774 AN INDUCED PLURIPOTENT STEM CELL (IPSC) VACCINE IS HIGHLY IMMUNOGENIC AND REDUCES LUNG METASTASES IN A MOUSE MODEL OF MELANOMA

Matthias Hundt*, Peter Bove, Ivan Hernandez, Michelle Li, Lucia Beviglia, Pratima Kundu, Babacar Ndoye, Nigel Kooreman, Stephen Wolpe, Lynne Bui. *Khloris Biosciences, Mountain View, CA, United States*

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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) model this state. In contrast to cancer cells, iPSC have never undergone immunoediting and therefore present hundreds of oncofetal antigens in their native conformations. In this study, we administered a vaccine comprising syngeneic iPSC together with the Toll-like receptor (TLR) 9 agonist CpG1826 as an adjuvant and assessed its immunogenicity and preclinical efficacy in a mouse model of melanoma lung metastases with and without checkpoint inhibition.

Methods C57BL/6 mice were immunized with 2 × 10^6 irradiated (60Gy) iPSC admixed with 500pmol CpG, or with PBS or CpG alone as controls. Four immunizations were administered subcutaneously one week apart. Mice were challenged with 1x10^5 B16F10 murine melanoma cells intravenously one week after the second immunization. After tumor cell injection some groups were also treated with anti-PD-L1 (200µg, 2X/week, i.p.). All mice were euthanized 19 days after intravenously B16F10 injection and lung metastases were counted in a blinded fashion. Cellular and humoral immune responses were measured by IFN-gamma ELISpot, serum IgG binding to iPSC and B16F10 and flow cytometric analysis of splenocytes.

Results Treatment of mice with anti-PD-L1+CpG, iPSC+CpG and iPSC+CpG+anti-PD-L1 significantly reduced the number of lung metastases in comparison to CpG (One-way ANOVA with Dunnett's multiple comparisons test) (table 1). Immunization with iPSC+CpG was as effective as treatment with anti-PD-L1+CpG. No synergism of iPSC+CpG with anti-PD-L1 was detectable. Only immunization with iPSC+CpG induced a significant increase in IFN-gamma spots after in vitro challenge with iPSC and B16F10 lysates in comparison to CpG. Comparable results were obtained for serum IgG binding to iPSC and B16F10. Percentage of regulatory T cells in the spleen was significantly reduced in iPSC+CpG and iPSC +CpG+anti-PD-L1 in comparison to CpG. Similar results were obtained in a second independent study.

Abstract 774 Table 1 Number of lung metastases

Treatment	PBS	CpG	αPD-L1	CpG+αPD-L1	iPSC+CpG	iPSC+CpG+αPD-L1
Median	66.0	69.5	49.0	24.0	21.5	26.0
Mean	62.4	64.3	43.8	33.7	28.4	31.9
SEM	8.5	7.7	11.6	7.7	5.6	6.4
N	5	12	4	9	10	10

Conclusions Irradiated syngeneic iPSC admixed with TLR9 agonist CpG1826 in combination with or without checkpoint blockade induced T cell and antibody responses to iPSC and B16F10 thereby reduced the number of melanoma lung metastases in mice. These results warrant further investigation of autologous iPSC vaccines in clinical trials.

Ethics Approval The studies were approved by Explora BioLabs' Animal Care and Use Committee; approval number EB17-010-118.