Systemic antitumor effects achieved with adoptive cell therapy-enabling armed oncolytic adenoviruses

Riikka Havunen[1,2], João M. Santos[1,2], Suvi Sorsa[1,2], Mikko Siurala[1,2], Victor Cervera-Carrascon[1,2], Akseli Hemminki[1,2,3]

[1]Cancer Gene Therapy Group, Department of Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland;
[2]TILT Biotherapeutics Ltd., Helsinki, Finland;
[3]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Background

- Oncolytic viruses induce systemic immunological effects with minor adverse events
- Systemic effects are achievable with local treatments
- Arming oncolytic viruses with interleukin-2 (IL-2) and tumor necrosis factor alpha (TNFa) enhance immunological antitumor effects and improve adoptive T cell therapies (Havunen et. al 2016; Siurala et. al 2016)
- Here we analyzed the systemic antitumor effects (the abscopal effect) induced by armed adenoviruses with regard to adoptive T cell therapy

The oncolytic virus is present in non-treated tumors but to minor extent in the organs.

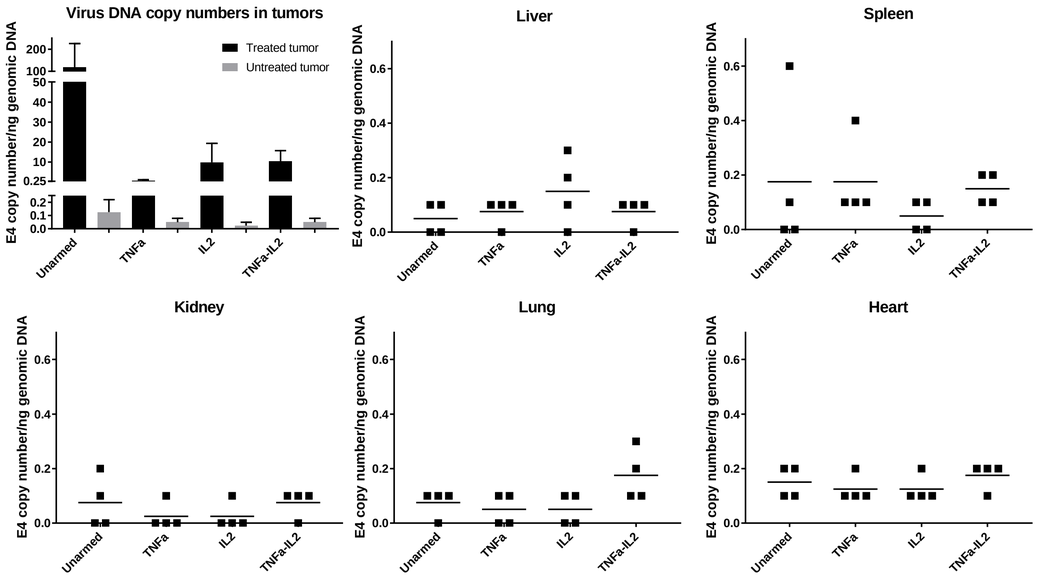

Figure 2 – The presence of viral genomes in tissues was detected with qPCR. The levels of viral DNA in the organs was in the lower limit of reliable detection.

The role of IL-2 and TNFa in antitumor efficacy is significant.

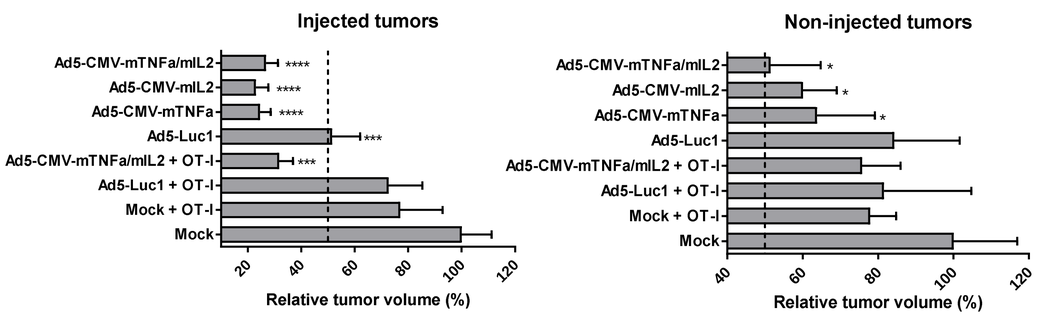

Figure 3 – Tumor growth of mouse B16-OVA melanoma was reduced in 8 days when injected once with armed but replication incompetent adenovirus (1*10^9 VP/tumor). The size of the non-injected tumors was also reduced to half with the cytokine combination indicating the important role of the transgenes in the system-wide antitumor efficacy.

Conclusions

- Local treatment with armed adenoviruses induces antitumor effects systemically (so called abscopal effect)
- Oncolytic adenovirus Ad5/3-E2F-d24 is able to travel to distant tumors but the spread to organs is minimal
- Arming the virus induces favorable changes in immune cell compartments in both injected and non-injected tumors

Treatment with oncolytic Ad5/3-E2F-d24-TNFa-IRES-IL2 reduces the growth of non-injected tumors.

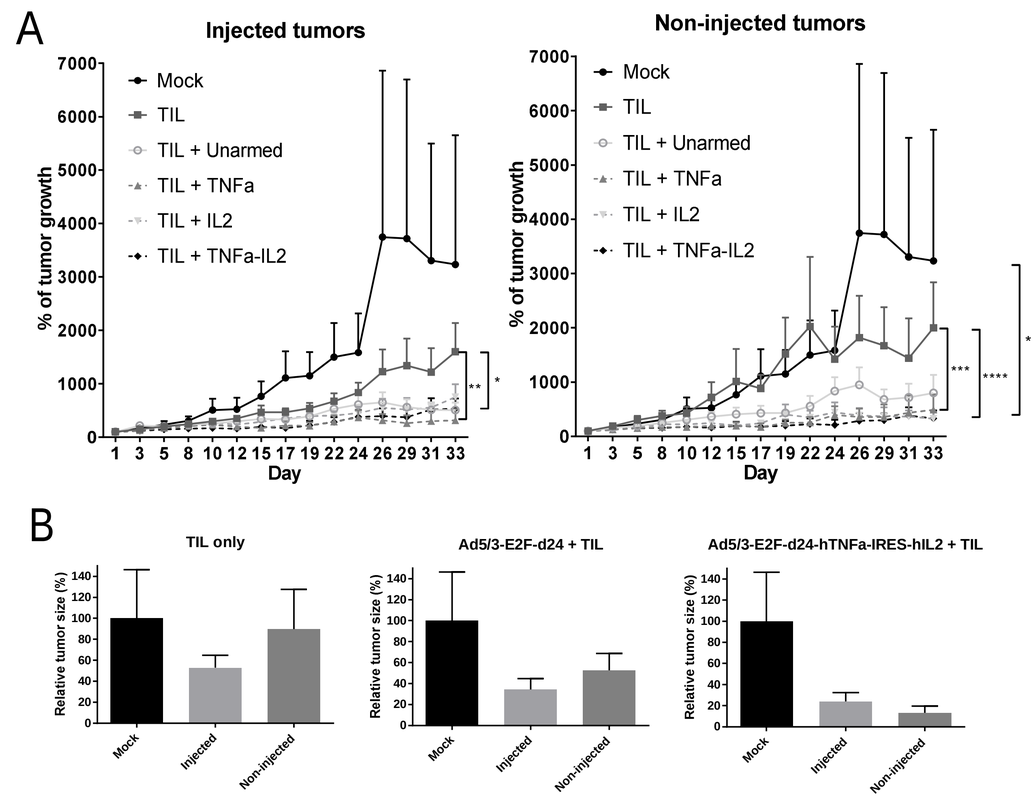

Figure 1 – Hamster pancreatic subcutaneous tumors were injected with 1*10^8 VP or left untreated. The growth of both injected and non-injected tumors was reduced. The results are shown over time (A) and comparing injected and non-injected tumor sizes on day 33 side by side (B).

Treatment with armed viruses affects the immune cell compartments in both injected and non-injected tumors.

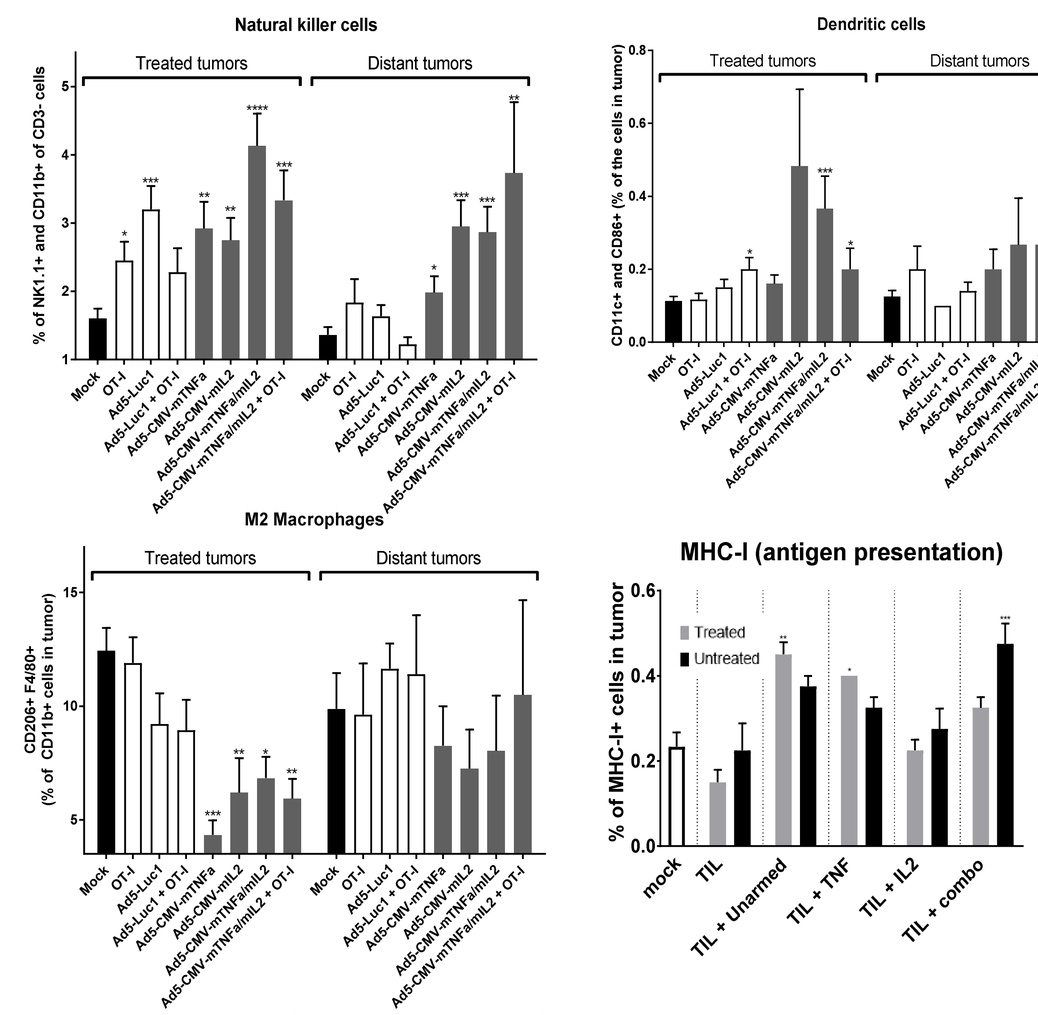

Figure 4 – Both injected and non-injected mouse tumors show increased numbers of natural killer and dendritic cells, whereas immunosuppressive M2 macrophage levels are lowered. The tumors were treated with replication incompetent adenoviruses armed with murine IL-2 or TNFa. In addition, oncolytic virus enhanced the antigen presentation of hamster tumor cells by upregulating MHC class I expression.

References

Havunen R, et. al: Oncolytic Adenoviruses Armed with Tumor Necrosis Factor Alpha and Interleukin-2 Enable Successful Adoptive Cell Therapy. Mol Ther Oncolytics 2016

Siurala M, et. Al Adenoviral Delivery of Tumor Necrosis Factor-α and Interleukin-2 Enables Successful Adoptive Cell Therapy of Immunosuppressive Melanoma. Mol Ther 2016