

Enabling checkpoint inhibitors with oncolytic viruses to deliver complete responses: a matter of timing

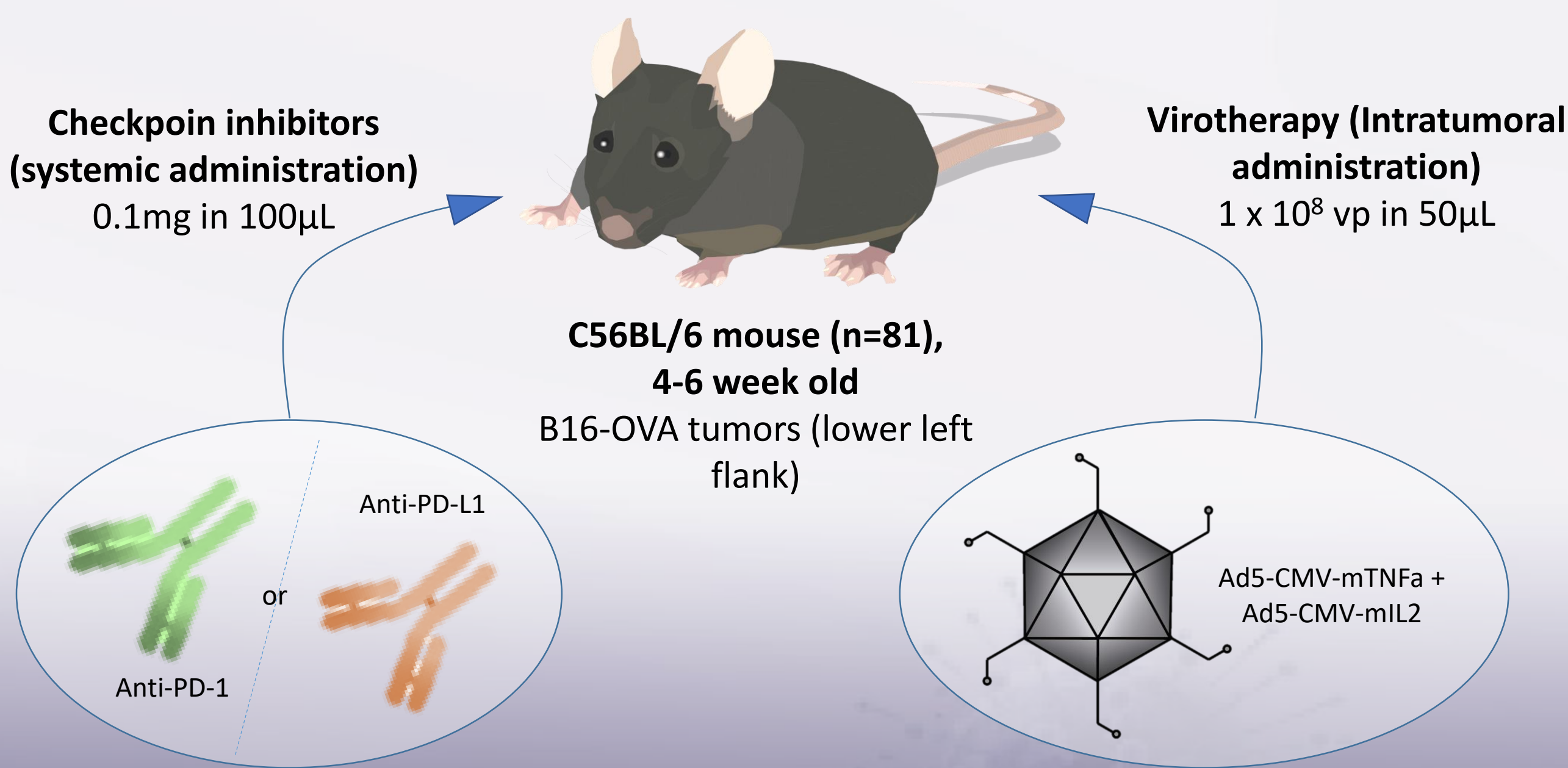
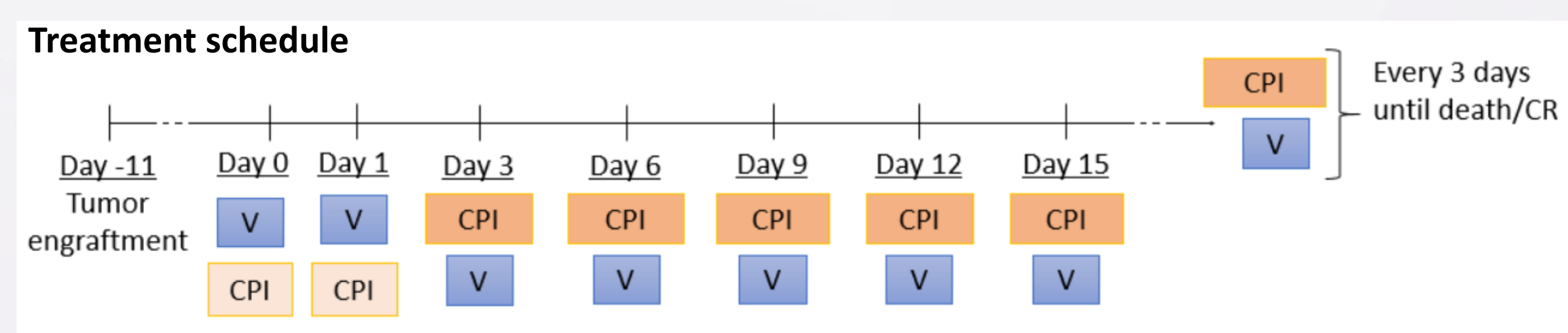
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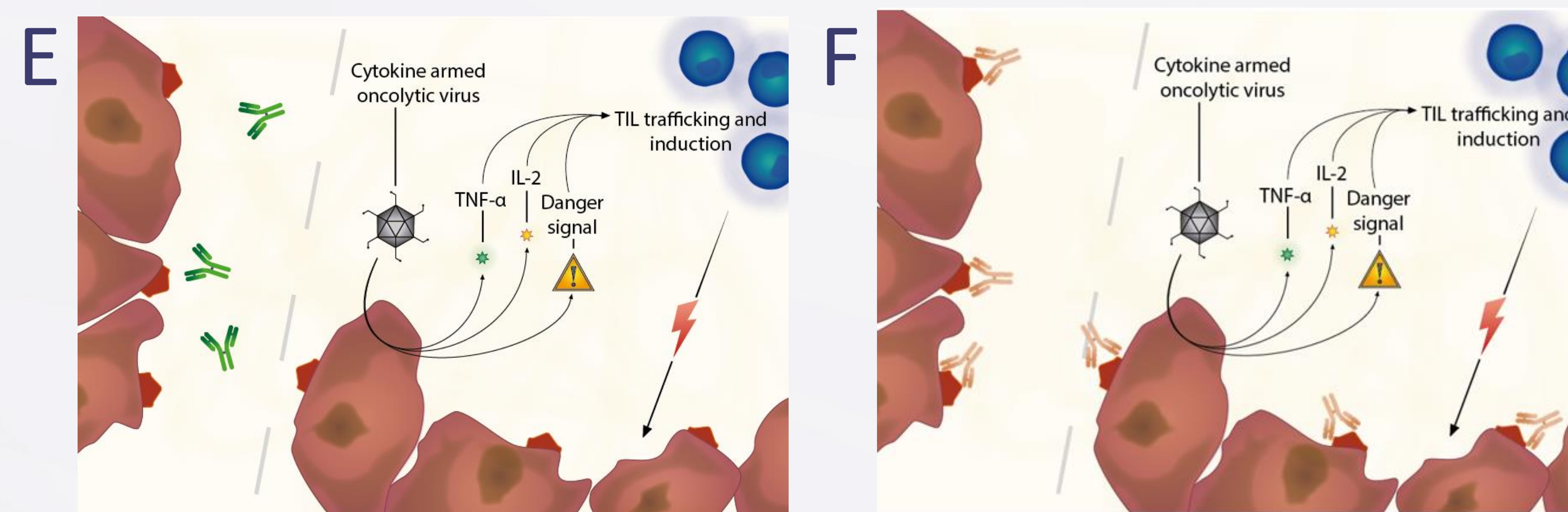
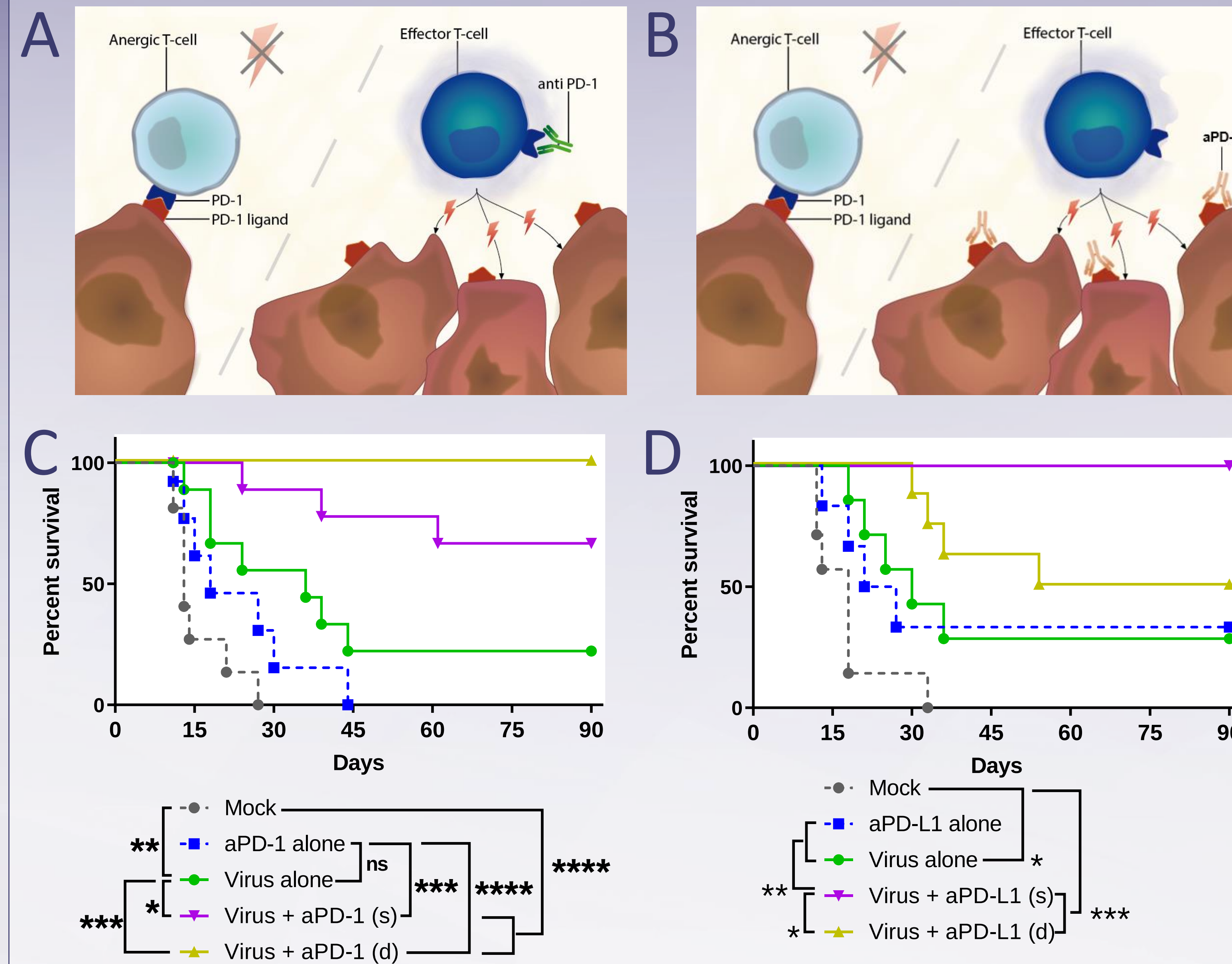
1. Background

Checkpoint inhibitors (CPIs) started a new golden era of immunotherapy for cancer treatment. Since approval of the first product in 2011, a number of these antibodies are now available for different indications. Thousands of trials are ongoing which could predict many further approvals soon. Unfortunately, only a minority of patients currently benefit from CPI treatment. One of the biggest limitations appears to be poor immune infiltration of many tumors, known as immune desert or excluded tumors. Oncolytic viruses are an interesting tool to use together with CPIs to increase the frequency and the quality of patients' responses. Besides their inherent ability to raise the immune alarm towards the tumour, resulting in recruitment of lymphocytes and other cells, they can be armed with transgenes to potentiate these effects. In a data driven approach, adenoviruses expressing Tumour Necrosis Factor Alpha and Interleukin 2 were identified as the optimal approach for recruiting and activating T-cells in tumors. In this approach, the regimen of administration must carefully optimized as it can affect the outcome of the treatment.

2. In vivo experimental design

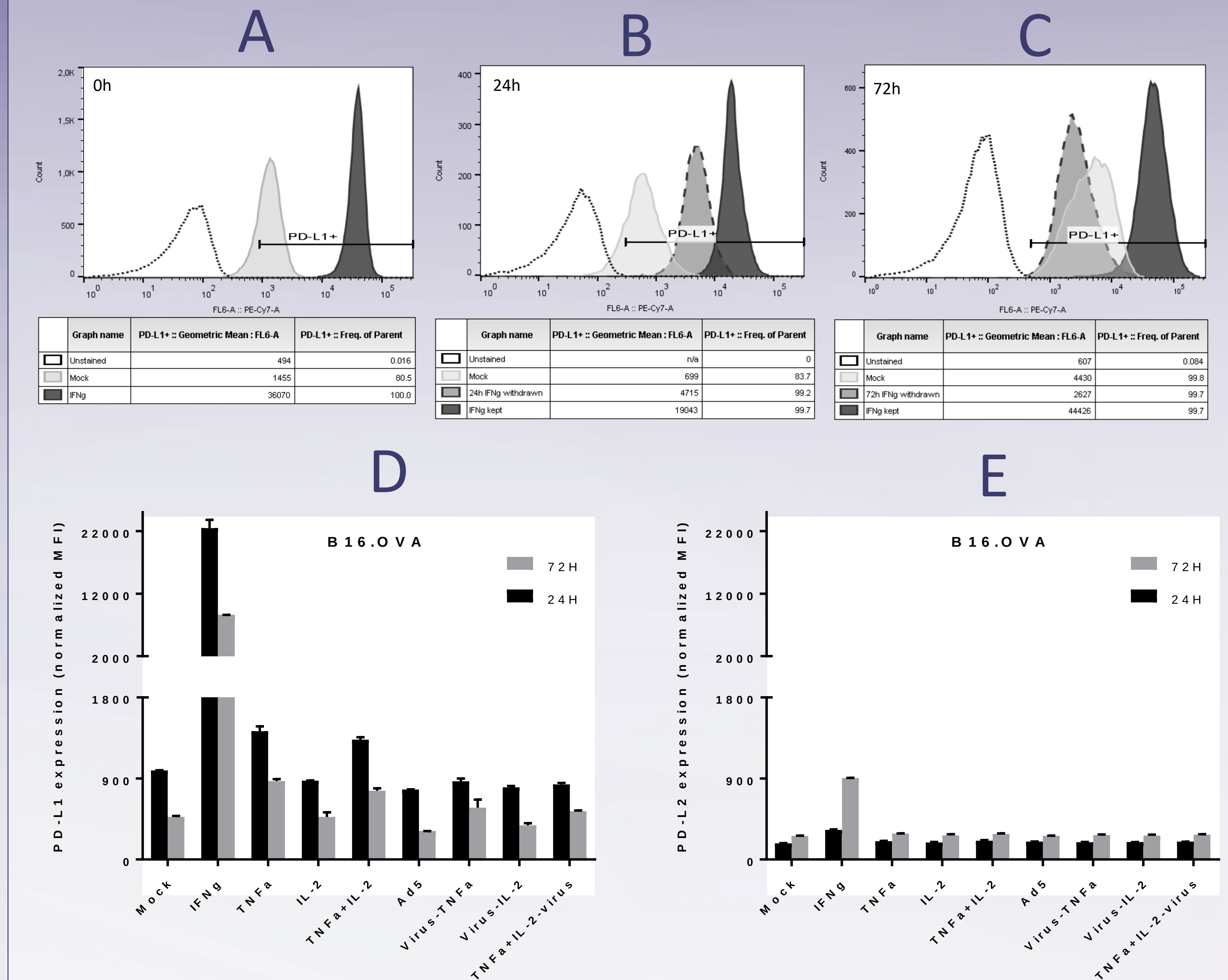


3. Optimal regimens of administration for anti-PD1 and anti-PD-L1 are different when combined with virotherapy



3A) PD-1/PD-L1 interaction shuts down T-cell responses and mechanism of action of anti-PD-1 . 3B). PD-1/PD-L1 interaction shuts down T-cell responses and mechanism of action of anti-PD-L1 .3C) Overall survival (Kaplan-Meier, Log rank Mantel-Cox test) in the context of anti-PD-1 and virotherapy (N_{mock}: 8, N_{aPD-1 alone}: 10, N_{virus alone}: 9, N_{virus+aPD-1 (Simultaneous)}: 9, N_{virus+aPD-1 (Prime and boost)}: 9.). 3D) Overall survival (Kaplan-Meier, Log rank Mantel-Cox test) in the context of anti-PD-L1 and virotherapy (N_{mock}: 7, N_{aPD-L1 alone}: 6, N_{virus alone}: 7, N_{virus+aPD-L1 (Simultaneous)}: 8, N_{virus+aPD-L1 (Prime and boost)}: 8.). 3E) Outcome of anti-PD-1 in tumors lacking T cells and proposed mechanism of synergy when virotherapy is used to enable anti-PD-1. 3F) Outcome of anti-PD-L1 in tumors lacking T cells and proposed mechanism of synergy when virotherapy is used to enable anti-PD-L1. (*p<0.05; **p<0.01, ***p<0.001, ****p<0.0001).

4. PD-L1 expression is reversible in tumor cells and it is triggered after interferon gamma exposure



5. Acknowledgements and Funding



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