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A NOVEL VIRAL IMMUNOTHERAPEUTIC TARGETING THE CD47/SIRP α AXIS DEMONSTRATES POTENT ANTI-TUMOR EFFECTS

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Background The CD47/SIRP α axis mediates a 'don't eat me' signal exploited by tumor cells to escape macrophage-mediated immune surveillance. Anti-CD47 therapies have shown promising clinical results in solid and hematological malignancies; however, efficacy is hindered by systemic toxicity. We hypothesized that local delivery of a therapeutic, able to interfere with the CD47/SIRP α axis within an oncolytic viral chassis, would induce high payload expression paired with oncolytic activity and low systemic exposure, ultimately resulting in improved tumor control.

Methods Alpha-201-macro1 is a first-in-class, replication-defective oncolytic virus encoding a protein payload able to interfere with the CD47/SIRP α axis. Disruption of the interaction between CD47 and SIRP α was confirmed in vitro using a plate-based CD47 displacement assay. Bioactivity was tested in an ex vivo phagocytosis assay using Raji cells and differentiated M1 macrophages treated with conditioned medium obtained from tumor cells infected with Alpha-201-macro1 or control vectors. Phagocytosis was measured by flow cytometry. Anti-tumor efficacy of Alpha-201-macro1, delivered intratumorally at 3×10^7 PFU, was assessed in A549 tumor-bearing BALB/c-Nude mice (N=8 per group) and compared to anti-CD47 antibody therapy (clone: B6H12; intraperitoneal, 10 mg/kg). Treatments were administered on day 1, 4, 7, 10, and 13 after randomization. All values are reported as mean \pm SEM.

Results Conditioned media from Alpha-201-macro1 infected cells selectively disrupted binding of SIRP α to CD47 in a payload- (and not vector-) dependent manner. Additionally, conditioned medium from Alpha-201-macro1 infected cells resulted in a dose-dependent increase in macrophage-mediated target cell phagocytosis (3 PFU/cell: $4.16 \pm 0.17\%$, 10 PFU/cell: $17.8 \pm 2.55\%$) that was greater than the effect of the anti-CD47 antibody ($6.86 \pm 1.68\%$, $p=0.017$ compared to 10 PFU/cell Alpha-201-macro1). Pretreatment with conditioned medium from Alpha-201 vectors encoding irrelevant payloads did not significantly affect macrophage phagocytosis, demonstrating the specificity of the effect of the therapeutic payload. In vivo, treatment with Alpha-201-macro1 resulted in tumor growth inhibition compared to the vehicle control group ($217.1 \pm 17.4 \text{ mm}^3$ vs. $312.7 \pm 30.5 \text{ mm}^3$, $p=0.023$). This effect was dependent on payload expression, as a control vector did not show statistically significant tumor activity. There was a trend towards greater efficacy with local Alpha-201-macro1 delivery compared to systemic anti-CD47 antibody ($217.1 \pm 17.4 \text{ mm}^3$ vs. $248.7 \pm 27.9 \text{ mm}^3$, $p=0.38$).

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

Ethics Approval All procedures involving the care and use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC).

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