery to treat cancer. Finally, the identification of epigenetic alterations and sensitivities can enable newer, CRISPR-enabled targeting of those loci (7) to remodel and alter the epigenetic insult that occurred to the cells, which enables not just a detection of an aberrant epigenetic state, but the means by which to fix it.

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Footnote

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