# NOVEL APPLICATIONS OF MVA TO IMPROVE OUTCOMES IN IMMUNOONCOLOGY

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## Background

Our understanding of the interaction between the host immune system and cancer has evolved rapidly over the previous 10 years due to the clinical success induced by checkpoint inhibition. Previous immunologic work can now be realized in combination strategies. Modified Vaccinia Ankara (MVA) offers significant opportunities due to its natural induction of innate and adaptive immunity, large payload, and excellent safety profile.

## Methods

MVA vectors were administered subcutaneously (SC), intravenously (IV) or intratumorally (IT) into tumor-bearing mice. Cytokine secretion profile in serum was assessed by Luminex analysis. NK and T cell infiltration and activation in various organs and cytolytic activity against target cells were determined by flow cytometry-based assays. PD-1 immune checkpoint blockade (ICB), low dose cyclophosphamide, tumor-targeting Abs or 15 Gy radiotherapy were administered along with IV MVA.

## Results

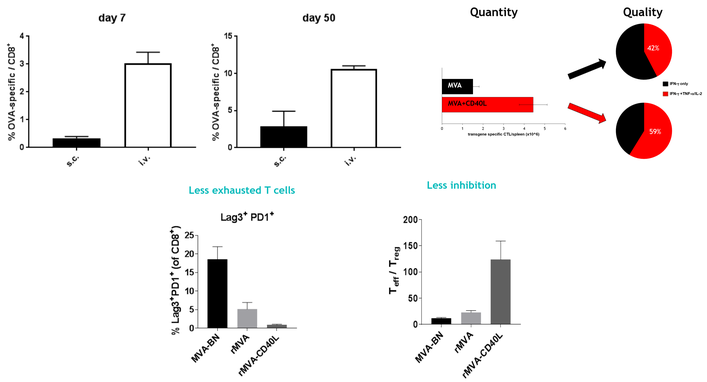
Recombinant MVA (rMVA) in which tumor antigens and costimulatory molecules are encoded can be customized for maximal effect by route of administration. rMVA administered intravenously (IV) causes superior induction of antigen specific T cells, cytokines and NK cells than previously seen with subcutaneous or intramuscular routes. Encoding CD40L in addition amplifies the effects and efficacy improves in relevant models. This is dependent on T cells and NK cells, indicating a potential solution to one tumor resistance mechanism, MHC loss and/or mutation. Furthermore, the combination of rMVA with tumor targeting antibodies, checkpoint inhibition, radiotherapy or chemotherapy often showed additional synergistic therapeutic effects. Administration of MVA alone intratumorally (IT) causes innate immune activation through toll like receptors (TLRs) as well as the cGAS / STING pathway. Recombinant antigen encoding rMVA improves systemic and local antigen specific T cell responses. These effects can be bolstered by encoding certain costimulatory molecules.

## Conclusions

IV and IT recombinant MVA may offer off the shelf solutions to resolve many of the host – tumor immunity interactions that result in lack of efficacy of checkpoint inhibition alone in most patients. Bavarian Nordic plans to initiate clinical trials with existing agents in 2019 applied IV and IT and will create novel constructs to maximize clinical effect, planned to initiate in 2020 and beyond.

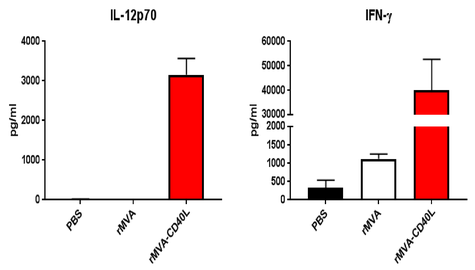
## IV MVA-TAA-CD40L Induces Multiple Anti-tumor Mechanisms

T cell



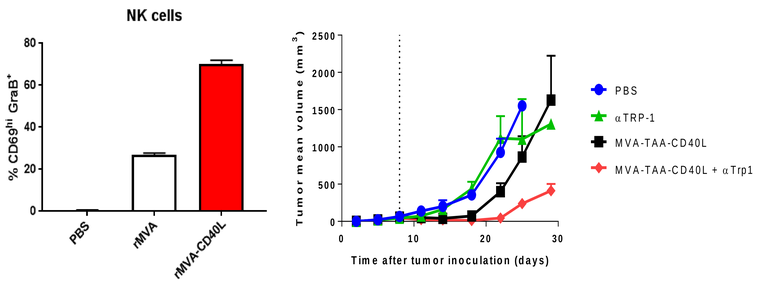

IV Administration of MVA-OVA results in greater quantity and quality of OVA-specific T cells than SC administration. This augmented when CD40L is encoded in the vector.

Cytokine



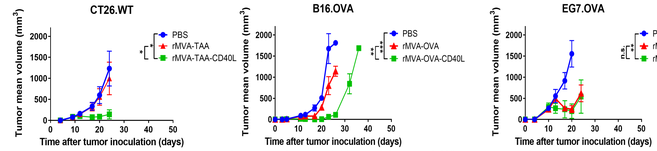

IV Administration of MVA-OVA results in increased peripheral cytokine production compared with SC administration. This is augmented when CD40L is encoded in the vector.

NK / ADCC




IV Administration of MVA-TAA-CD40L improves activation and expansion compared with MVA-TAA. When co-infused with ADCC inducing monoclonal antibody (here targeting Trp1), tumor control is further improved.

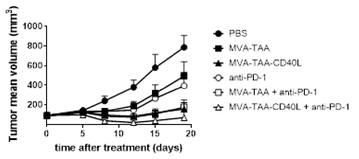
## rMVA-CD40L promotes tumor growth control in unrelated tumor models

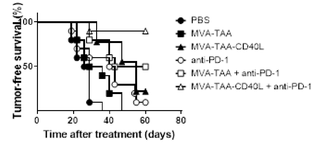



n=5 mice/group, One-way ANOVA, * p> 0.05; ** p<0.01; *** p<0.005; n.s., non-significant

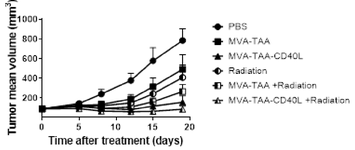
IV Administration of MVA-TAA-CD40L improves tumor growth in relevant model compared with MVA-TAA.

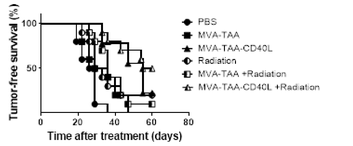
## IV MVA-TAA-CD40L + PD-1 Synergy



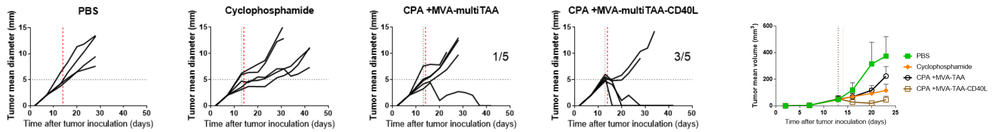




## IV MVA-TAA-CD40L + Radiation Synergy

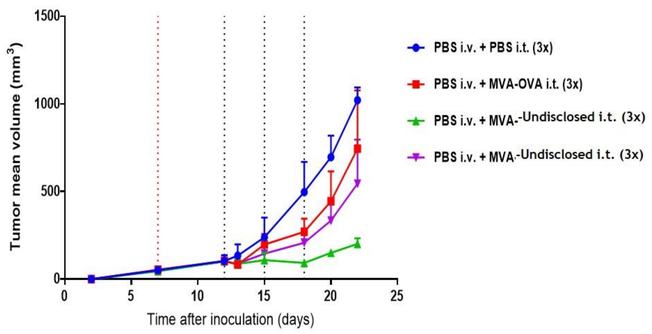



## IV MVA-TAA-CD40L + Chemotherapy Synergy




## Intratumoral rMVA -Co-Stimulatory Molecule Controls Tumor Growth




Proposed mechanisms (literature)

TLR activation
Samuelsson .. Hochrein JCI May 2008

cGAS/STING
Ablasser .. Hornung Nature 2013
Dai .. Deng PLOS Pathogens 2014
Eaglesham ... Kranzusch Nature 2019

TME remodeling
Ager ... Curran CIR 2017
Demaria ... Gilliet PNAS December 2015
Corrales ... Gajewski Cell Reports May 2015
Foote .. Emens CIR 2017

Tumor killing resulting in immunogenic cell death

Infection and killing of TAMs and MDSCs
Norbury Natur Immunol 2002
Sagoo Nature Med 2015
Brault 2018
Altenburg Scientific Reports 2017
Liu BMC Immunology 2008

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