Sustained delivery of low-dose anti-CTLA-4 by genetically engineered encapsulated cells drives tumor response and prolongs survival in a colorectal cancer model

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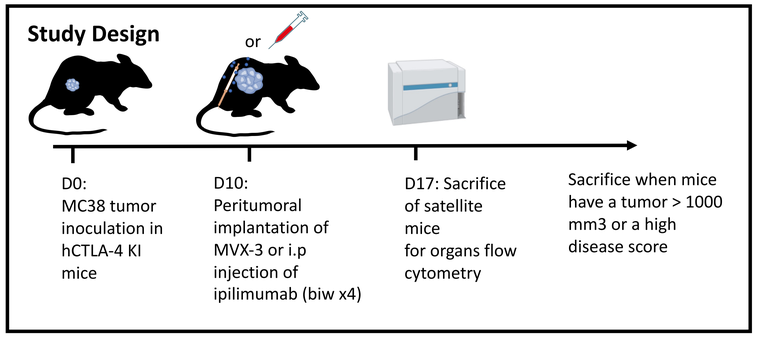
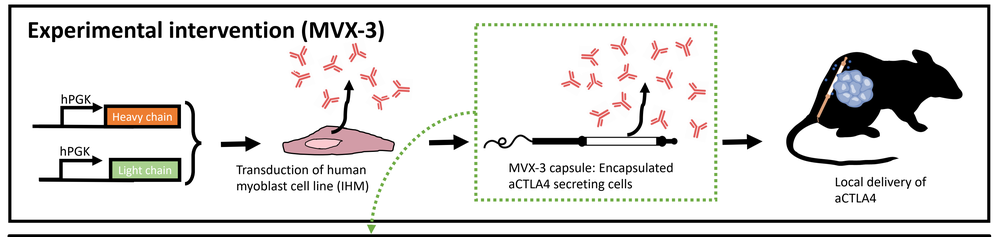
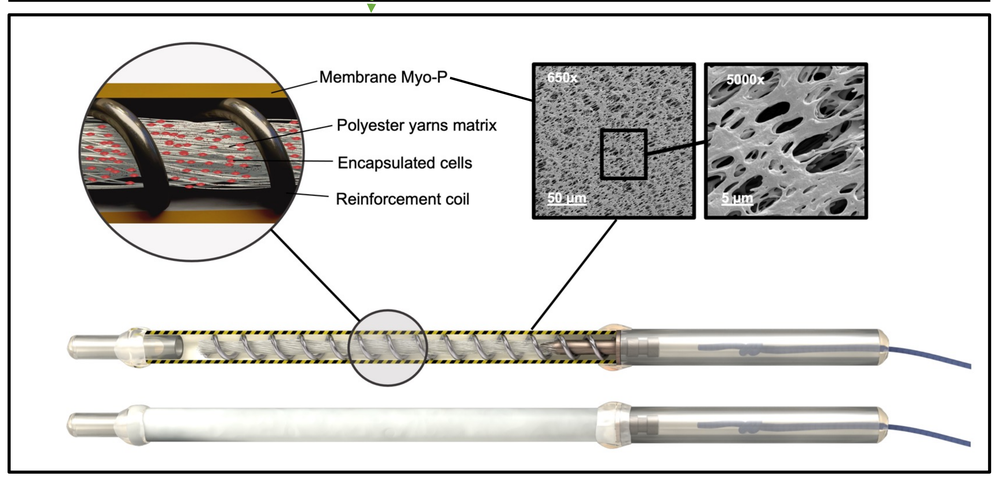
ABSTRACT

Systemic therapy with CTLA-4 blocking antibody (aCTLA4) restores endogenous antitumor immunity and induces remarkable long-term clinical benefits in patients with melanoma. Yet immune-related side effects remain a major hurdle to extend its label to many more types of cancer. Intra- and peritumoral administration of aCTLA4 has recently emerged to optimize its dose/efficacy ratio while preventing its on-target, off-tumor systemic toxicities. Sustained delivery of low-dose aCTLA4 by genetically engineered encapsulated cells (MVX-3) could offer a promising option for cancer treatment addressing the shortcomings of systemic therapy.

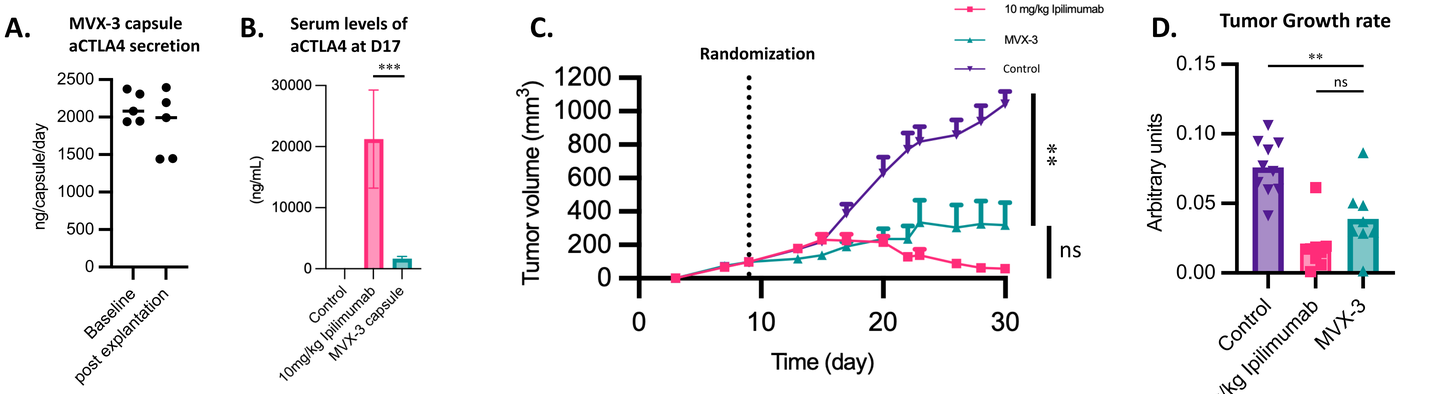
MATERIALS AND METHODS

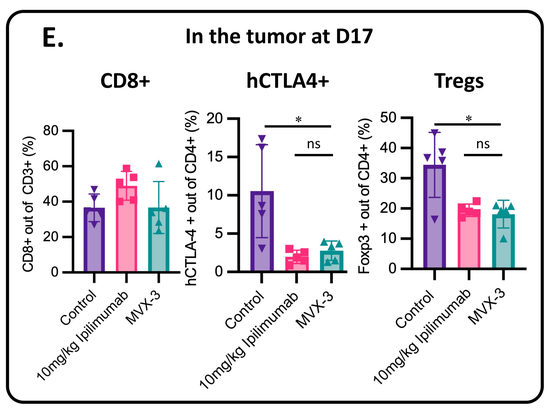


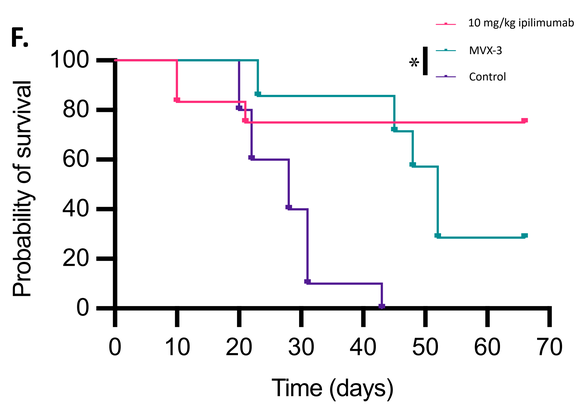




RESULTS







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	Control	10mg/kg Ipilimumab	MVX-3
Partial inhibition	0%	0%	57%
Complete inhibition	0%	75%	29%
Toxic death	0%	25%	0%

A. aCTLA4 secretion rate from MVX-3 before and after 7 days in vivo. B. aCTLA4 was detected in the serum at day 17 in both the MVX-3 and the ipilimumab (10mg/kg) treated conditions. C. Mean tumor volume per group over time. D. Average tumor growth rate from day 1 after tumor engraftment until end of the study determined by the method described by Hather et al. (2014). E. Proportion of Intratumoral CD8+ cells, Tregs (Foxp3+) and Human CTLA4+ cells at day 17. F. Kaplan-Meier curves showing the probability of survival over time. G. Response rate and toxic death rate per group. Results are expressed as mean ± standard deviation (SD). Statistical significance was assessed by Student's t test for comparison between two groups or by Log-rank (Mantel-Cox) for the Kaplan-Meier curve. Statistical significance between groups is presented as follows: *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001. Data analyses were performed using the software package GraphPad Prism 9 (GraphPad Software).

CONCLUSIONS

- Peritumoral administration of MVX-3 induced durable complete tumor rejection (2/7) and tumor growth control (4/7) when administered at doses 1'000 times lower than i.p ipilimumab, whereas rapid tumor growth without any tumor rejection were observed in negative control mice.
- I.p. ipilimumab induced durable complete tumor rejection (9/12), while treatment related toxicities upon dosing led to premature mice termination (3/12).
- MVX-3 was found as equally effective as i.p. ipilimumab in decreasing the proportion of CTLA4+ helper and regulatory T cells in the tumor at Day 7 post treatment.
- Survival was also improved by MVX-3 compared to control.

These findings suggest that a sustained, controlled delivery of low-dose aCTLA4 by genetically engineered encapsulated cells could achieve similar therapeutic benefit as the systemic therapy, without the commonly associated severe toxicities. The safety and biological efficacy profile of MVX-3 encourage further preclinical and clinical explorations.

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