Enhancing adoptive T-cell therapy with oncolytic adenovirus encoding CD40-ligand

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Background

- T-cell therapy has resulted in remarkable recent clinical breakthroughs in the treatment of melanoma and CD19+ leukemia
- However, several immune evasion mechanisms have been shown to limit the efficacy of infiltrating T-cells, eventually leading to tumor tolerance.
- Oncolytic adenoviruses cause biological effects which could be utilized to reverse the immunosuppression
- Therefore, we constructed selectively oncolytic serotype 3 adenovirus (Ad3) featuring human telomerase (hTERT) promoter and human CD40L (Ad3-hTERT-CMV-hCD40L).
- To achieve optimal activation of the T-cell graft, we armed viruses with CD40L, which can trigger several immune mechanisms. One of these is a T-helper type 1 (Th1) response which leads to activation of cytotoxic T-cells and reduction of immune suppression.

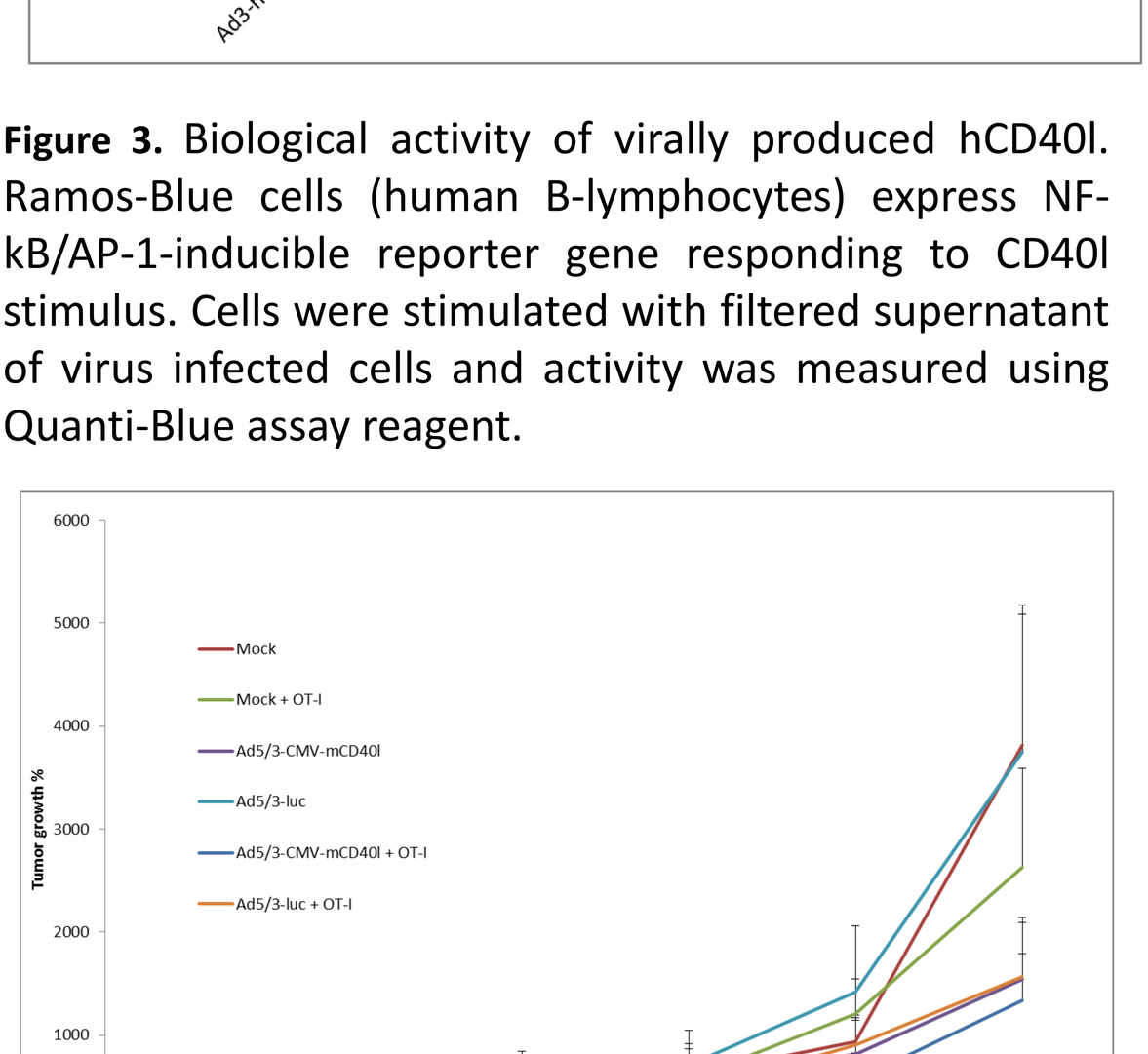

Figure 3. Biological activity of virally produced hCD40l. Ramos-Blue cells (human B-lymphocytes) express NF-kB/AP-1-inducible reporter gene responding to CD40l stimulus. Cells were stimulated with filtered supernatant of virus infected cells and activity was measured using Quanti-Blue assay reagent.

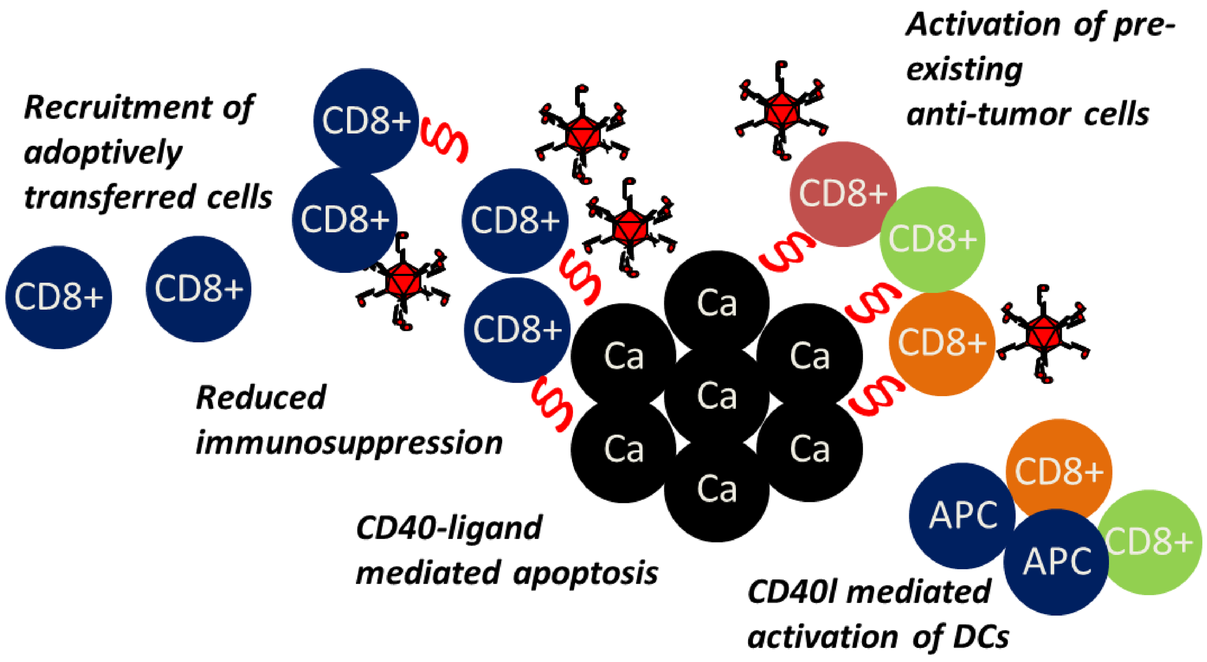

Figure 1. Proposed mechanism of action.

Results

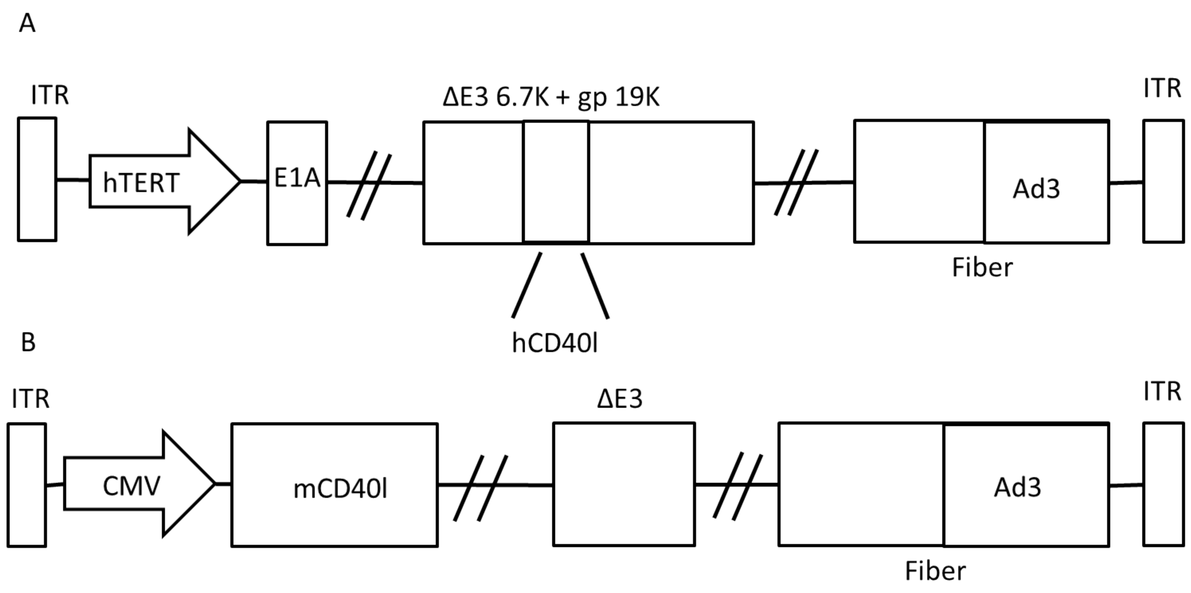

Figure 2. Schematic representation of virus construction A) Ad3-hTERT-E1A-hCD40l and B) Ad5/3-CMV-mCD40l

Figure 4. B16-OVA tumor-bearing C57 mice were treated intratumorally with 1 x 10e9 viral particles of armed adenovirus on days 1, 3, 7 and intraperitoneally with 1.5 x 10e6 CD8-enriched OT1 T-cells on day 1.

Conclusions

- We have constructed tumor targeted serotype 3 adenovirus encoding biologically functional CD40l (Ad3-hTERT-CMV-hCD40L)
- Promising signs of efficacy were seen in murine model in combination with adoptive transfer
- Further studies are needed to assess the efficacy of the human CD40l encoding virus as a single agent and as a combination with T-cell therapy