

T-cell therapy –enabling oncolytic adenoviruses for the treatment of melanoma

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Background

Adoptive T cell therapies have shown promising results in clinical trials for solid tumor indications, but efficacy and safety are still suboptimal. We constructed non-replicating and replicating adenoviruses encoding the immunostimulatory cytokines Tumor Necrosis Factor alpha (TNFα) and Interleukin-2 (IL-2), and studied their ability to enhance adoptive T cell therapy. TCR transgenic OT-I T cells were used in mouse studies, while tumor-infiltrating lymphocytes (TIL) grown from syngeneic Syrian hamster tumors were used in studies with oncolytic adenoviruses, since this rodent species supports human adenovirus replication in its tissues. In addition, delivery of IL-2 into solid tumors from an adenoviral vector was compared directly with systemic IL-2 administration in the context of T cell transfer.

Results

Cytokine-armed adenovirus vectors control B16.OVA melanoma growth in combination with OT-I T cell transfer

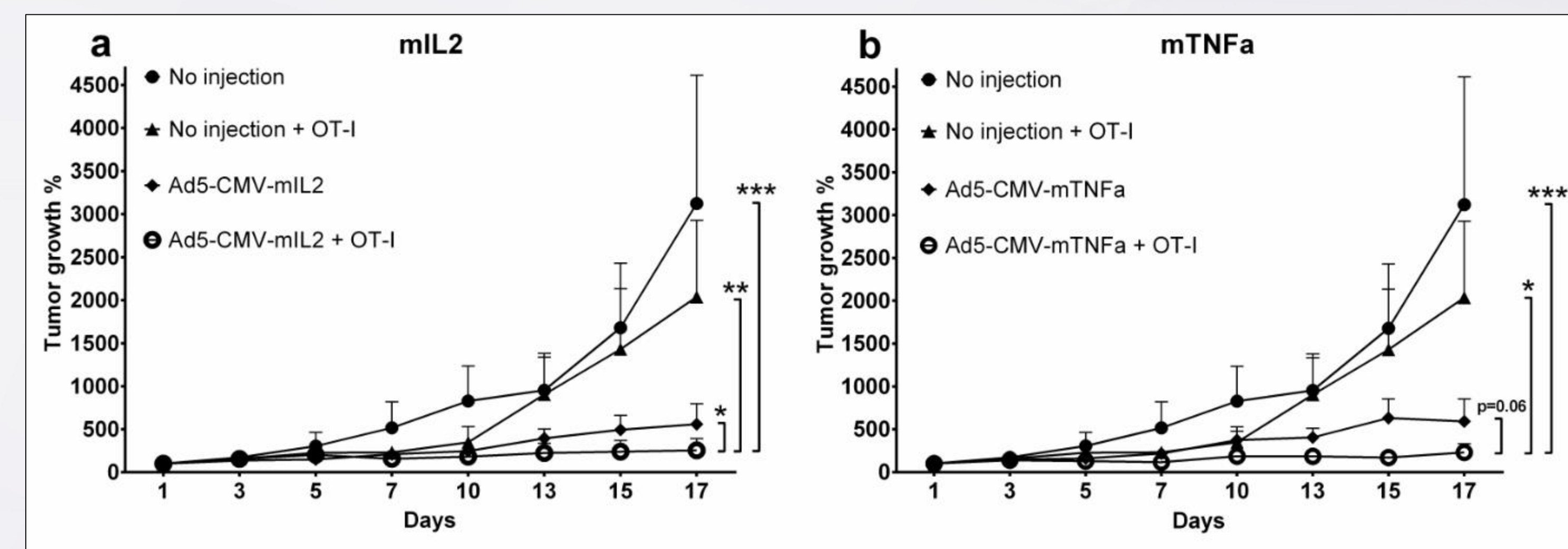


Figure 1. B16.OVA tumor-bearing C57BL/6 mice were administered 1.5×10^6 CD8-enriched OT-I T cells intraperitoneally on Day 1 with concurrent intratumoral injections of 1×10^9 viral particles of adenoviruses armed with (a) mIL2 and (b) mTNFα.

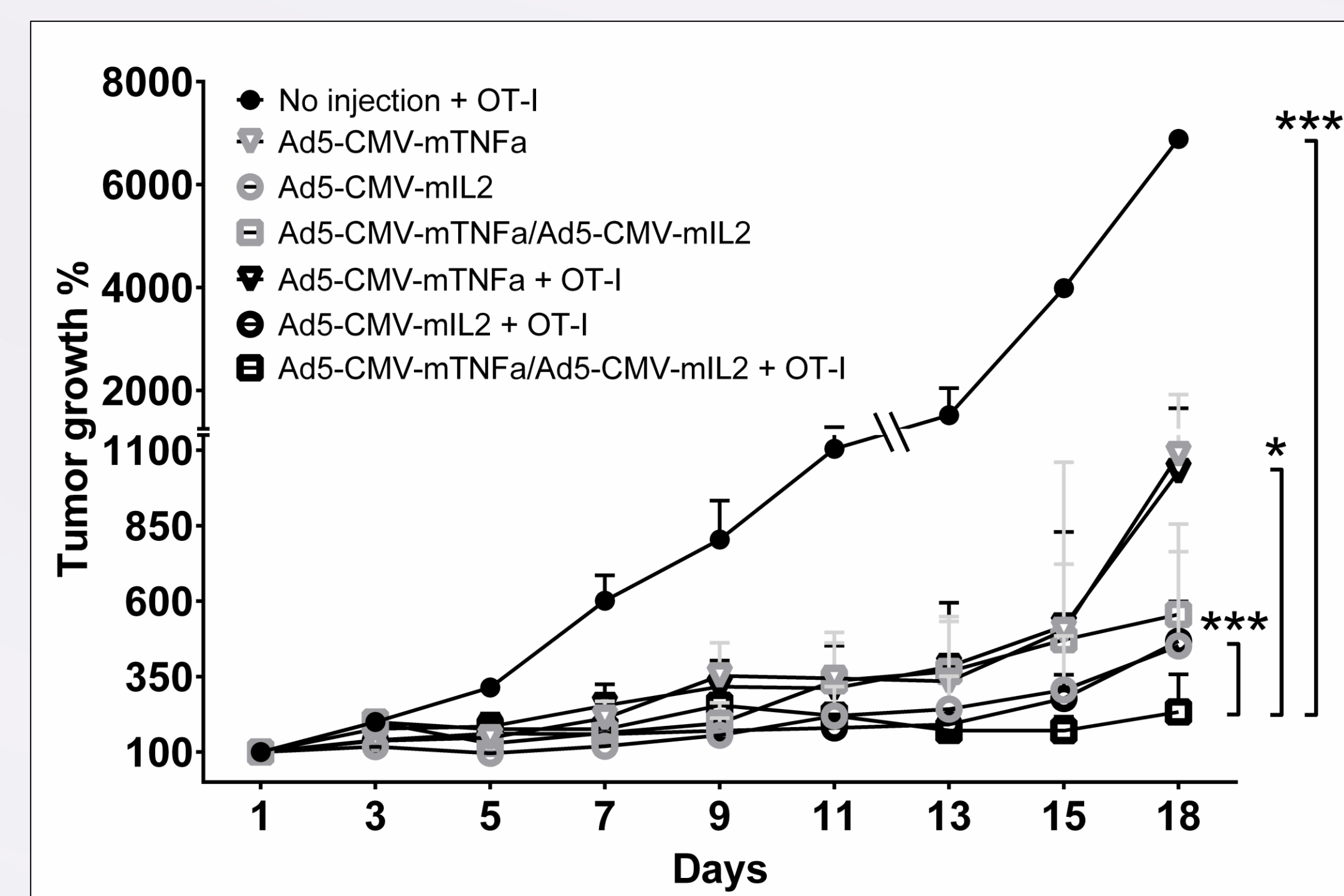


Figure 2. Adenoviruses coding for mTNFα and mIL2 were combined in a 1 to 1 ratio to treat B16.OVA tumors in combination with adoptive transfer of 1.5×10^6 CD8-enriched OT-I T cells.

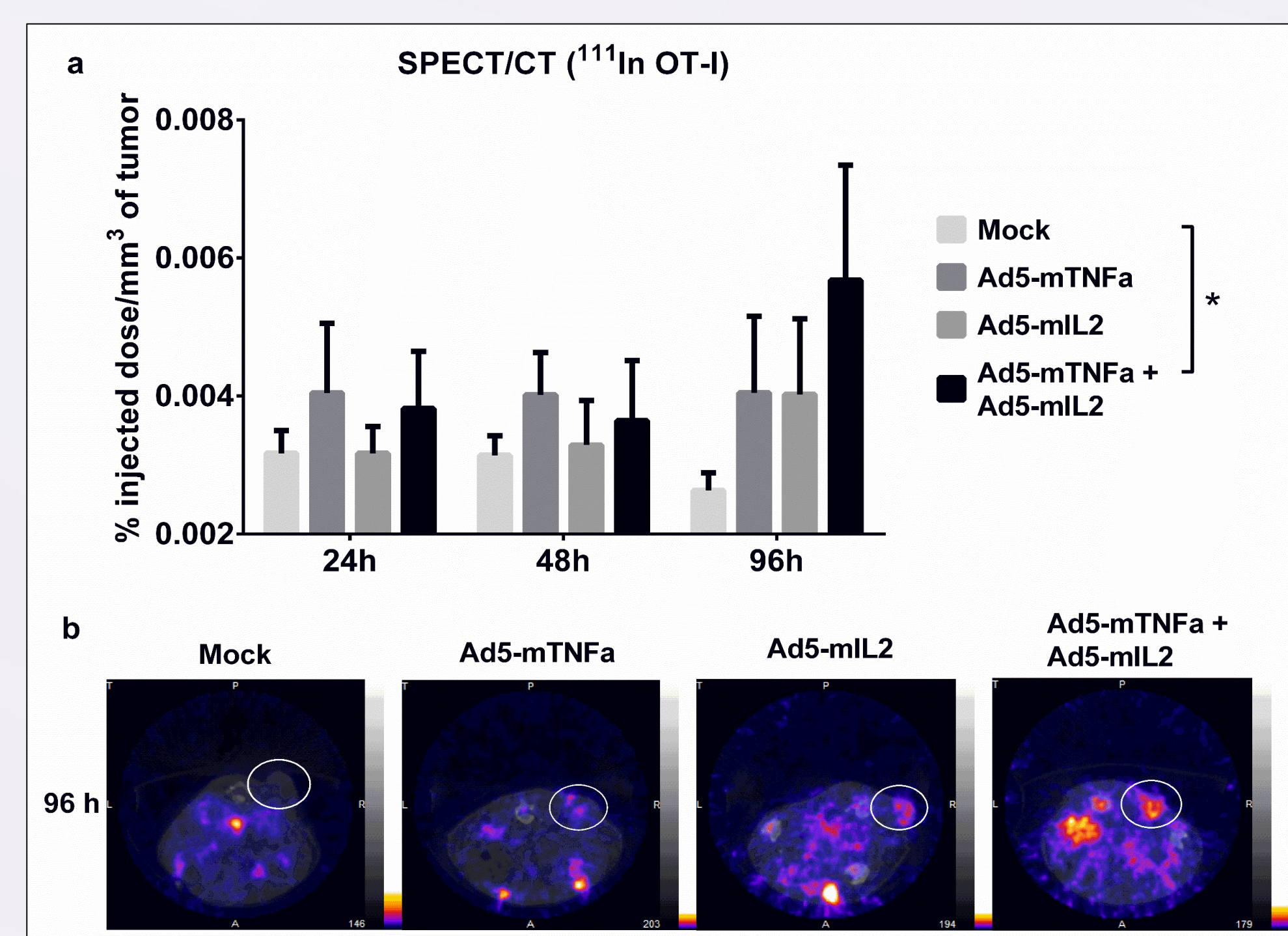


Figure 3. Tumor-bearing mice were administered 6×10^6 ¹¹¹In-oxine labeled OT-I T cells with simultaneous intratumoral injection of cytokine-coding adenoviruses. Mice were imaged on 24, 48, and 96 hours after treatment with a four-headed gamma camera with integrated CT system (nanoSPECT/CT), and results were calculated as percentage of the injected dose per tumor volume (a). Representative SPECT/CT images of 96-hour timepoint showing the location of subcutaneous tumors (b).

hTNFα and hIL-2 -coding oncolytic adenoviruses combined with adoptive TIL transfer induce complete tumor regression and protection from tumor rechallenge in Syrian hamsters

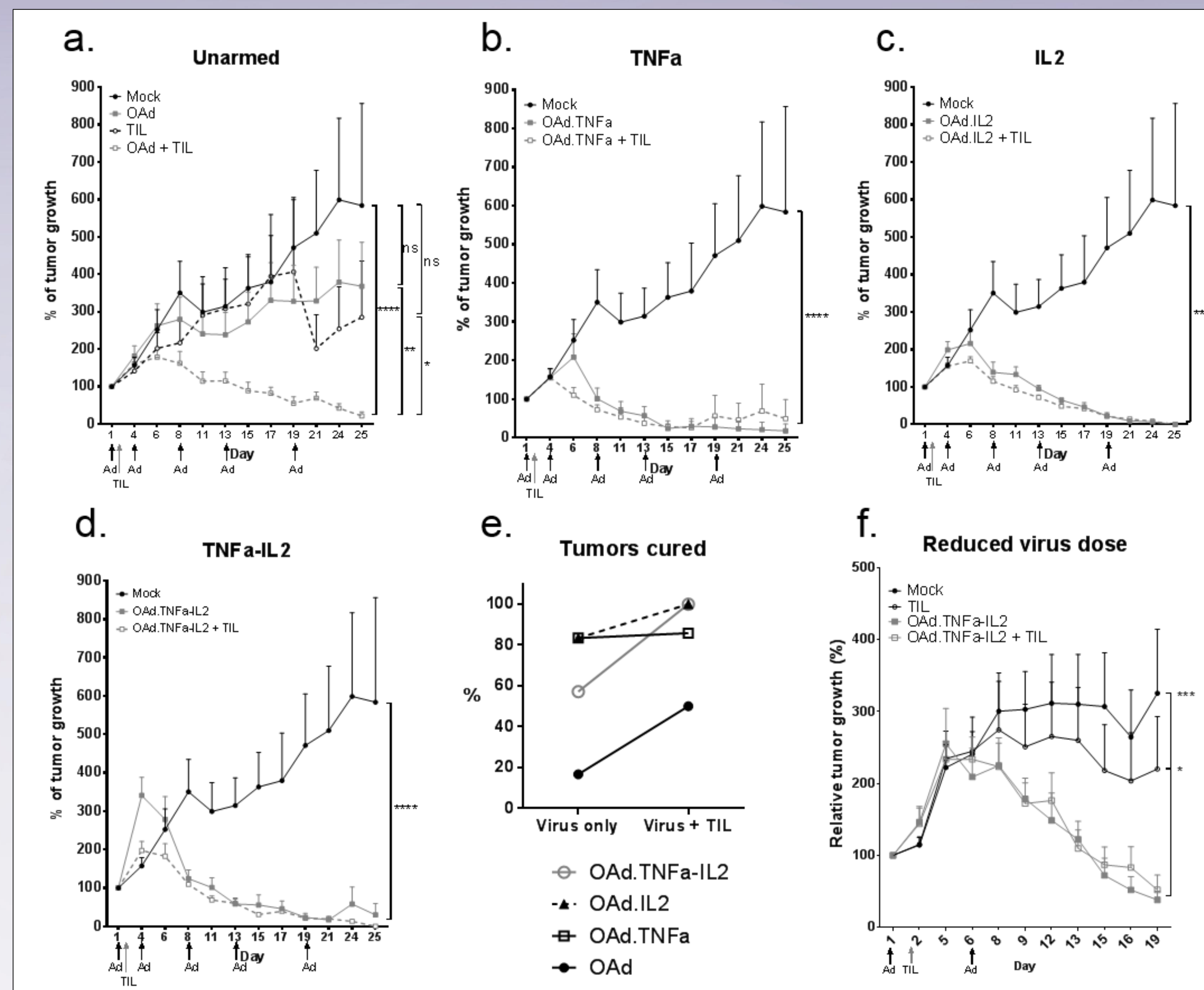


Figure 4. Syrian hamsters with established subcutaneous HapT1 tumors were treated intratumorally with oncolytic adenoviruses and/or syngeneic TIL (extracted from HapT1 tumors and expanded *ex vivo* in hIL-2 and Con A) (a-f).

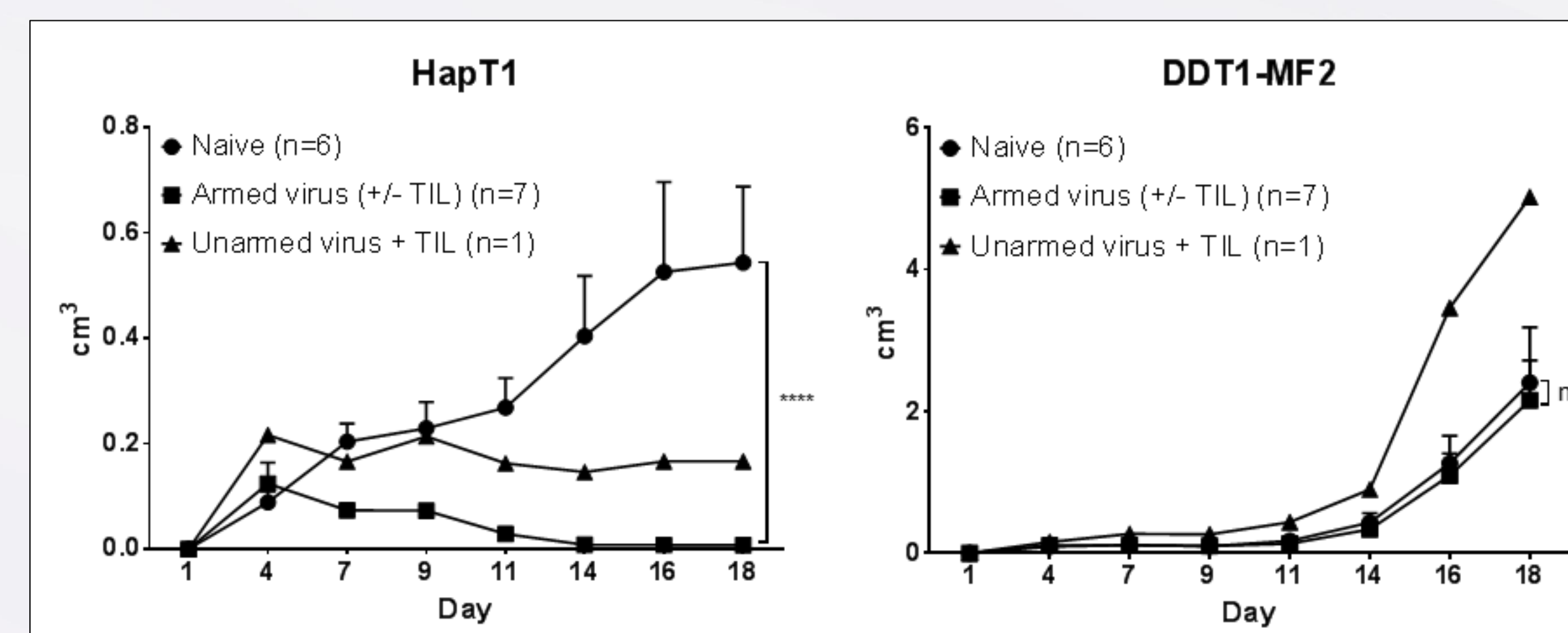


Figure 5. Previously cured hamsters were rested for 2 weeks before being subjected to tumor rechallenge with the same tumor (HapT1) or a different tumor (DDT1-MF2).

Conclusions

- Adenovirus-mediated TNFα and IL-2 delivery enhances adoptive TCR transgenic T cell therapy of murine melanoma by inducing T cell trafficking into tumors
- Oncolytic adenoviruses coding human TNFα and IL-2 synergize with adoptive TIL transfer against pancreatic cancer tumors in adenovirus-permissive Syrian hamsters
- Local IL-2 delivery is more effective than traditional systemic IL-2 administration

Adenovirus-mediated local IL-2 delivery is superior to systemic administration in the context of adoptive T cell therapy

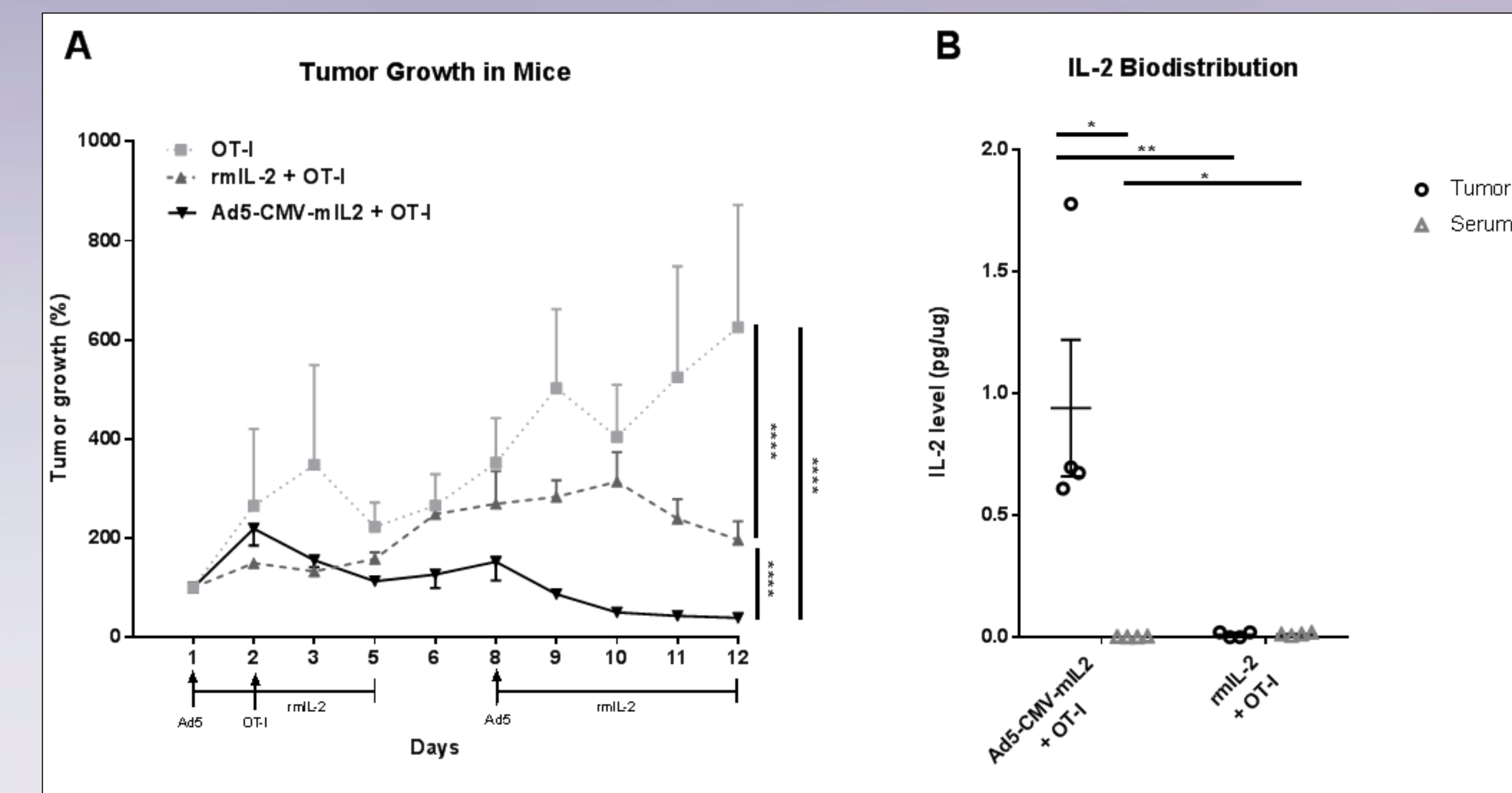


Figure 6. B16.OVA tumor-bearing mice were administered recombinant mIL-2 (rmIL-2) 5+5 days intraperitoneally (100 000 IU/injection) or Ad5-CMV-mIL2 (1×10^8 VP/tumor) on Days 1 and 8 with OT-I T cell transfer (a). Endpoint tumors and sera were assayed for IL2 and normalized to total protein content (b).

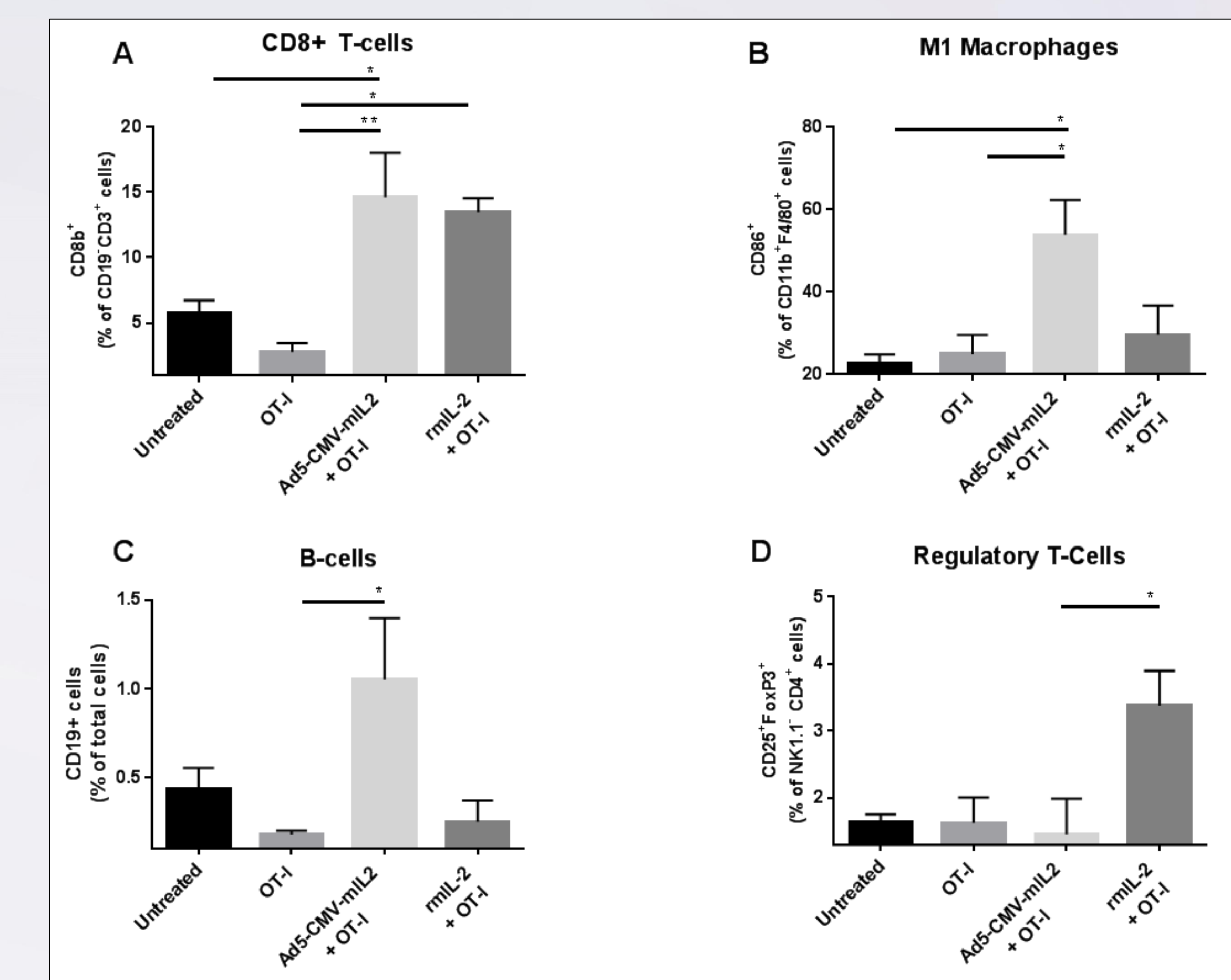


Figure 7. Immune cell subsets in B16.OVA tumors following local (intratumoral Ad5-CMV-mIL2) or systemic (intraperitoneal rmIL-2) IL-2 administration in combination with OT-I T cell transfer.