Modulation of Viral Latency in EBV-associated Lymphomas as a Mechanism to Sensitize Tumors to EBV-directed Cellular Therapy

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Abstract: Tumor viruses cause nearly 20% of all human cancers. 200,000 Epstein-Barr virus associated malignancies occur worldwide annually. Despite significant advances in T-cell immunotherapy against EBV-infected lymphomas that express the full EBV latency III program comprised of 10 viral proteins, a critical barrier has been that most EBV-infected tumors express restricted forms of latency. These include Burkitt lymphoma (BL) and diffuse large B-cell lymphomas (DLBCL), aggressive lymphomas that typically express the viral latency I program, in which the single Epstein-Barr nuclear antigen EBNA1 is produced. EBNA1 is poorly immunogenic, enabling BL and DLBCL to evade otherwise promising cytotoxic T-lymphocyte (CTL) therapeutic approaches. Consequently, many EBV-associated B-cell cancers remain untreatable. Yet, very little is known about intrinsic host factors that maintain the latency I state. To overcome this barrier, our collaborative approach leverages the expertise of the Roth/Cesarman, Gewurz and O'Reilly laboratories, which have pioneered highly synergistic areas of EBV investigation. Aim I uses the latest Broad CRISPR/Cas9 technology to systematically identify B-cell factors necessary to maintain the latency I epigenetic state. Aim 2 uses cutting-edge approaches to then identify bioactive small molecules that induce BL and DLBCL latency III expression. Our Aim 3 studies use novel immuno-therapy approaches to eradicate EBV reprogramed BL and DLBCL cells. Collectively, our studies address a long-standing question in the EBV tumor virology field and lay the foundation for innovative immune-oncology approaches to EBV-driven human malignancies.