A novel viral immunotherapeutic targeting the CD47/SIRPα axis demonstrates potent anti-tumor effects
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Background
- The CD47/SIRPα axis mediates a “don’t eat me” signal exploited by tumor cells to escape macrophage-mediated immune surveillance (Fig. 1).
- Anti-CD47 therapies have shown promising clinical results in solid and hematological malignancies; however, efficacy is hindered by systemic toxicity.
- Dual targeting of CD47/SIRPα and PD-1/PD-L1 axes has enhanced efficacy in preclinical studies.
- We hypothesized that local delivery of a therapeutic, able to interfere with the CD47/SIRPα axis within an oncologic viral chassis, would induce high payload expression paired with oncolytic activity and low systemic exposure, ultimately resulting in improved tumor control.

Distinct cellular responses to Alpha series vector infection are observed
Alpha-201 is a viral chassis engineered for enhanced immunostimulatory activity coupled with sustained payload expression and regulated oncolysis. Cellular responses to viral chassis infection were profiled by RNAseq analysis (Fig. 2). Gene Set Enrichment Analysis (GSEA) demonstrated that Alpha series vector infection induces stronger immune responses compared with a Control Vector (Fig. 3).

Alpha-201 viral chassis regulates pathways associated with responses to ICI
A striking, positive correlation between hallmark GSEA pathways associated with immune checkpoint inhibitor (ICI) response and those regulated by Alpha-201 infection was observed, suggesting that Alpha-201 can orchestrate changes in the tumor microenvironment supportive of ICI response (Fig. 4). The Alpha-201 viral chassis also had a modest anti-tumor effect itself in a syngeneic tumor model similar to that achieved with anti-PD-1 antibody therapy (Fig. 5). Given the interplay between CD47/SIRPα and PD-1/PD-L1 axes, this supported the use of Alpha-201 as the viral chassis for a viral immunotherapeutic targeting the CD47/SIRPα axis.

Conclusions
- Alpha-201-macro1 disrupts binding of SIRPα to CD47, enhances macrophage phagocytosis ex vivo, and exerts anti-tumor efficacy in vivo, effects which exceed those of anti-CD47 antibody therapy.
- Further in vivo studies of Alpha-201-macro1 and modified, multi-payload versions of this vector, in combination with immune checkpoint inhibitors, are ongoing.

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Figure 1: Activation of innate immune surveillance by interfering with the CD47/SIRPα pathway, image was partly generated using Servier Medical Art [1].

Figure 6: Conditioned media from Alpha-201-macro1 infected cells selectively disrupted binding of SIRPα to CD47 in vitro in a payload- (and not vector-) dependent manner (Fig. 6).

Figure 7: Effect of conditioned media (CM) from Alpha-201-macro1 infected cells on phagocytosis of M1 macrophages. CM was harvested 48 h post-infection. CM was tested for its ability to disrupt the interaction between SIRPα and CD47 in vitro, and results were compared to an anti-CD47 antibody.

Figure 8: A549 in vivo tumor study design. A549 cells were injected into the rear flank of Balb/c nude mice. Treatment (3x10⁴ PFU Alpha-201 vectors, i.t. or 10 mg/kg, i.p. antibodies) began when tumors reached ~100 mm³. N=8 mice per group. Figure 8A: Isotype control, Figure 8B: A549 cells infected with Alpha-201-GFP, Figure 8C: A549 cells infected with Alpha-201-macrophage-anti CD47 antibody, Figure 8D: A549 cells infected with Alpha-201-macrophage-anti CD47 antibody.

Figure 9: Tumor growth curves for Alpha-201-macro1 and anti-CD47 antibody treated mice. Figure 9A: Control, Figure 9B: Alpha-201-GFP, Figure 9C: Alpha-201-macro1, Figure 9D: IgG, Anti-CD47 Ab. *p<0.05.

Figure 10: Immunohistochemical assessment of macrophage infiltration of tumors. A549 tumor sections collected at day 12 were stained with F4/80 to visualize intratumoral macrophages. 10X magnification.

References
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