Preclinical studies support therapeutic application of the leukemic cell-based cancer relapse vaccine DCP-001 in ovarian cancer

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Introduction

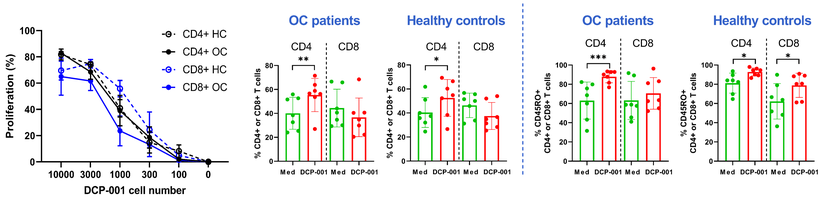
Ovarian cancer (OC) is the gynecological malignancy with the highest mortality due to the late diagnosis of disease and a high rate of relapse following initial therapy. Immunotherapy in combination with standard treatment modalities has emerged as an encouraging treatment approach to surmount this unmet medical need.

DCP-001 is a cancer relapse vaccine derived from the DCOne human leukemic cell line and is currently progressing through clinical trials in hematological malignancies. During manufacturing, DCOne cells are shifted towards a mature dendritic cell phenotype, rendering the cells highly immunogenic and providing the basis for DCP-001, which is administered as an intradermal vaccine. DCOne cells express multiple common tumor associated antigens (TAA) such as WT-1, RHAMM, PRAME and MUC-1, which have been documented as potential target antigens in ovarian cancer. This observation suggests that DCP-001 vaccination may also have an anti-tumor effect in OC. To support this hypothesis, the capacity of DCP-001 to induce immune responses against OC was studied in human peripheral blood mononuclear cells (PBMC) and a humanized mouse model for OC.

Methods

The effect of DCP-001 on T cells from OC patients or healthy controls was evaluated after a 3 week culture of peripheral blood mononuclear cells (PBMC) with or without DCP-001. Cytotoxic activity was analyzed by specific IFNγ production and CD107a expression when these cells were subsequently cultured with OC cell lines SKOV3 or OV90. The effect of DCP-001 vaccination *in vivo* was evaluated in humanized NCG mouse subcutaneously engrafted with SKOV3 OC cells. Mice received intra-peritoneal (i.p.) vaccination with DCP-001 prior to SKOV3 engraftment and tumor size was measured to evaluate the efficacy of DCP-001.

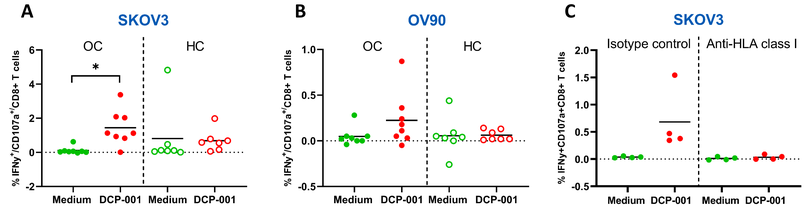
DCP-001 stimulates T cell proliferation and increases memory CD4⁺ T cells in OC patients' PBMC



CFSE-labelled PBMC from 3 healthy controls (HC) or 3 ovarian cancer patients (OC) were co-cultured for 6 days with increasing numbers of DCP-001 cells. Mean percentage proliferation (± SD) of CD4⁺ and CD8⁺ T cells was measured by flow cytometry

PBMC from ovarian cancer patients (n=7) or healthy controls (n=7) were co-cultured with medium or DCP-001 for 21 days and percentages CD4⁺ or CD8⁺ T cells (left) or CD45RO⁺/CD4⁺ or CD45RO⁺/CD8⁺ T cells (right) were measured by flow cytometry. Data from 4 independent experiments are shown; each bar represents the mean ± SD. * = p< 0.05; ** = p<0.01, *** = p < 0.005 by repeated measures 1-way ANOVA

DCP-001 induces HLA-class I-dependent CTL towards ovarian cancer cell lines



PBMC from ovarian cancer patients (OC; n=8) or healthy controls (HC; n=7) were co-cultured with medium or DCP-001 for 21 days. Cytotoxicity was measured by incubation of these PBMCs with cells from ovarian cancer cell lines SKOV3 (A) or OV90 (B) (T:E ratio 1:10) in the presence of anti-CD107a antibody (marker for cytotoxicity) for ~6 hours. Hereafter cells were stained for T cell surface markers followed by an intracellular IFNγ staining and measured by flow cytometry. Data from 5 independent experiments are shown; each dot represents the mean results obtained using PBMC from one individual; the horizontal bar represents the mean of all donors. The same procedure was repeated in the presence of either anti-HLA class I antibody or isotype control during the cytotoxicity test with SKOV3 for PBMC from 4 ovarian cancer patients (C). * = p < 0.05 by repeated measures 1-way ANOVA

Higher frequencies of DCP-001-induced CTL from OC patients' PBMC

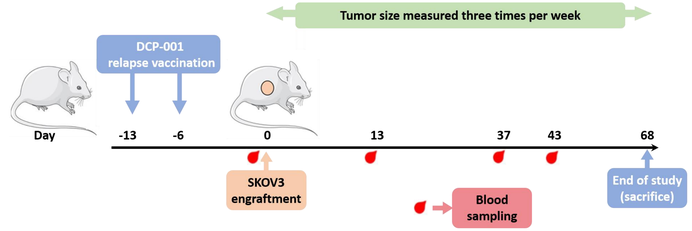
Response Score[1]	SKOV3		OV90	
	OC patients[2]	Healthy donors	OC patients[2]	Healthy donors
+++	5/8	1/7	1/8	0/7
++	0/8	2/7	0/8	0/7
+	1/8	1/7	4/8	2/7
Total positive responders	6/8	4/7	5/8	2/7

Number of individuals/total number of individuals from whom PBMC after a 21-day co-culture with DCP-001 versus medium alone showed increased percentages of IFNγ⁺CD107a⁺ CD8⁺ T cells towards ovarian cancer cell lines SKOV3 or OV90

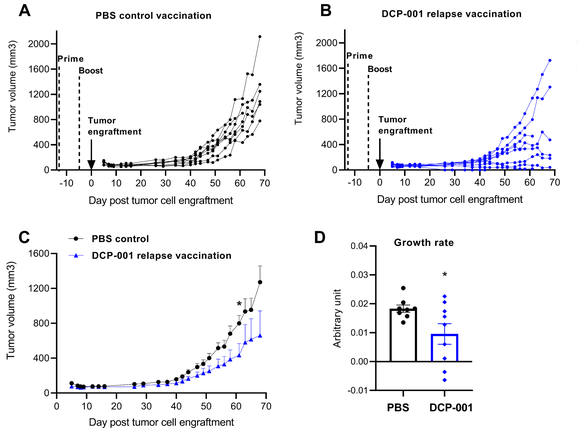
[1] +++ = ≥ 10-fold increase; ++ = 5- to 10-fold increase; + = 3- to 5-fold increase, or when the medium alone culture yielded percentages ≤ 0 with DCP-001 co-culture percentage > 0

[2] One OC patient showed a negative response score, due to a pre-existing response to both SKOV3 and OV90 which was not further enhanced by ex-vivo stimulation with DCP-001

Experimental schedule ovarian cancer model



DCP-001 vaccination results in tumor regression and reduced tumor growth rate



A) Tumor volumes of individual animals in PBS control group.
B) Tumor volumes of individual animals in DCP-001 relapse vaccination group; 5 out of 9 animals showed partial or complete tumor regression
C) Mean tumor volumes (± SEM) per group. From day 56 onwards the number of animals per group decreased as they needed to be sacrificed based on their health status, resulting in 6 animals per group at the end of the study. * = p < 0.05, unpaired t-test at day 61.
D) Average tumor growth rate from 5 days after tumor engraftment until end of the study determined by method of Hather et al. (2014). Symbols and bars (± SEM) represent average tumor growth rates of each individual animal and per treatment group resp. * = p < 0.05, unpaired t-test

Conclusion

In vitro studies show that DCP-001 is able to induce a T-cell response in ovarian cancer PBMC, including a response directed against ovarian cancer cell lines. *In vivo* studies performed show that DCP-001 vaccination leads to tumor growth control. These results support the potential use of DCP-001 as a cancer relapse vaccine in ovarian cancer, with the aim to reduce disease recurrence following initial standard of care therapy.