

Background

- Effective immune attack by adoptive T-cell transfer is hindered by several immune evasion mechanisms, which contribute to tumor tolerance
- Oncolytic virotherapy is the use of cancer cell specific, conditionally replicative viruses in the treatment of cancer
- Virus-induced oncolysis of tumor cells cause epitope spreading and increase immunogenicity of the established tumor in the form of pathogen-associated molecular patterns (PAMP)

Aims

- To study the combination adenovirus and OVA-specific OT-I T-cell therapy in a highly resistant and poorly immunogenic B16.OVA mouse melanoma model

Results

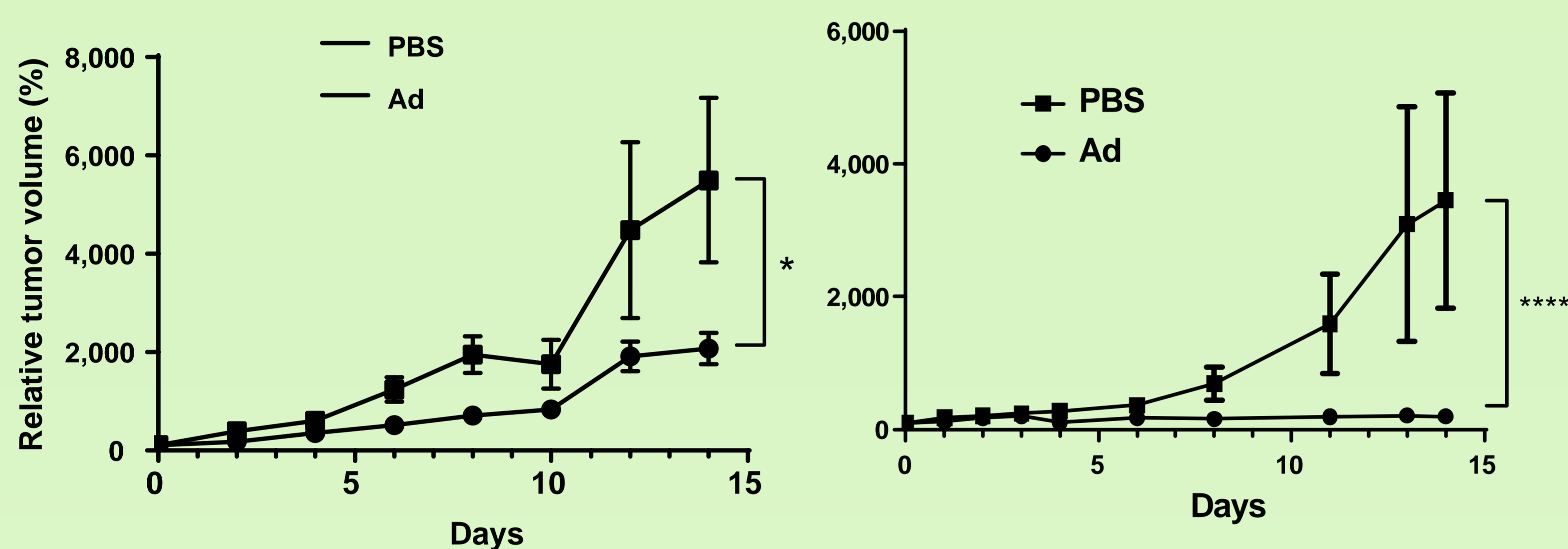


Figure 1 – Adenovirus enhances the efficacy of adoptive T-cell therapy. (a) Adenovirus treatment alone had little effect on B16.OVA tumor growth compared to PBS treatment. (b) Adoptive transfer of tumor-specific OT-I cells in combination with 5/3 fiber-chimeric adenovirus resulted in significant tumor growth control.

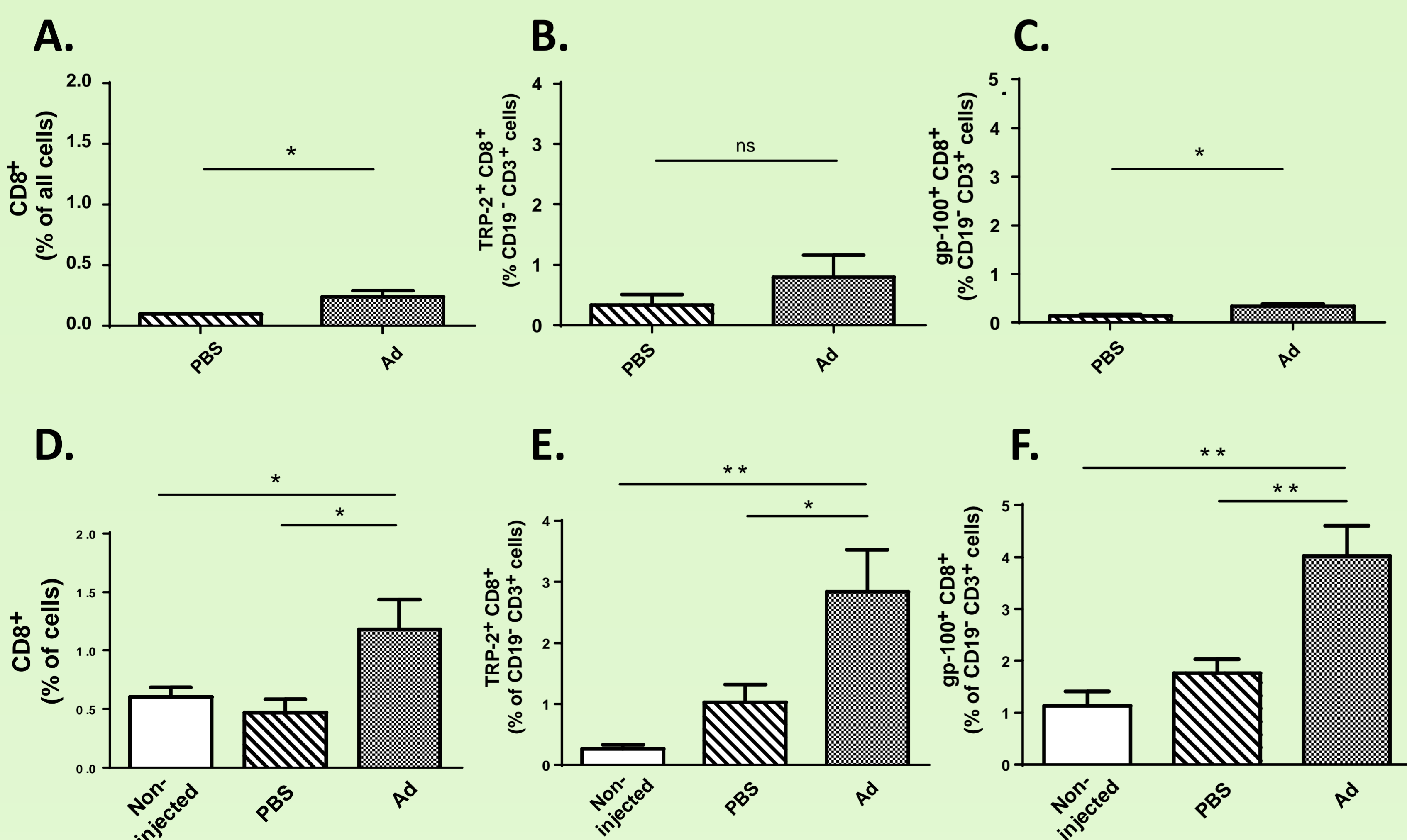


Figure 2 – Combination of adoptive T-cell therapy and adenovirus increases the level of endogenous anti-tumor T-cells. (a-c) Adenovirus injections alone can induce low level anti-tumor immune responses. (d-f) Combining of adenovirus to adoptive OT-I therapy on the other hand increased the levels of CD8+ tumor-infiltrating lymphocytes (TILs) and induced a strong endogenous anti-tumor T-cell response targeting melanoma antigens TRP-2 and gp100.

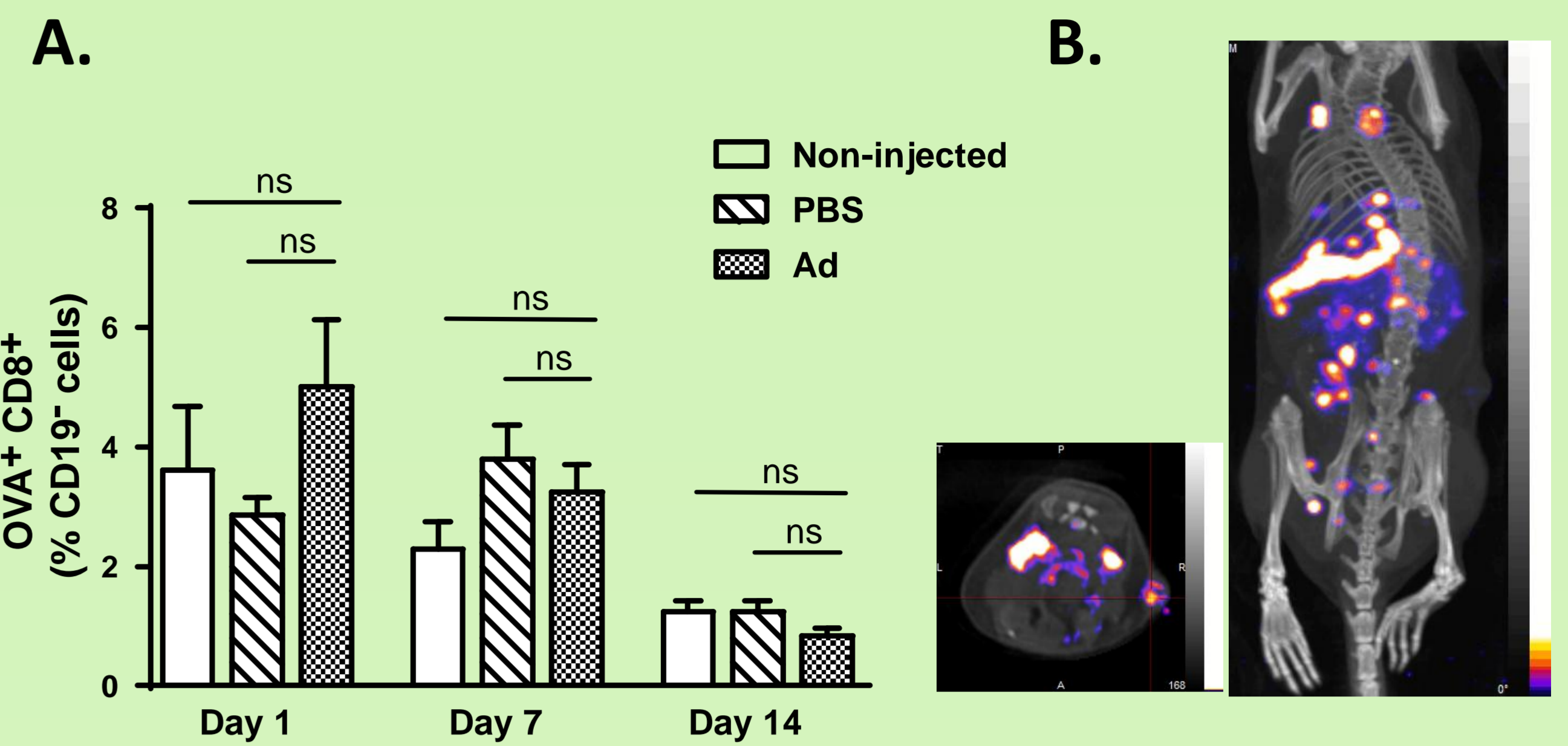


Figure 3 – Trafficking of transferred OT-I cells into tumor is not enhanced by adenovirus injection. (a) The number of tumor-infiltrating OT-I cells was studied *ex vivo* by flow cytometry. (b) Transferred OT-I cells were detected in tumor, spleen, axillary lymph nodes and the lymphatic system by SPECT/CT *in vivo* imaging.

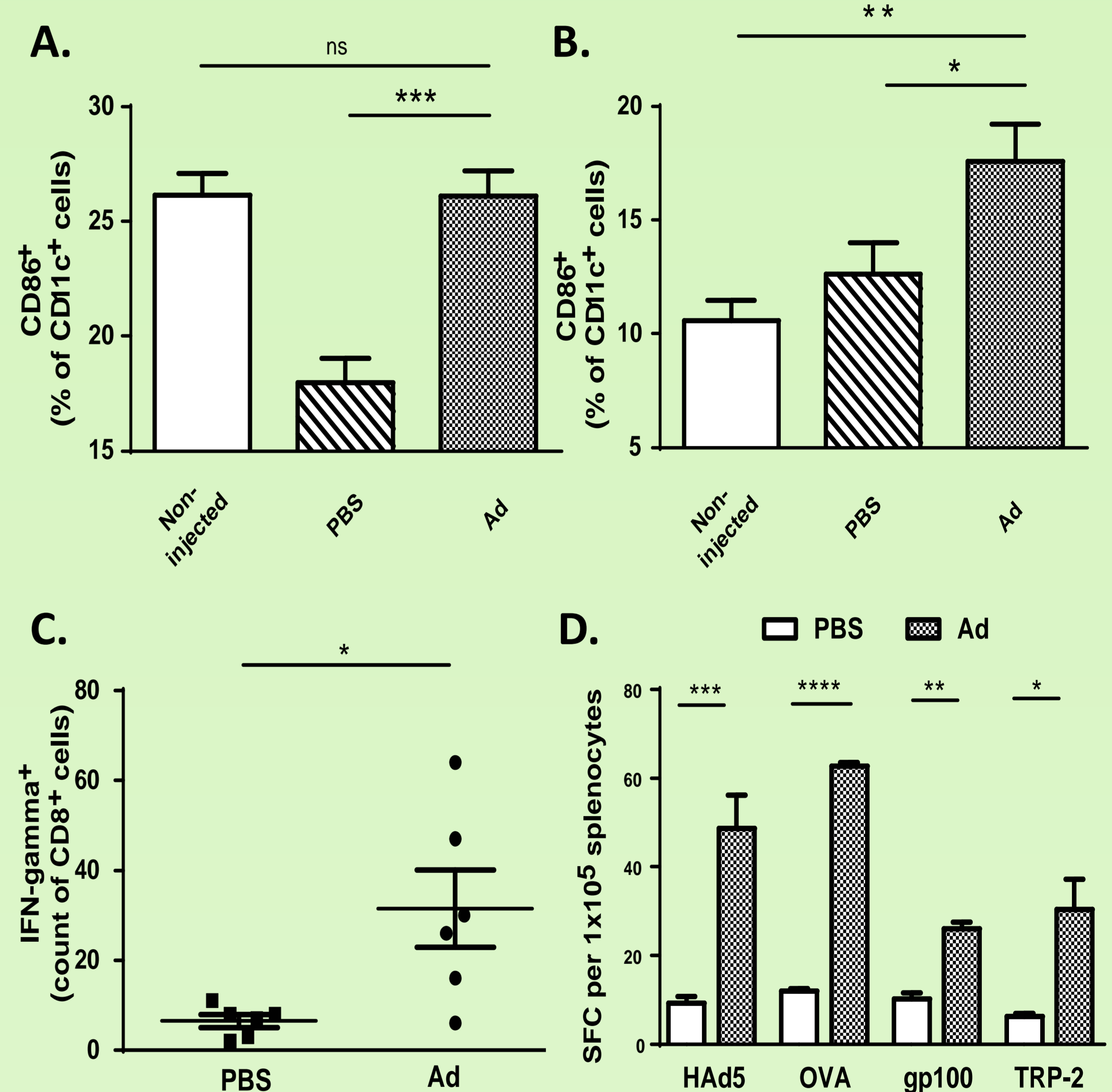


Figure 4 – Adenovirus combined with OT-I therapy augments the maturation of antigen-presenting cells (APCs) and activation of T-cells. (a-b) Expression of co-stimulatory signals (CD86) on APCs was increased in (a) tumor-draining lymph node and (b) tumor following combination therapy. (c) Virus-treated tumors were enriched for IFN- γ -expressing CD8+ TILs compared to control tumors. (d) T-cell mediated immune reactions to tumor epitopes were stronger in virus-treated mice compared to control mice.

Conclusions

- Treatment with adenovirus can overcome resistance of B16.OVA murine melanoma tumors to T-cell therapy by recruitment and stimulation of tumor-infiltrating immune cells, thus improving the efficacy of adoptive T-cell therapy in solid tumors
- Given the encouraging safety of oncolytic adenovirus in patients, this combination represents a highly feasible translation into clinical trials