Generation of clinical grade autologous TLR 7/8-polarized fast dendritic cell vaccines for active immunotherapy of patients with AML

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Introduction

Despite various new therapeutic aproaches to treat AML, the course of disease remains unpredictable with high variations from patient to patient and in general a high early relapse rate resulting in low overall long-term patient survival. Vaccination with dendritic cells (DC) after induction chemotherapy has been reported to have clinical effects in some AML patients and encourage further optimization of this therapy.

We have developed a new protocol for generating autologous monocyte-derived fast DCs, using a maturation cocktail containing the TLR7/8 ligand R848, which are currently under investigation in a clinical phase I/II study (NCT02405338).

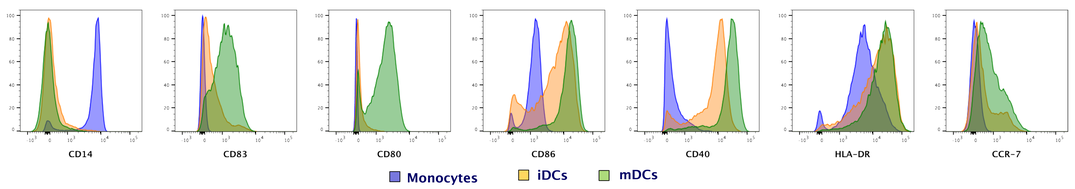
Twenty AML patients without alternative treatment options have been included in the study and treated with autologous DCs loaded with mRNA encoding the AML specific antigens WT-1 and PRAME.

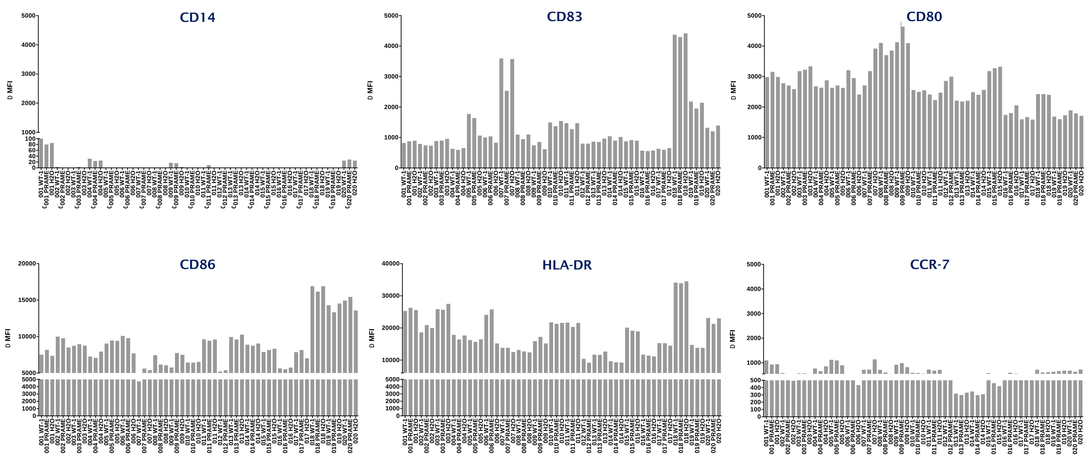
Here we present data from the production of the dendritic cell vaccines for these 20 patients.

Vaccination Plan

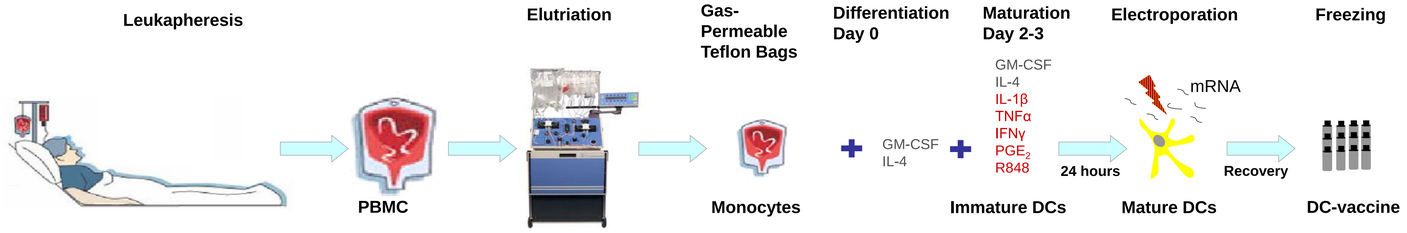
Dosage/antigen: 2.5 - 5 x 10^6 DCs Dosage/vaccination: 5 - 10 x 10^6 DCs

Phenotype





DC Production



Batch Information

No. according to batch size	Number of Vaccines	Cells/vial	Viability (%)	Contaminating Cells (%)	TNC start of Culture (x10^9)
01	64	5,0x10^6	>80	5,9	2,9
02	43	2,5x10^6	>80	1,4	2,4
03	40	2,5x10^6	>70	6,1	2,6
04	39	5,0x10^6	>80	24,9	1,65
05	38	2,5x10^6	>90	22,9	2,1
06	36	5,0x10^6	>80	11,6	1,1
07	35	5,0x10^6	>70	0,9	2,3
08	31	5,0x10^6	>70	11,7	1,7
09	30	5,0x10^6	>80	4,5	2,0
10	29	5,0x10^6	>80	7,9	1,8
11	28	5,0x10^6	>70	28,3	1,9
12	28	5,0x10^6	>80	30,5	2,25
13	26	5,0x10^6	>80	24,3	1,6
14	25	5,0x10^6	>80	18,7	2,1
15	24	2,5x10^6	>70	1,5	1,5
16	23	5,0x10^6	>70	10,1	2,1
17	20	2,5x10^6	>90	10,8	1,3
18	19	5,0x10^6	>80	9,4	1,5
19	19	5,0x10^6	>70	25,7	1,25
20	18	5,0x10^6	>70	13,2	1,6
21	18	2,5x10^6	>70	8,3	1,3
22	17	5,0x10^6	>80	5,3	1,8
23	11	5,0x10^6	>70	3,8	1,75
24	11	2,5x10^6	>60	34,6	1,3

Summary and Perspectives

All DC productions showed a mature phenotype with high expression of typical DC surface markers and down regulation of the monocyte marker CD14.

All productions met the specification of <40% contaminating (non-DC) cells with a purity of >70% in general.

Viability after thawing of vaccines was >70% with one exception.

17 out of 24 DC vaccine productions yielded 20 or more vaccine doses, allowing vaccination for more than one year.

In summary, we clearly demonstrate that we have established a robust GMP production protocol for polarized fast DCs generated in a time period of 72 to 96 hours. These mature DC vaccines could be prepared from heavily pre-treated patients with a malignant disorder of the myeloid hematopoietic line, thus enabling long term treatment.