



Localized oncolytic virotherapy for systemic tumor immunotherapy

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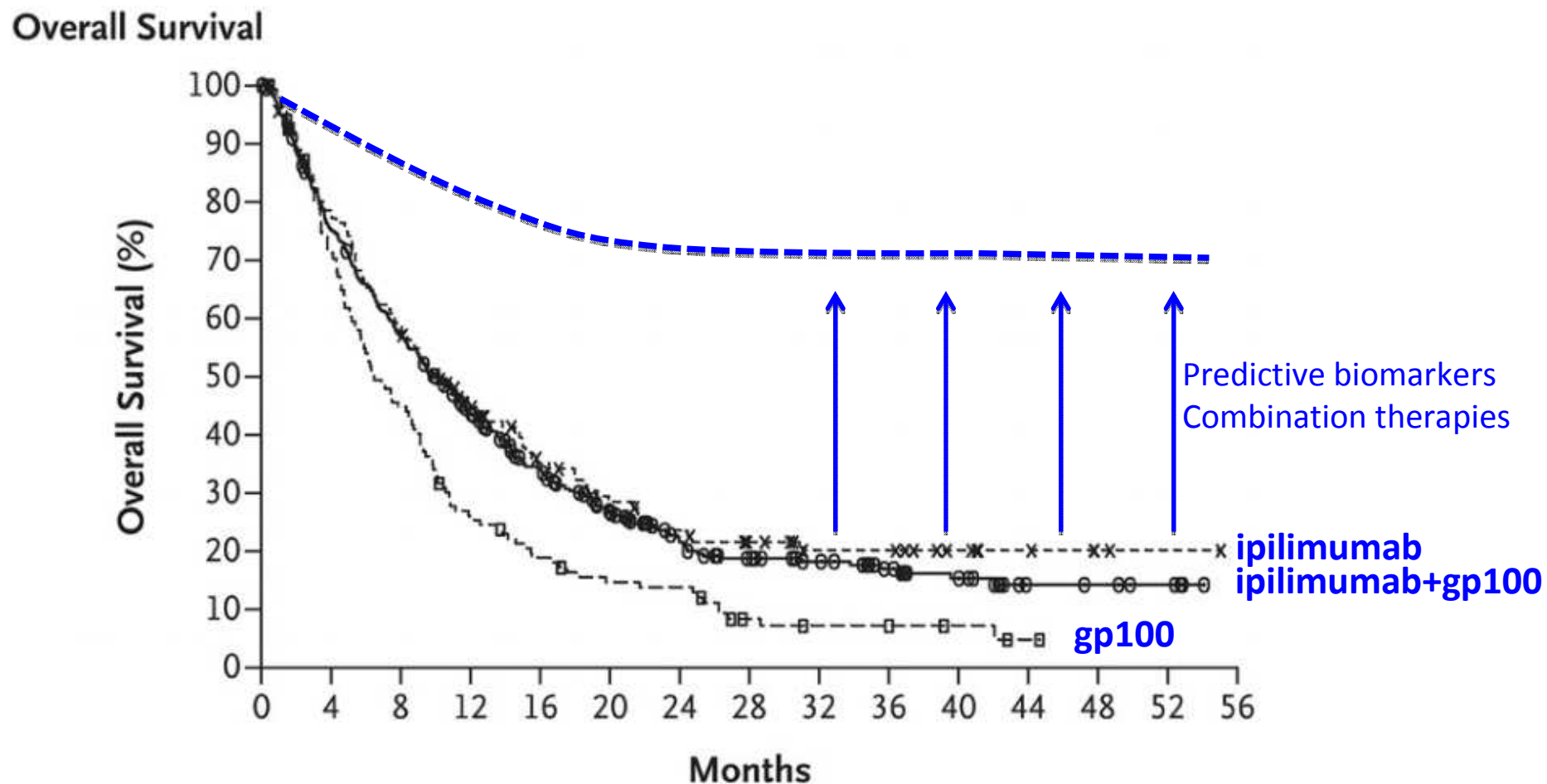
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Presenter Disclosure Information

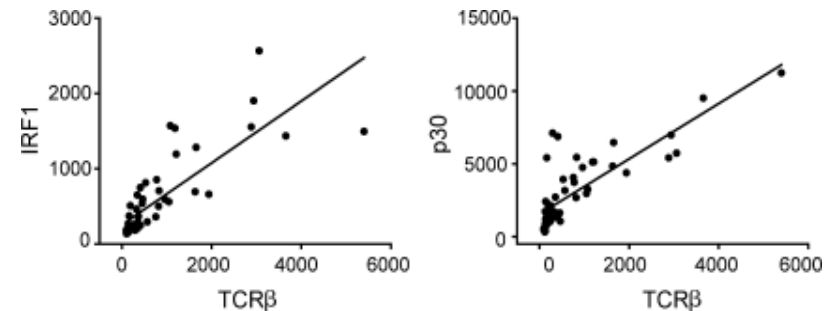
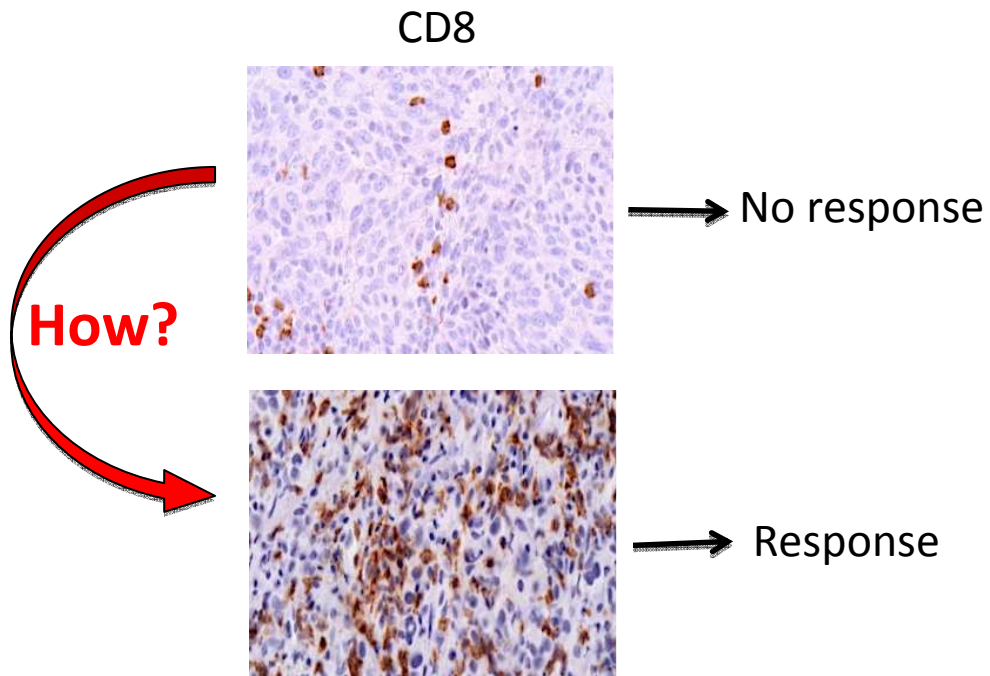
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No Relationships to Disclose

Anti-CTLA-4 antibody ipilimumab improves overall survival in patients with metastatic melanoma



Pre-existing immune infiltration in human melanomas is associated with response to immunotherapies

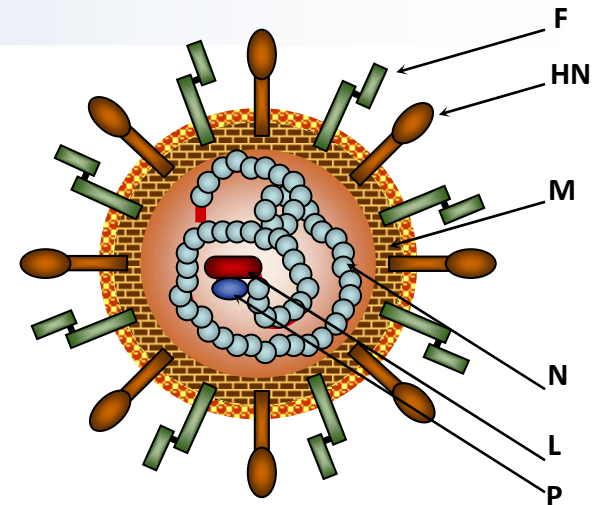


Positive correlation between increased T cell infiltration and type I IFN-induced transcripts
Fuertes M.B. et al., JEM. 208:2005-16 (2011)

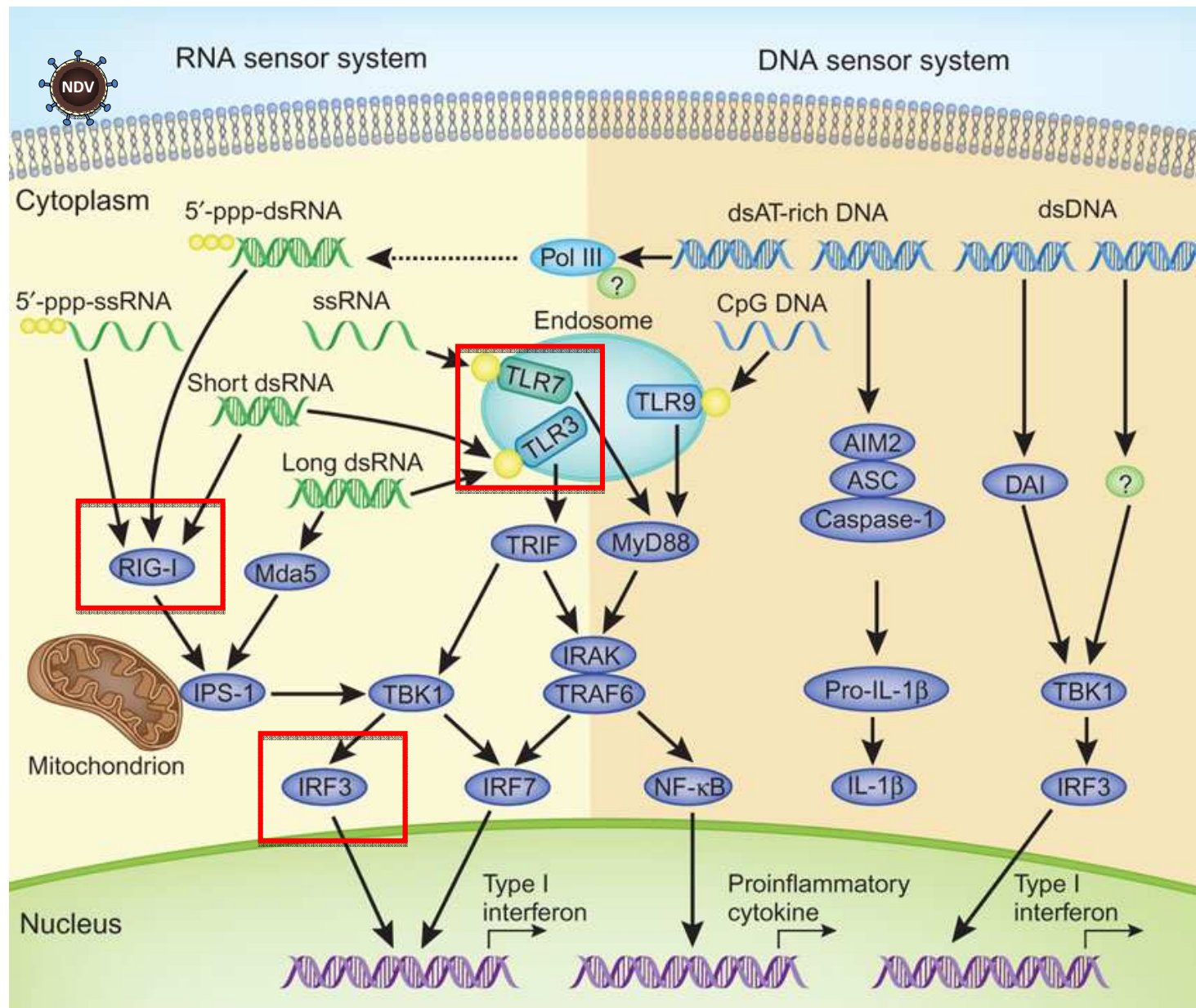
Could an oncolytic virus with strong type I interferon inducing properties drive tumor immune infiltration?

Newcastle disease virus (NDV) as an oncolytic agent

- Member of Paramyxoviridae family (same as mumps, measles), which **do not integrate into human genome**
- Birds are a natural host, thus humans **do not have pre-existing immunity** to the virus
- Readily **infects the majority of cancer cells** due to ubiquity of the receptor (sialic acid)
- Specificity for cancer cells is mediated by selective viral replication in cells with **deficient innate immune responses and cells resistant to apoptosis**
- Clinical trials with systemically-administered NDV in humans demonstrated **safety** and **durable clinical benefit** in multiple cancer types

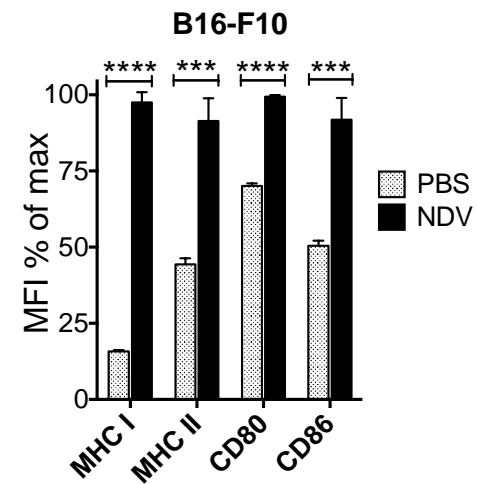
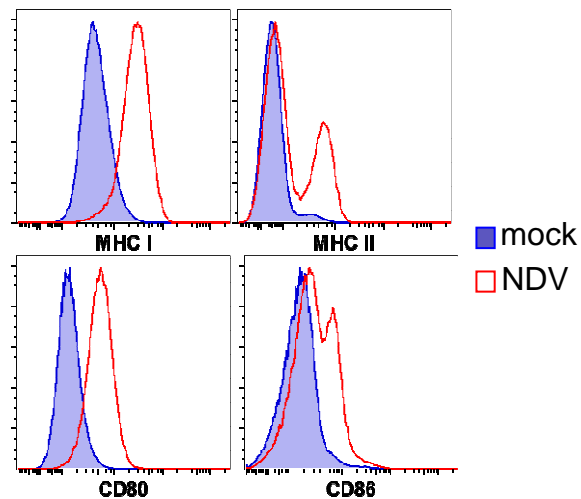


NDV is a strong inducer of type I interferon through activation of TLR7 and RIG-I pathways

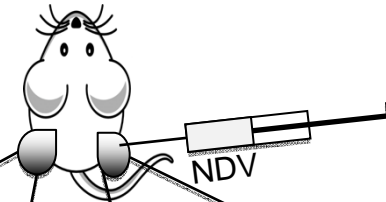


Nature Immunology **10**, 1049 - 1051 (2009)

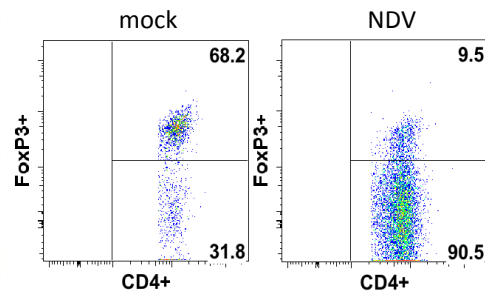
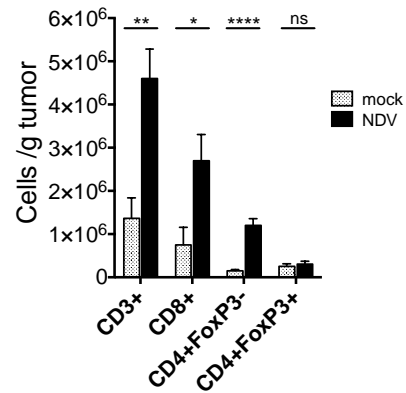
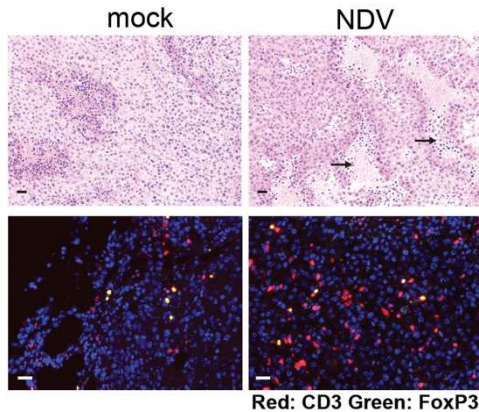
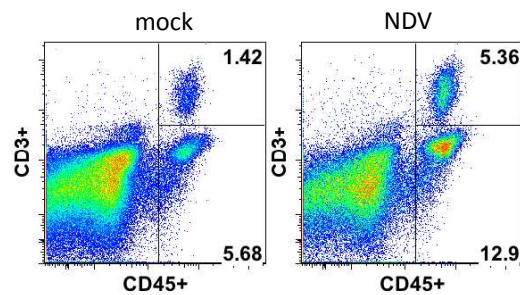
NDV infection upregulates MHC and co-stimulatory molecules on the surface of tumor cells



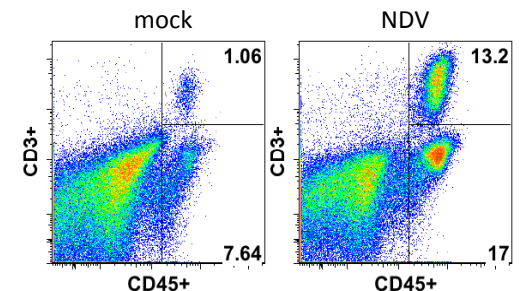
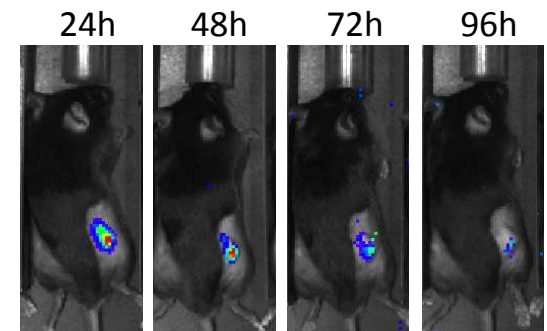
NDV treatment leads to B16 melanoma lymphocyte infiltration and decreases the frequency of Tregs in both virus-injected and distant tumors



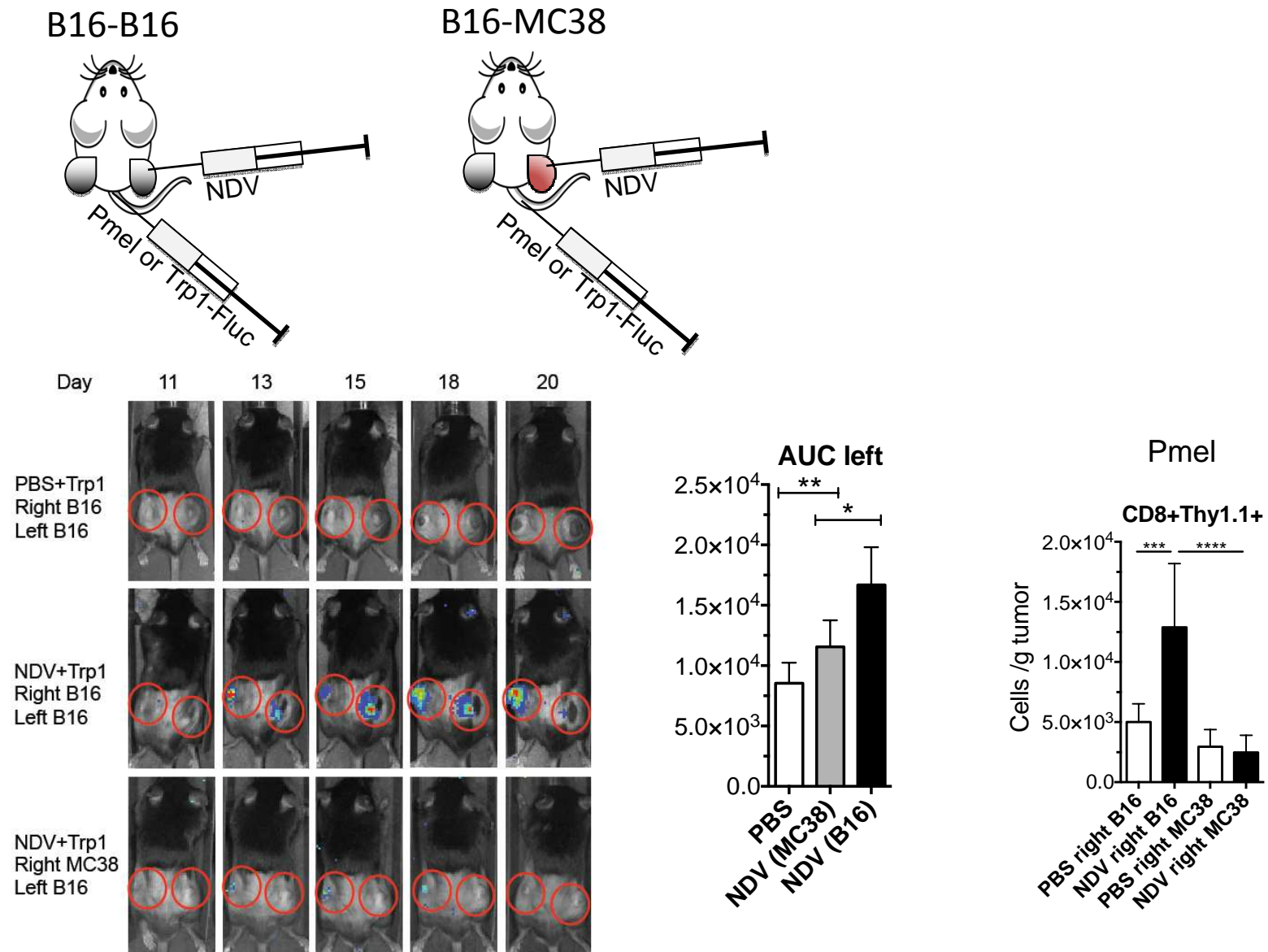
Distant tumor



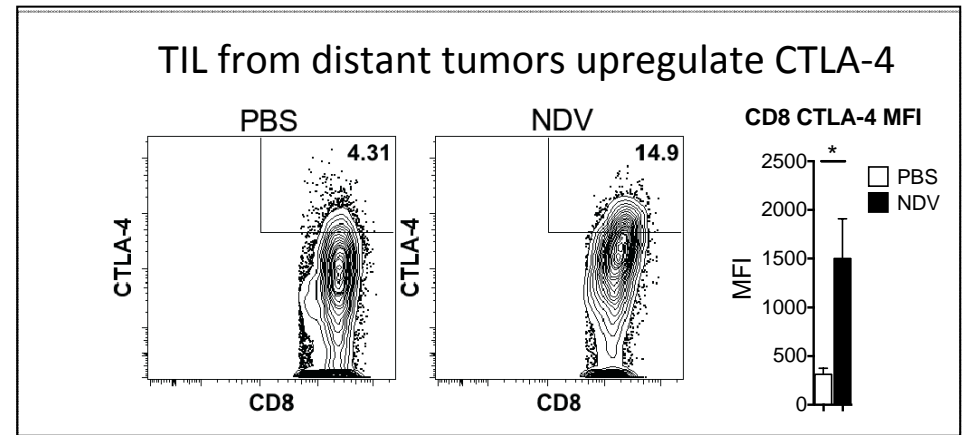
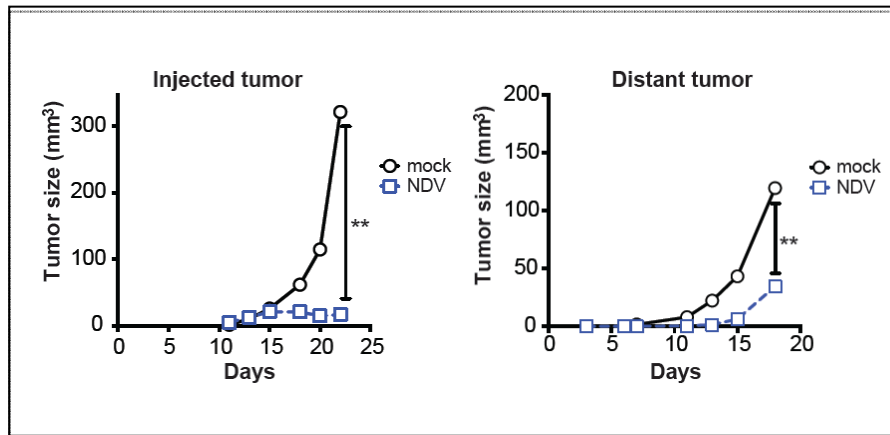
Virus-treated tumor



NDV therapy induces distant tumor infiltration with antigen-specific cells

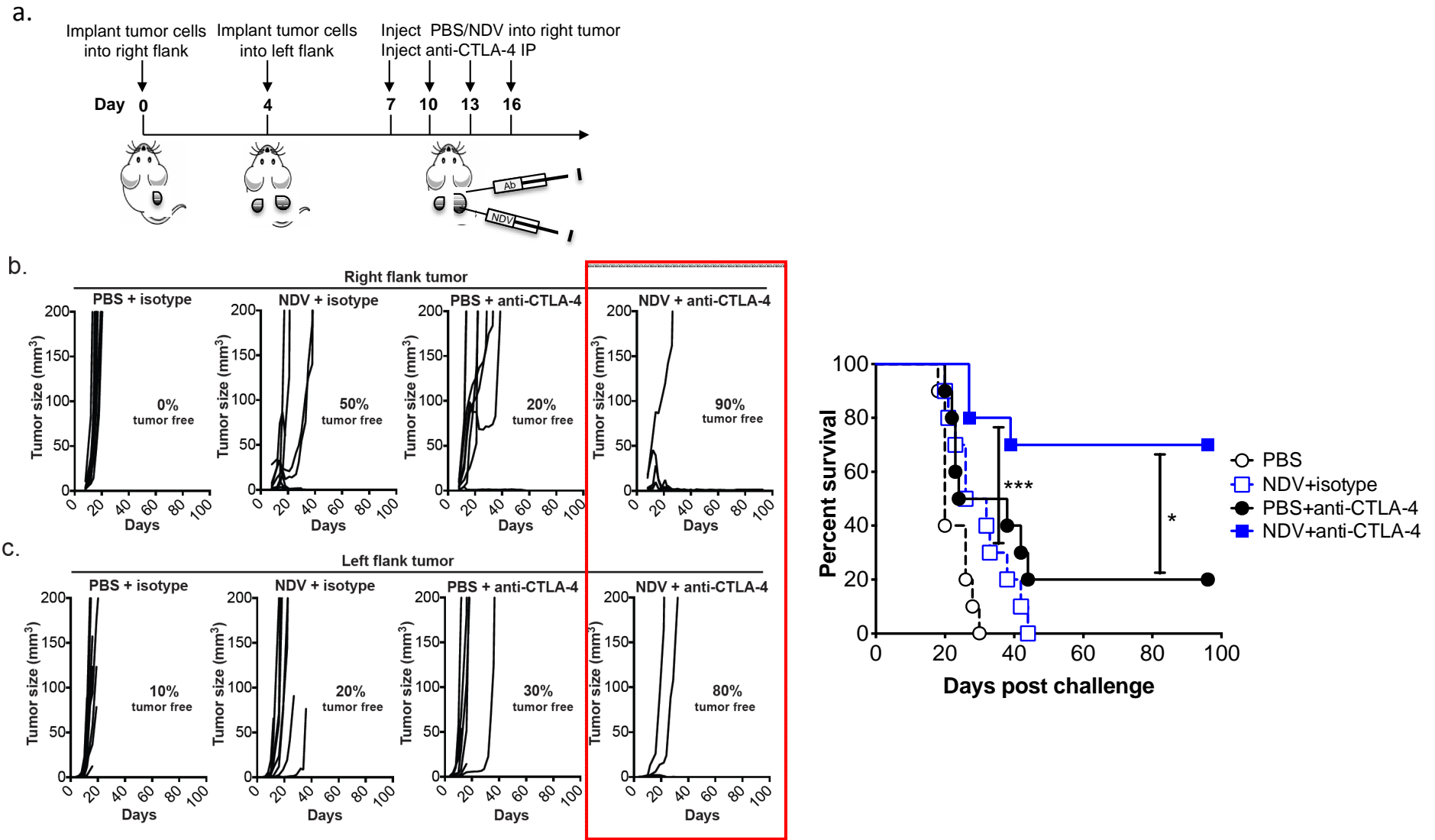


NDV induces distant tumor growth delay, but few complete regressions

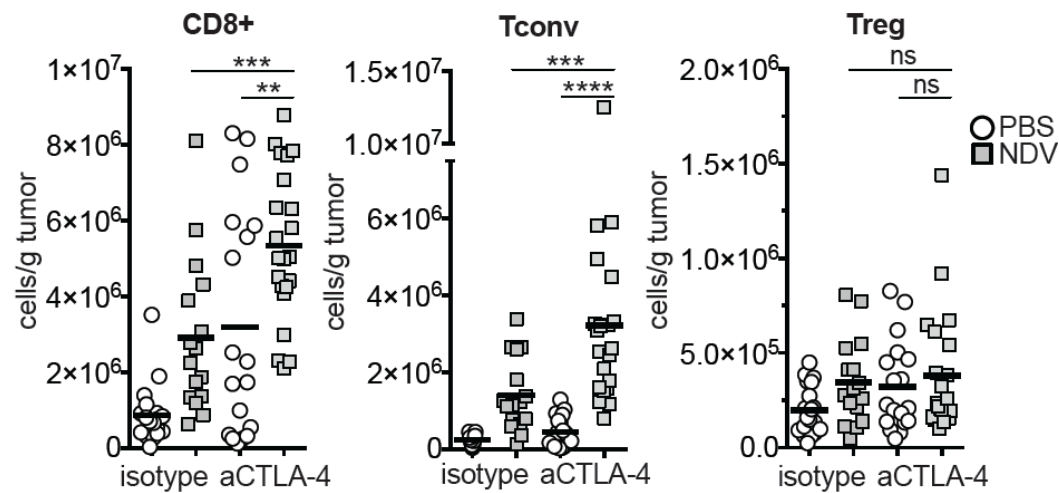
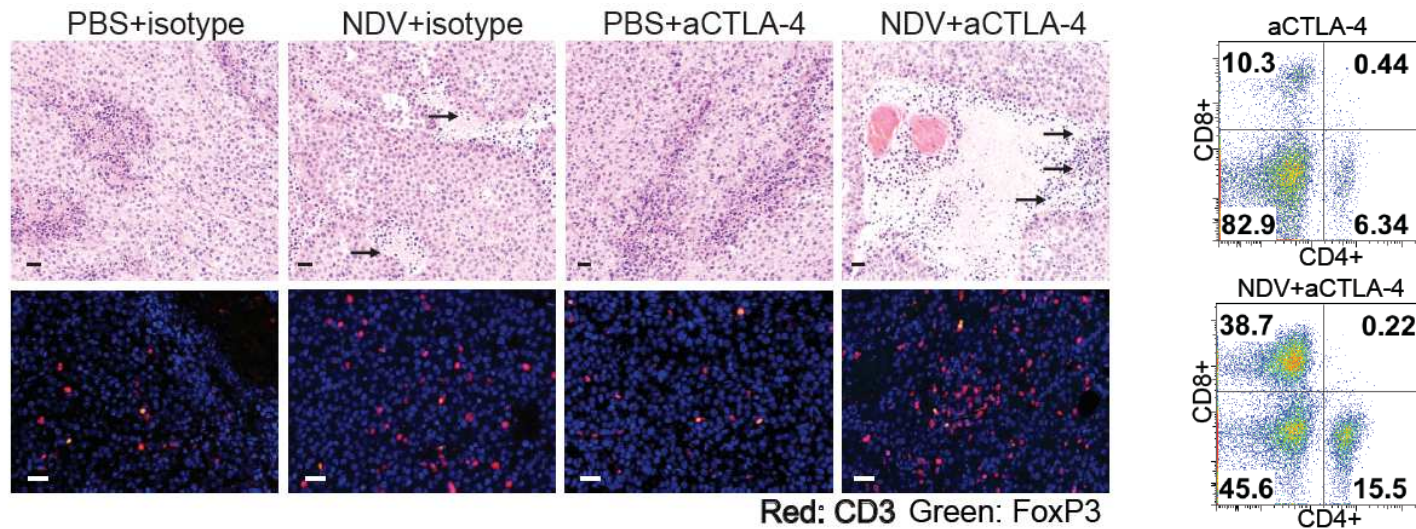


Can NDV-induced tumor inflammatory response increase tumor sensitivity to CTLA-4 blockade?

Combination therapy with NDV and CTLA-4 blockade leads to rejection of injected and distant B16-F10 tumors and long-term survival

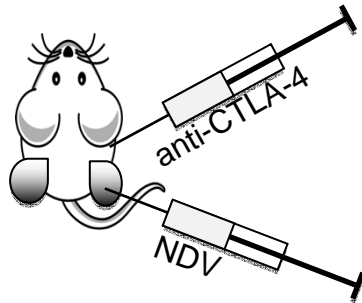


Combination therapy with NDV and CTLA-4 blockade induces inflammatory changes in distant tumors

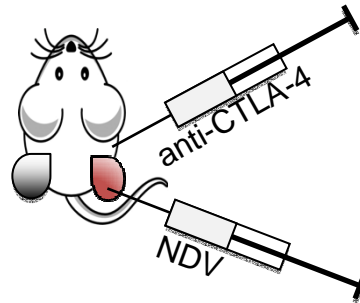


Systemic anti-tumor effect is specific to the injected tumor type

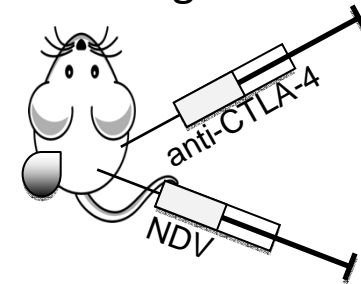
B16-B16



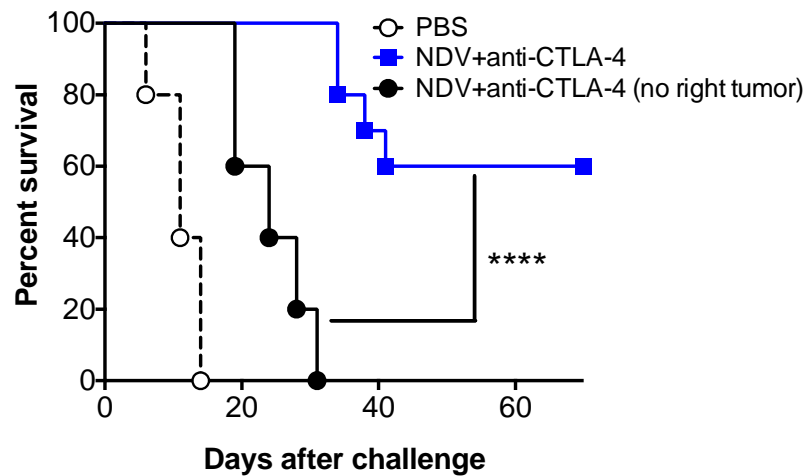
B16-MC38



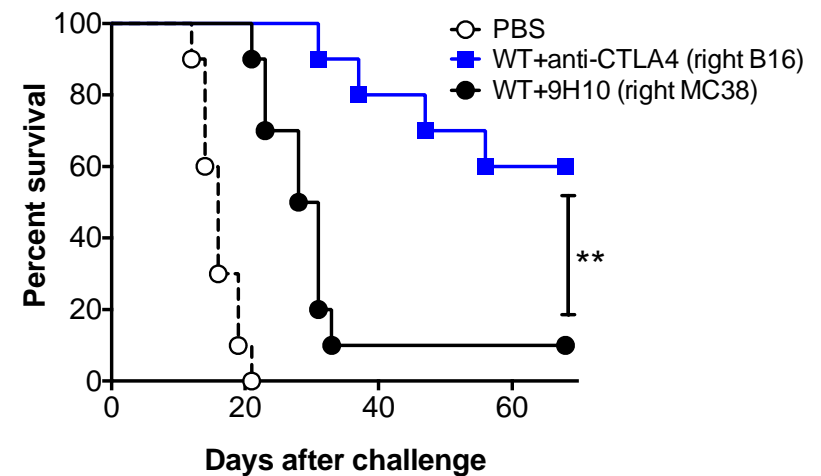
B16-no right tumor



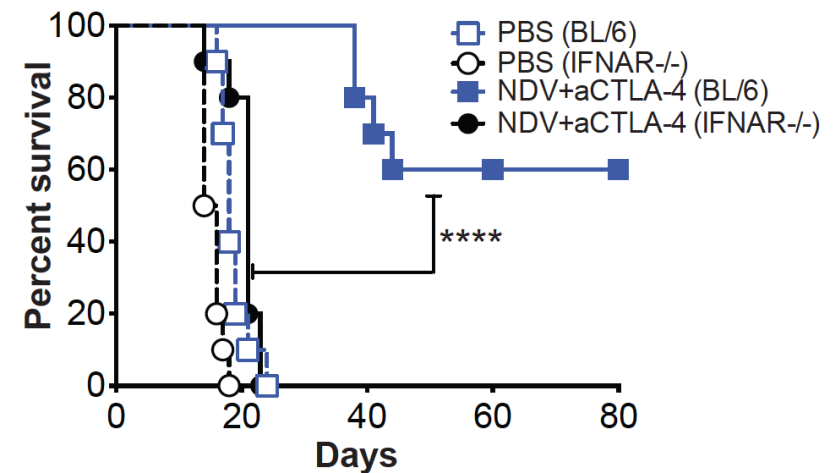
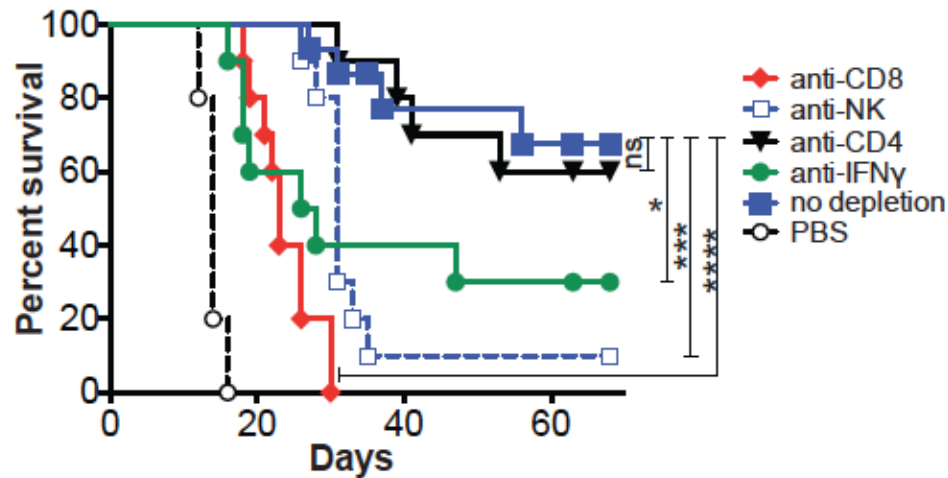
No right tumor



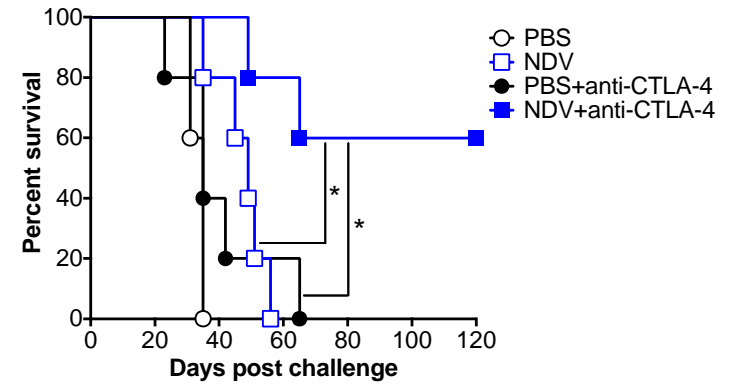
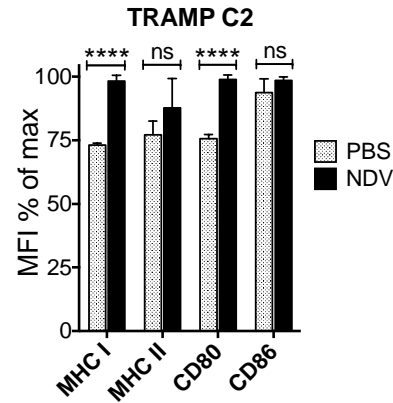
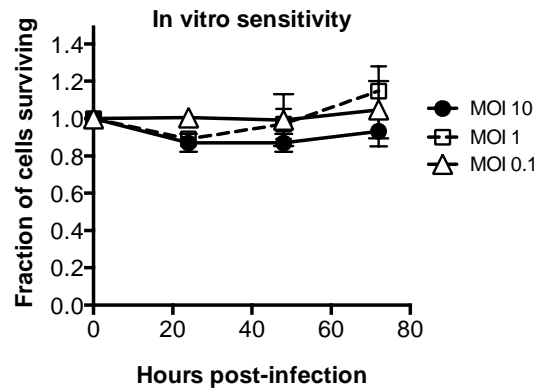
Right MC38 tumor



Anti-tumor activity of NDV combination therapy is dependent on CD8 cells, NK cells, and type I and II interferons

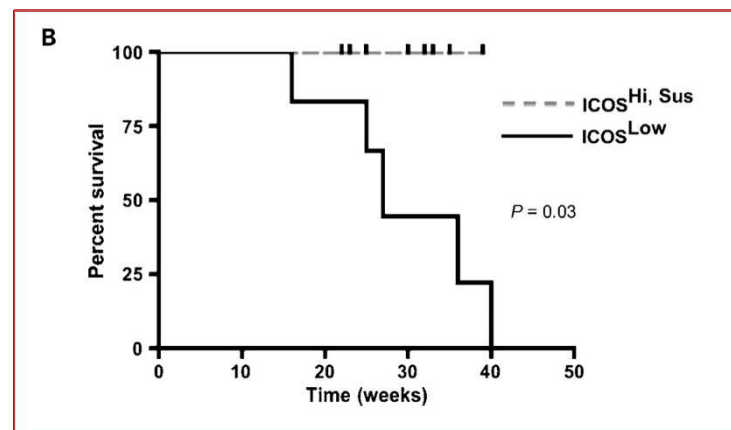
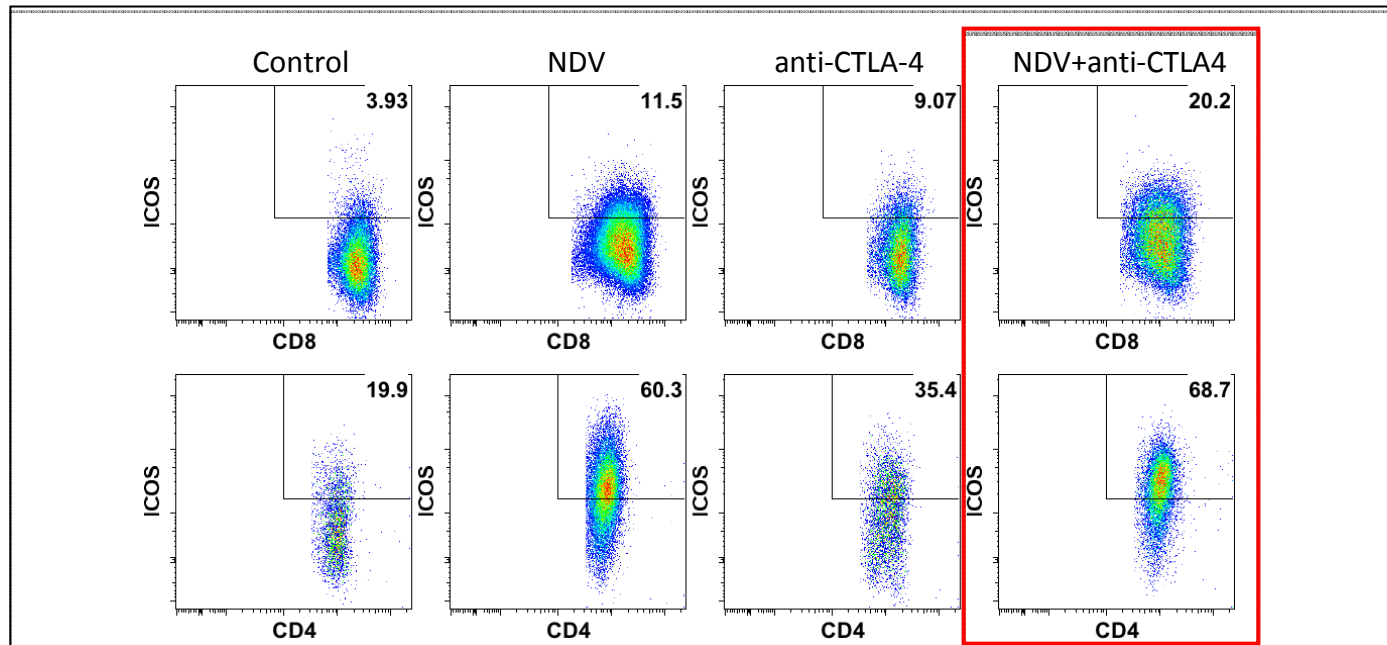


Combination therapy with NDV and anti-CTLA-4 is effective systemically against non-virus-permissive prostate TRAMP tumors



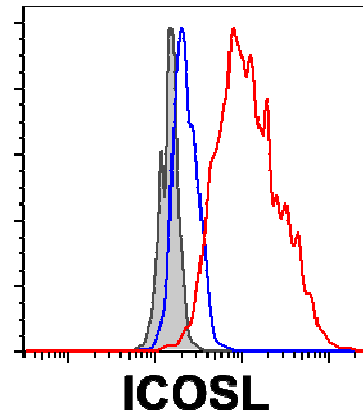
Success of combination therapy does not require strong tumor sensitivity to virus-mediated lysis, highlighting the importance of NDV-induced immune response in anti-tumor effect.

Therapy with NDV induces upregulation of inducible costimulator (ICOS) on TILs



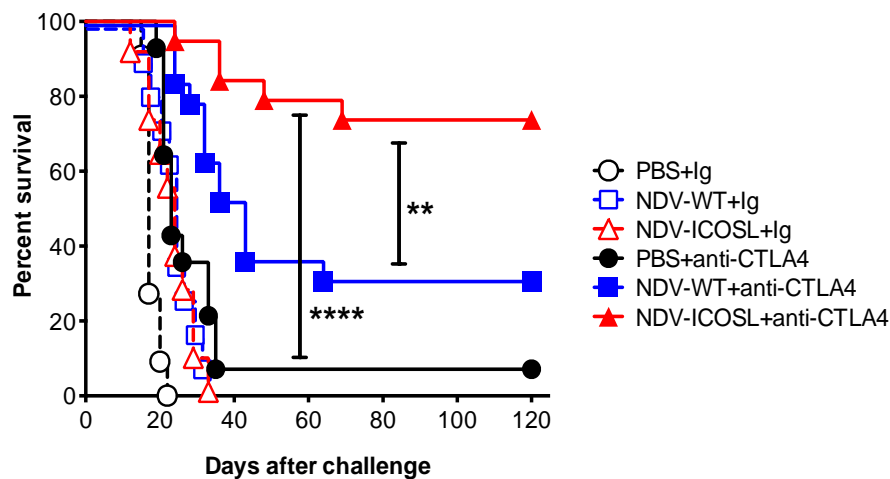
Sustained ICOS upregulation on peripheral CD4 lymphocytes is strongly correlated with clinical benefit from anti-CTLA-4 therapy (Carthon et al. Clin Cancer Res 2010)

Engineered NDV expressing ICOSL (NDV-ICOSL) results in superior therapeutic efficacy

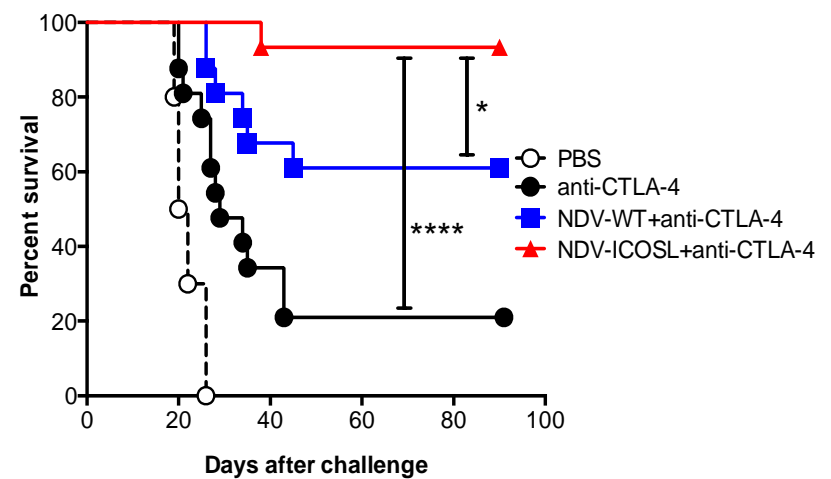


NDV-mICOSL
NDV-WT
Non-infected

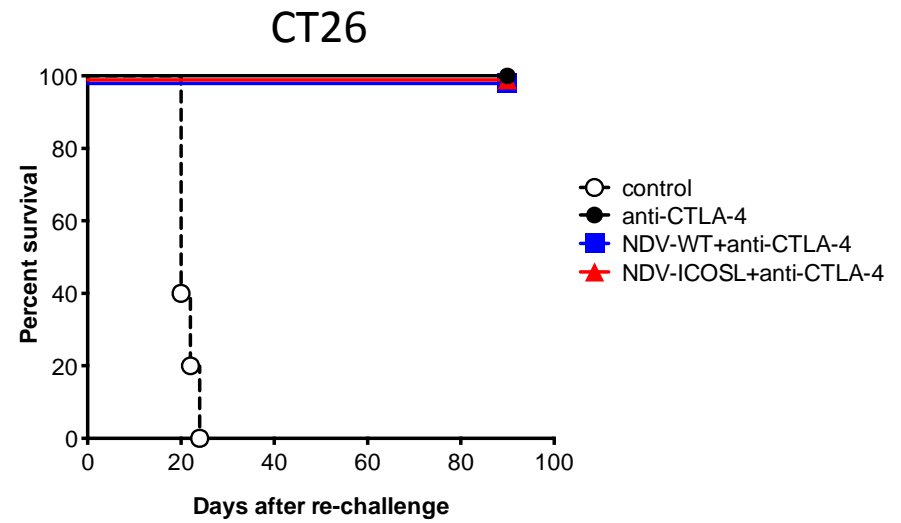
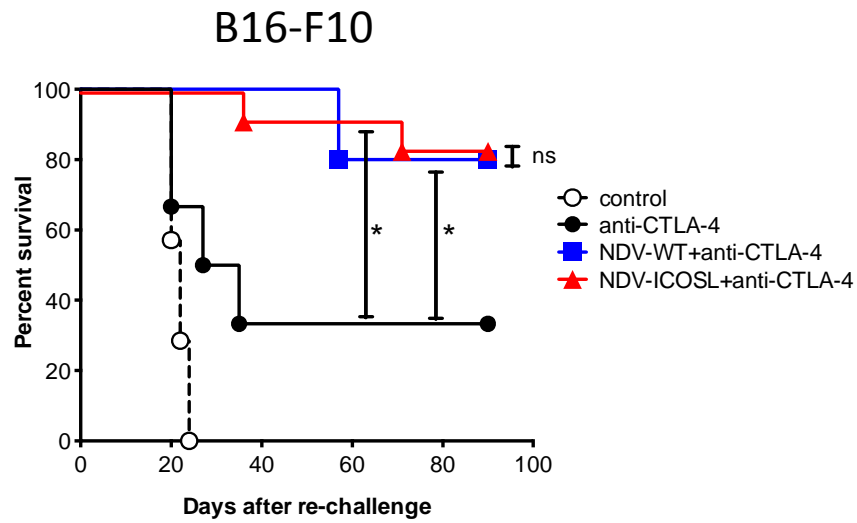
B16-F10



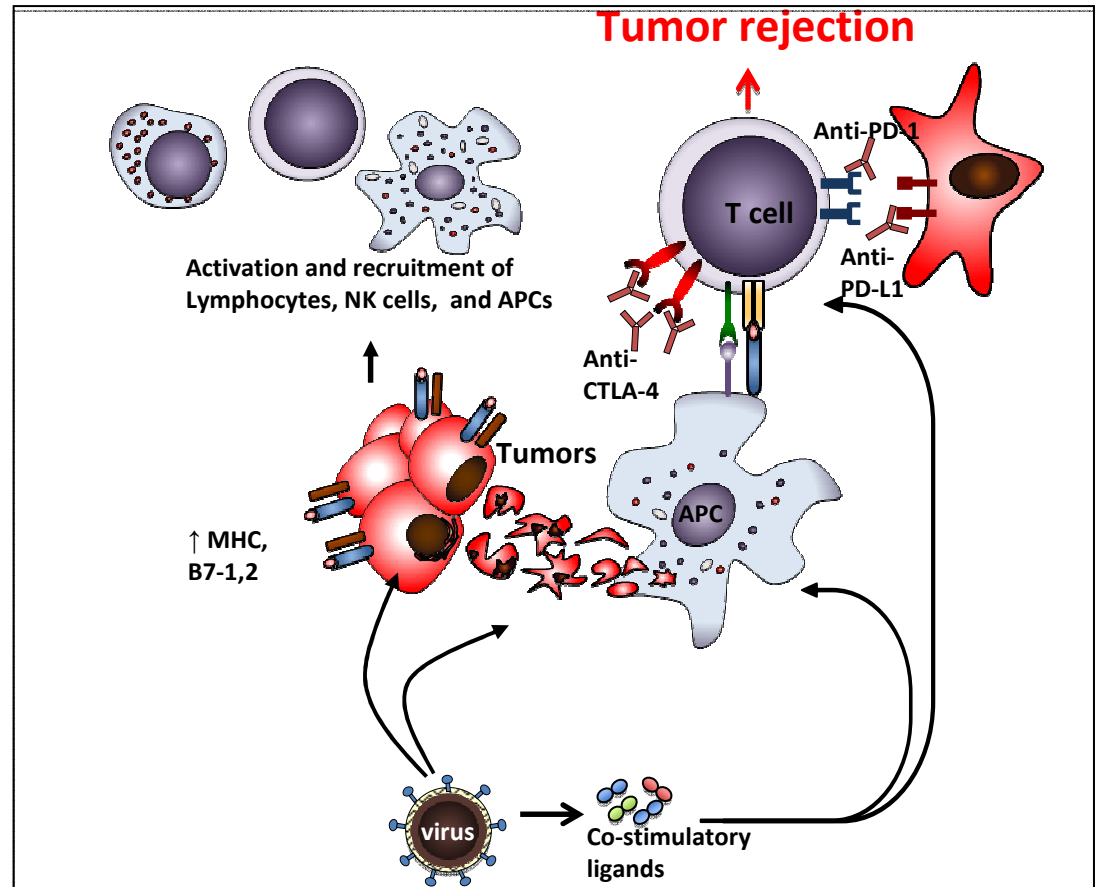
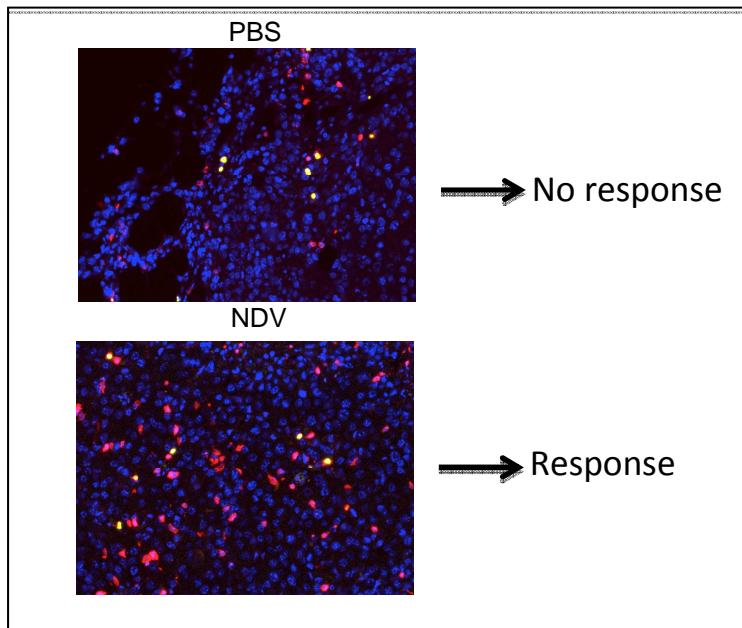
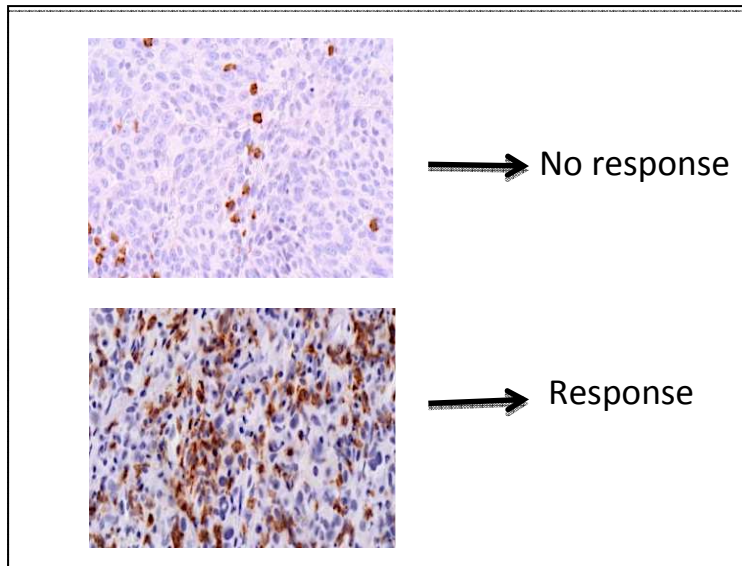
CT26



Animals cured by combination therapy are protected from further tumor challenge



Summary and model



Potential impact on the field

Combination therapies of engineered oncolytic viruses and immunomodulatory antibodies present an attractive therapeutic strategy for clinical exploration in different tumor types

Acknowledgements

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