AN INDUCED PLURIPOTENT STEM CELL (IPSC) VACCINE DECREASES TUMOR GROWTH AND IMPROVES SURVIVAL IN A THERAPEUTIC MOUSE MODEL OF COLON CANCER

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Background Extensive data on gene expression, metabolic state and glycosylation of cancer cells suggest that cancer represents a reversion of adult cells to an embryonic state and that induced pluripotent stem cells (iPSC) are good surrogates for this state. In contrast to cancer cells, iPSC have never undergone immunoediting and therefore present hundreds of onco-fetal antigens in their native conformations. In this study, we administered syngeneic iPSC together with the Toll-like receptor (TLR) 9 agonist CpG1826 in a therapeutic mouse model of colon cancer with and without checkpoint inhibition.

Methods C57BL/6 mice (n=10) were injected with 5x10^5 MC-38 murine colon adenocarcinoma cells s.c. One week later, mice received a course of 4 weekly injections with 10x10^6 irradiated (60Gy) iPSC admixed with 1nmol CpG1826, or PBS or CpG alone as controls. Some groups also received anti-PD-1 (200 µg, 2X/week, i.p.) for 4 weeks. Tumor growth and survival were monitored for 108 days post tumor injection. Mice were euthanized when tumor volume reached 2000 mm³. Serum IgG binding to iPSC and MC-38 was measured by flow cytometry 1 week after the last immunization in all 60 mice and IFN-gamma ELISPOTs were determined after in vitro challenge of splenocytes with iPSC and MC-38 lysates in 10 surviving mice at the end of the study.

Results Treatment of mice with anti-PD-1, anti-PD-1+CpG, iPSC+CpG and iPSC+CpG+anti-PD-1 significantly increased median survival in comparison to CpG alone (Gehan-Breslow-Wilcoxon test) by ~50% (table 1). Therapeutic vaccination with iPSC+CpG was as effective as treatment with anti-PD-1, and anti-PD-1+CpG. Similar data were obtained for tumor growth; iPSC+CpG vaccination was as effective in reducing tumor growth as anti-PD-1. Only immunization with iPSC+CpG and iPSC+CpG+anti-PD-1 induced a significant increase in serum IgG binding to iPSC and MC-38; IFN-gamma spots after in vitro challenge with iPSC and MC-38 lysates were only detectable in mice that had been injected with iPSC.

Conclusions Irradiated syngeneic iPSC admixed with TLR9 agonist CpG1826 with or without combination with checkpoint inhibition induced T cell and antibody responses to iPSC that cross-reacted with MC-38. The iPSC vaccine was effective in delaying and decreasing tumor growth and in increasing median survival in a therapeutic model of colon cancer comparable to checkpoint inhibition.

Ethics Approval The study was approved by Valley Bio Services’ Institutional Animal Care and Use Committee; approval number VBS1002.