CODALYTIC™, A NOVEL CODON-PAIR DEOPTIMIZED INFLUENZA VIRUS CREATES AN IMMUNE-STIMULATORY TUMOR MICROENVIRONMENT LEADING TO MONOTHERAPY EFFICACY IN A PRECLINICAL MODEL OF BREAST CANCER

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Background Oncolytic viruses (OVs) of multiple species have been demonstrated to induce beneficial changes in the tumor microenvironment (TME), increasing immune cell infiltration and activating stimulatory immune responses, which ultimately support induction of an anti-tumor immune response. The majority of OVs are attenuated by either gene deletion or mutations and then armed with immunomodulatory transgenes to promote anti-tumor immune responses. Here, we describe a next-generation OV that is rationally attenuated via codon-pair deoptimization and capable of activating anti-tumor immune responses in a mouse model of triple-negative breast cancer without the need of transgenes.

Methods Hemagglutinin and neuraminidase genes of influenza virus strain A/California/07/2009 were codon-pair deoptimized using an algorithm to design synthetic viral genomes, yielding CodaLytic, a genetically stable OV with over 600 silent mutations across the two genes. For in vivo studies, EMT6 cells were implanted into inguinal mammary fat pads and treated intratumorally with CodaLytic three times a week for up to 4 weeks for efficacy studies or for up to 5 doses for pharmacodynamic readouts. Tumor infiltrating immune cells were characterized by flow cytometry or RNA was isolated for transcriptomic analysis. Anti-tumor memory was assessed by intravenous EMT6 rechallenge and interferon- γ ELISpot in splenocytes of long-term survivors.

Results CodaLytic treatment of orthotopic EMT6 tumors led to dose-dependent tumor growth retardation and increased survival with significant tumor growth inhibition of 60% and 40–60% complete regressions at 108 pfu/dose across repeat experiments. Intravenous rechallenge of long-term survivors led to a 27-fold reduction in lung nodule formation (colony mean 0.75 vs 19.92 in naïve control animals, $p = 0.005$). Anti-tumor efficacy after CodaLytic treatment was accompanied by a change in the composition of the tumor immune infiltrate with significant increases in CD4+ T, B and NK cells and increased gene expression of interferon- γ , MHC-II and CCL-5. Further evidence of induction of anti-tumor immunity was an EMT6-specific interferon- γ recall response in splenocytes from long-term survivors.

Conclusions These data demonstrate the induction of innate and adaptive changes in the TME and anti-tumor efficacy after intratumoral treatment of EMT6 tumors with CodaLytic. Additional holistic gene expression analysis is ongoing to further characterize the mechanisms of immune activation. Taken together with preclinical safety data and demonstrated clinical safety and immunogenicity of this attenuated influenza virus after intranasal administration in healthy individuals, CodaLytic is a promising immunotherapeutic to be further developed as monotherapy and in combination with immune checkpoint inhibitors or other modalities.

Ethics Approval All animal studies were conducted in compliance with protocol 2019-01-17-COD-1, approved by the Mispro Biotech Services Institutional Animal Care and Use Committee.