Weill Cornell Medicine

# Epigenetic Modifying Agents Sensitize EBV+ Lymphomas to Immunotherapy


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## Background & Unmet Need

- The Epstein-Barr virus (EBV) is one of the most common human viruses and is associated with the development of a number of lymphomas, such as Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and Hodgkin's lymphoma
- EBV has a strong propensity to remain latent, and can be classified into different latency patterns based on expression of immunogenic EBV proteins
- Most EBV-driven lymphomas express the latency I program, in which the single EB nuclear antigen (EBNA1) is produced which allows tumors to evade immune responses
- A minority of EBV-driven lymphomas display the highly immunogenic latency II/II program, which is responsive to common immunotherapies
- **Unmet Need:** There is an urgent need for methods to transform EBV-driven lymphomas to make them more amenable to immunotherapy treatment

## Technology Overview

- **The Technology:** Use of epigenetic modifying agents to convert treatment-resistant latency I lymphomas into immunotherapy-responsive latency II/III lymphomas
- **The Discovery:** A high throughput screen with follow-up tests was used to identify the hypomethylating agents decitabine and 5-azacytidine as potent inducers of immunogenic EBV proteins (Figure 1)
- Decitabine treatment of latency I BL cells *in vitro* sensitized them to lysis by EBV-specific cytotoxic T-cells (EBV-CTLs; Figure 2A)
- **PoC Data:** Decitabine treatment of mice with latency I BL xenografts followed by EBV-CTLs resulted in T-cells effectively targeting and inhibiting tumor growth (Figure 2B)
- Combination treatment method is applicable to additional modes of immunotherapy (e.g., CAR-T, checkpoint inhibitors)

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**Patents:**
US Application Filed

**Publications:**
Dalton et al. *Blood*. 2020.

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**Cornell Reference:**
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## Technology Applications

- Treatment of EBV+ latency I lymphomas with a combination of epigenetic modifying agents and an immunotherapy (e.g., EBV-CTLs, CAR-T cells, and checkpoint inhibitors)
- Technology is also potentially useful for treating nasopharyngeal and gastric cancers

## Technology Advantages

- Induction of immunogenic antigens by epigenetic modifying agents occurs at low doses and persists long after agent removal
- In addition to DCB and 5-Aza, the technology also provides a screening method for discovering additional molecules that alter EBV latency

## Supporting Data / Figures

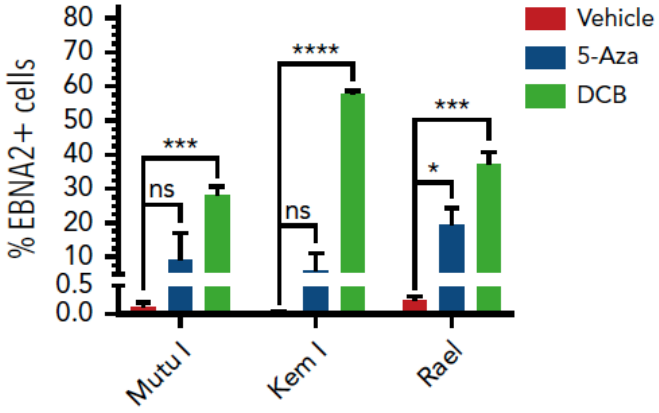


**Figure 1:** 5-azacytidine (5-Aza) and decitabine (DCB) induce immunogenic EBV antigens (EBNA2) in BL cell lines (Mutu I, Kem I, and Rael).


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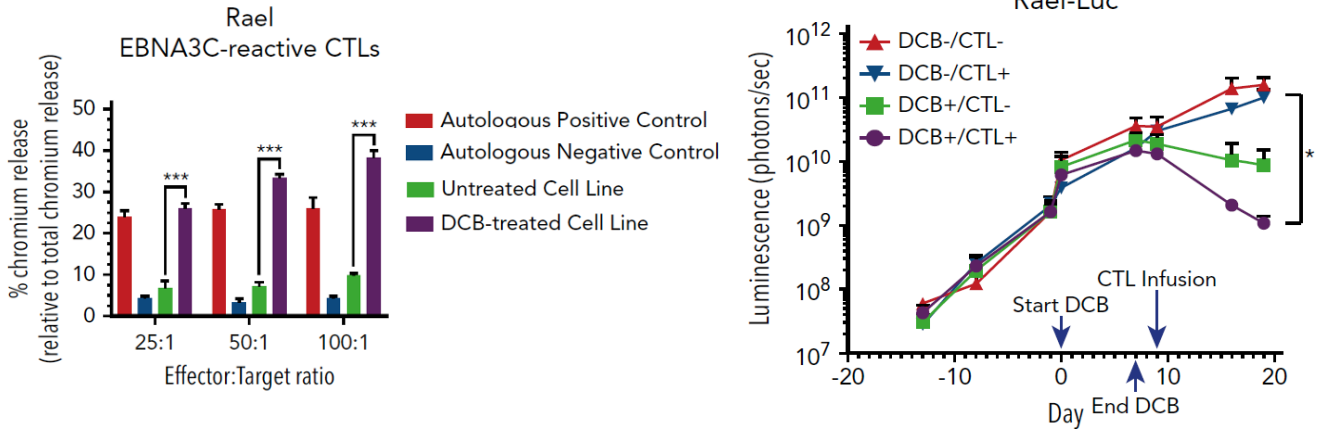


**Figure 2: A.** DCB treatment induced lysis sensitization *in vitro* in latency I BL cell using a chromium-51 release assay. **B.** DCB treatment followed by EBV-CTLs treatment in mice with latency I BL xenografts inhibited tumor growth (indicated by lower bioluminescence).


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