Combining cancer vaccines based on arenavirus vectors with 4-1BB (CD137) agonists enhances efficacy in a non-inflamed tumor model

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INTRODUCTION
Clinical efficacy of checkpoint inhibitor (CPI) immunotherapy is dependent on tumor-specific T cells. Consequently, one of the main reasons for the low efficacy of immunotherapy with CPIs in non-inflamed (cold) tumors is the lack of effective anti-tumor T cell responses.

Arenavirus-based cancer vaccines are ideally suited to induce tumor specific T cells but are hampered by the presence of the immunosuppressive factors within the tumor.2,3 Due to their capacity to promote activation, expansion, and effector function of activated T cells, we hypothesized that 4-1BB agonists could help to overcome intratumoral immune suppression by maintaining or even enhancing the functionality of vector-induced T cell responses.4

RESULTS
A single administration of vector and α4-1BB prolonged survival and increased the number of complete responders in the cold B16.F10 tumor model.

4-1BB agonists used for experiments presented here were an α4-1BB antibody (clone 1D12/1.3, rlg12) and the engineered arenavirus vectors artLCMV-GP70/α4-1BB and artLCMV-TRP2/α4-1BB, which are based on LCMV encoding the tumor-associated antigen GP70 or TRP2. artLCMV vectors are replication competent but stably attenuated by means of artificial genome organization.

α4-1BB positively affects number, cytotoxicity, proliferation and survival of GP70-specific CD8+ T cells in the tumor and tumor draining lymphnodes.

METHODS
artLCMV-GP70/ artLCMV-TRP2: the engineered arenavirus vector based on lymphocytic choriomeningitis virus (LCMV) encoding the tumor-associated antigens GP70 or TRP2. artLCMV vectors are replication competent but stably attenuated by means of artificial genome organization.

CONCLUSION
The engineered arenavirus platform induced strong tumor self-antigen-specific CD8+ T responses in the periphery and leading to efficient tumor control in a stringent mouse tumor.

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REFERENCES

AUTHOR DISCLOSURES
Hookipa Pharma. Judith Strauss, Diana Reckendorfer, Kimberly Pojar, Theresa Polzlaibauer, Mohamed Habbeddine, Maiilles Scheinost, Sarah Ahmad-Elber, Sarah Schmidt, Josipa Raguz, J. Christoph Lampert, Klaus K. Orlinger, and Henning Lauterbach
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A single administration of vector and α4-1BB prolonged survival and increased the number of complete responders in the ‘cold’ B16.F10 tumor model

Vector-encoded 4-1BB further enhances anti-tumor efficacy in the ‘cold’ B16.F10 model, but not in the immunogenic MC-38 model

Figure 1: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).

Figure 2: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).

Figure 3: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).

Figure 4: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).

Figure 5: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).

Figure 6: The anti-tumor effect of artLCMV-TRP2 or artLCMV-GP70 was further substantiated by a single injection of agonistic α4-1BB antibodies in the B16.F10 model. A single injection of α4-1BB pasted to artLCMV-TRP2 or artLCMV-GP70 led to enhanced tumor infiltration and decreased tumor size as compared to the vector control groups. STATISTICAL ANALYSIS: Data were analyzed by two-way ANOVA with Dunnett’s multiple comparison test. *p < 0.05 (n = 5-8/group).