VIROTHERAPY WITH CODALYTIC™, A CODON-MODIFIED INFLUENZA VIRUS, INDUCES AN ANTI-TUMOR IMMUNE MICROENVIRONMENT ACROSS PRECLINICAL MODELS WITH DIFFERENT IMMUNE CONTEXTURES

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Background Multiple oncolytic viruses have been shown to induce beneficial changes in the tumor microenvironment (TME) by increasing immune cell infiltration and activating stimulatory immune responses, which ultimately support induction of anti-tumor immunity and efficacy. We have previously demonstrated that CodaLytic™, a codon-modified influenza virus, can activate the cancer immunity cycle at various steps in EMT6, a murine triple-negative breast cancer model with moderate responsiveness to immunotherapies, leading to 67% complete tumor regressions. Here, we are confirming the mechanisms of action of the virus alone and in combination with immune checkpoint inhibition in several murine models and human tumor explants with different baseline immune contexture.

Methods Efficacy after intratumoral injection of 10⁸ PFU CodaLytic 3x/week for up to 12 doses as a monotherapy and/or in combination with systemic anti-PD-1 checkpoint blockade was determined in EMT6 breast cancer, CT26 colon cancer and B16F10 melanoma mouse models. Pharmacodynamic changes in the TME after treatment were characterized using flow cytometry. Anti-tumor immune memory was assessed by interferon-γ ELISpot in splenocytes of long-term survivors. Human breast cancer tumoroids maintaining the original patient TME were incubated ex vivo with 10⁸ PFU CodaLytic, 10 μg/ml pembrolizumab or both. Tumor cell killing (TCK) was detected by high-content imaging at 72h and the TME was characterized by flow cytometry, cytokine release and RNA sequencing at 24h and 48h.

Results CodaLytic monotherapy led to significant tumor growth inhibition (TGI) across tumor models, including 76% in EMT6 with moderate, immunologically active infiltration and 69% TGI in poorly infiltrated B16F10 melanoma resistant to PD-1 blockade. In this model, efficacy further improved to 86% with addition of anti-PD-1. In all models, CodaLytic treatment increased infiltration of CD45+ leukocytes, CD8+ T cells and cross-presenting dendritic cells. Ex vivo recall responses to tumor cell lysate (EMT6) or AH1 peptide (CT26) were observed in long-term survivors, confirming generation of an anti-tumor T cell response. Efficacy of the CodaLytic/anti-PD-1 combination was confirmed in well-infiltrated human breast cancer tumoroids (51% TCK vs 24% with pembrolizumab alone, 6% with CodaLytic alone, and 2% in poorly-infiltrated tumoroids), a system in which priming and immune cell recruitment from a systemic reservoir are absent.

Conclusions CodaLytic treatment induced favorable changes in multiple murine tumor models independently of their intrinsic immune contexture and sensitized B16F10 melanomas to PD-1 blockade. Ongoing work investigates correlates of TCK in human tumoroid cultures beyond baseline immune infiltration to support future development of CodaLytic for immuno-virotherapy.

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REFERENCE

Ethics Approval The animal work in this study was approved after MisPro Biotech Services IACUC review, protocols 2019-01-17-COD-1 and 2022-COD-02.

The human tissue component of this study was approved by Vanderbuilt University’s Ethics review board; approval no. 031078.