



Intra-lymph Node DNA Vaccination as a Platform for Safe and Effective Immunotherapy of Cancer

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BACKGROUND

Features of MKC's immunotherapy

- Intra-lymph node delivery: enhances antigen presentation & immune response
- Synthetic, "off-the-shelf" injectable agents
 - Plasmid prime, peptide boost immunization approach
- Multivalent and applicable to a variety of tumor types

PRECLINICAL RESULTS

Superiority of intra-lymph node immunization

Figure 1. Intra-lymph node immunization with E7 peptide and pl:C mediates immunologic regression of solid tumors

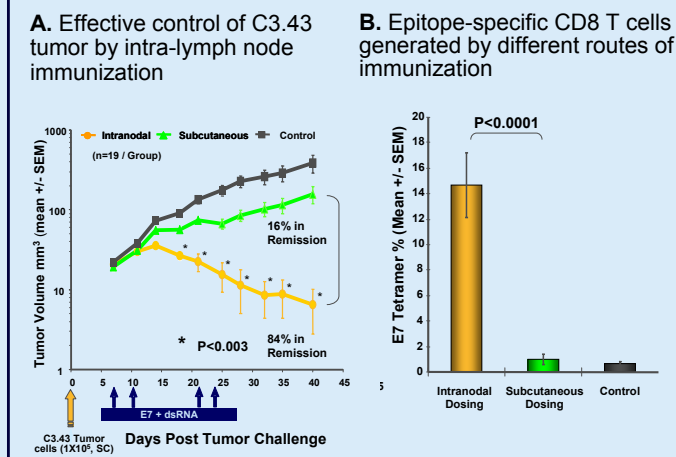


Table 1. Gene expression of inhibitory receptor genes in CD8⁺ T cells

Gene Symbol	Fold change (DNA versus control)	Fold change (peptide versus control)
Klra, lectin subfamily A	2.27 ↓	10.89 ↓
Cd160	1.08 ↑	2.34 ↓
Lag3	1.41 ↑	3.36 ↑
Ctla4	1.66 ↓	5.43 ↑
Pdcd1	1.88 ↑	7.82 ↑
Ptger2	1.09 ↑	7.06 ↑

Role of PD-1 expression in T cell proliferation

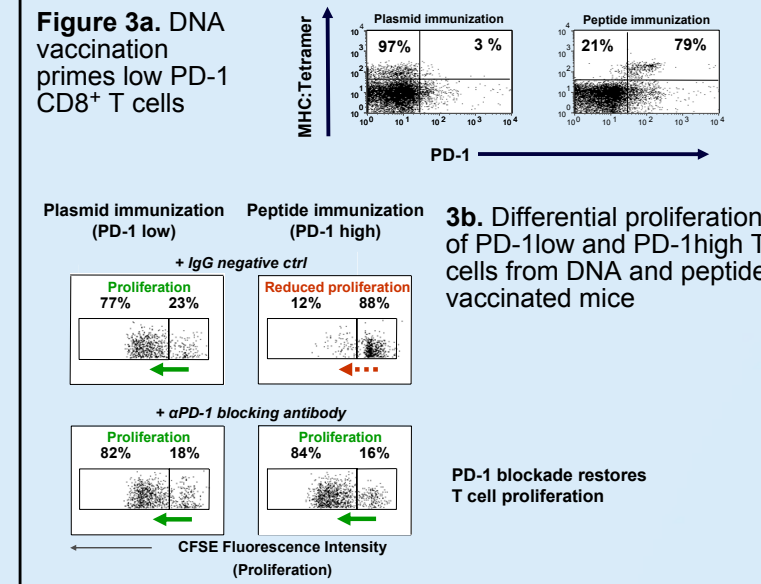
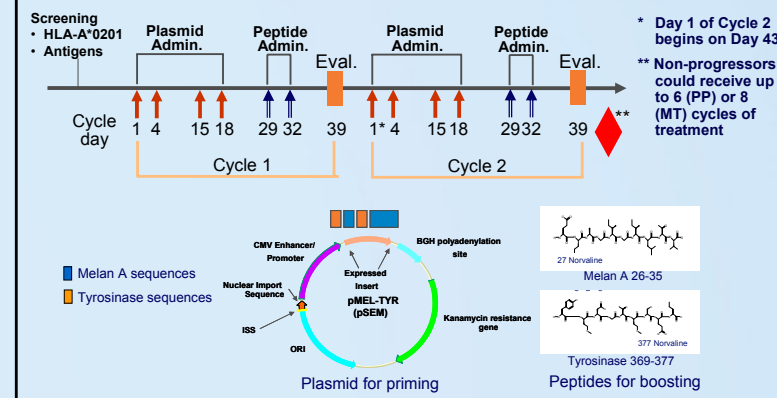


Figure 4. Dosing schedule and investigational agents



CLINICAL TRIAL RESULTS

Summary of clinical safety:

- No drug-related SAEs have been reported
- Most frequent drug related AEs: fatigue, groin pain, fever

Clinical responses

Trial	Pts treated	CR	PR	SD	PSA** Response	PD
MKC1106-MT-001	18	0	3	1	N/A	14
MKC1106-PP-001	26	0	1*	9	1	15

Immune responses

- Immune response was assessed by tetramer and ELISPOT analysis.
- Expansion of epitope-specific T cells seen in >40% (MT trial) >60% (PP trial) of evaluable patients by tetramer measurement based on pre-set criteria

* Unconfirmed ** PSA response: decline ≥ 50%

Immunity versus Clinical Outcome

Figure 5. Stage dependent immunity and clinical responsiveness of melanoma patients from MKC1106-MT trial

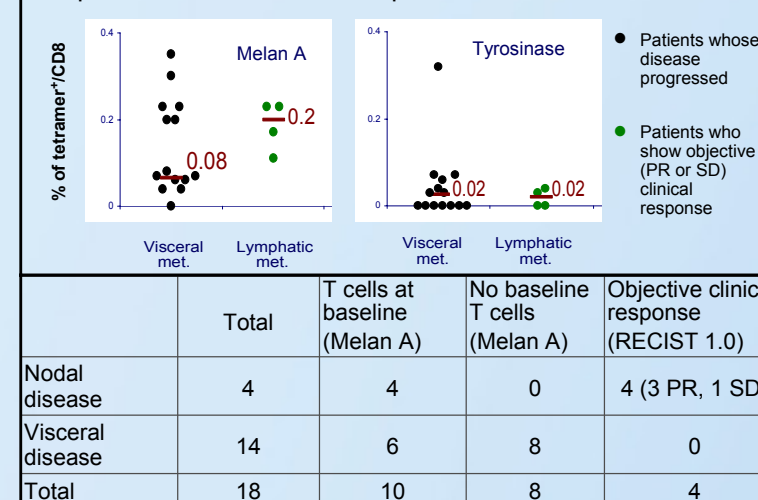


Figure 6. Association between immune response pattern and clinical outlook in MKC1106-PP patients

Tumor type	PRAME						PSMA						Best clinical response
	Baseline T cells	Treatment cycle					Baseline T cells	Treatment cycle					
Pattern 1: Robust and persistent increase of specific T cells throughout the first 2 cycles and beyond													
PC1119	0	0	0	0	0	0	0.03	0	0	0	0	0	SD 9+ M
PC1106	0	0	0	0	0	0	0.06	0	0	0	0	0	SD 6M
MEL1024	0.13	0	0	0	0	0	0	0	0	0	0	0	SD 18+ M
RC1019	0	0	0	0	0	0	0.04	0	0	0	0	0	*
ESO1028	0.15	0	0	0	0	0	0.15	0	0	0	0	0	PD
Pattern 2: Transient increase of specific T cells followed by diminution within first 2 cycles													
PC1091	0.14	0	0	0	0	0	0.19	0	0	0	0	0	SD 9+ M
PC5083	0.03	0	0	0	0	0	0.03	0	0	0	0	0	SD 9+ M
PC1063	0.11	0	0	0	0	0	0.20	0	0	0	0	0	SD 3 M
PC1044	0.53	0	0	0	0	0	0.43	0	0	0	0	0	PD
PC5056	0.04	0	0	0	0	0	0.04	0	0	0	0	0	PD
MEL1000	0.62	0	0	0	0	0	0.27	0	0	0	0	0	PD
MEL1002	0.40	0	0	0	0	0	0.40	0	0	0	0	0	PD
MEL5037	0.04	0	0	0	0	0	0.04	0	0	0	0	0	PD
MEL1118	0.03	0	0	0	0	0	0.03	0	0	0	0	0	PD
Pattern 3: Modest or no increase of specific T cells throughout first 2 cycles													
MEL1049	0.30	0	0	0	0	0	0.30	0	0	0	0	0	SD 3 M
MEL1038	0.16	0	0	0	0	0	0.16	0	0	0	0	0	PD
MEL1142	0.17	0	0	0	0	0	0.17	0	0	0	0	0	PD
MEL1058	0.23	0	0	0	0	0	0.23	0	0	0	0	0	PD
PC1100	0.17	0	0	0	0	0	0.17	0	0	0	0	0	PD
PC1057	0.19	0	0	0	0	0	0.19	0	0	0	0	0	PD
PC1104	0.04	0	0	0	0	0	0.06	0	0	0	0	0	SD 3 M
RC5075	0.48	0	0	0	0	0	0.48	0	0	0	0	0	SD 9+ M

Legend:
 Red: ≥ 2 fold over baseline
 Blue: < 3X LLD
 Green: > 3X LLD
 White: Not measured
 * neo-adjuvant: surgical resection of skin metastasis with durable, no evidence of disease status

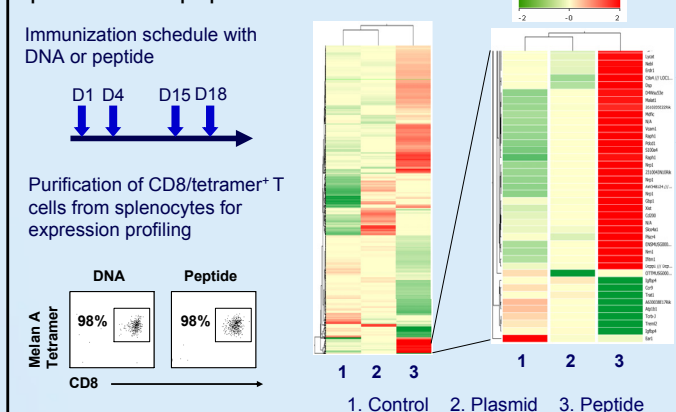
CONCLUSIONS

- Intra-nodal DNA delivery is a promising immune priming approach
 - Lower expression of co-inhibitory molecule PD-1
 - Potential for antigen-specific T cells persistence, cellular expansion and functional conversion
- Repeat intra-nodal immunization with the regimen was safe, well tolerated, and immunogenic in man
- Objective tumor response was observed in patients with melanoma and other cancers
- Different potential immune correlates of clinical outcome were observed in the two trials

References: 1). Smith KA., et al (2009). *Clin Cancer Res.* 15:6167-6176. 2). Wong RM., et al (2009). *Immunol Lett.* 127:60-67. 3). Smith KA., et al (2009). *Vaccine* 27:2603-2615. 4). Weber J., et al (2008). *J Immunother.* 31:215-223.

Transcriptome analysis of plasmid induced T cells

Figure 2. Hierarchical cluster analysis comparing plasmid and peptide immunization



CLINICAL TRIAL DESIGN

MKC1106-PP-001 Trial	MKC1106-MT-001 Trial
Open label, multicenter Advanced carcinoma or melanoma Refractory to standard therapy HLA- A*0201 positive Tumor antigen positive	Open label, multicenter Advanced melanoma (stage IIIb, IIIc, or IV) Refractory to standard therapy HLA- A*0201 positive
Low peptide dose Cohort (n=13) 22.5µg PRAME 30µg PSMA Fixed dose plasmid (2,400µg)	Low peptide dose Cohort (n=7) 100µg Melan A 100µg Tyrosinase Fixed dose plasmid (2,400µg)
High peptide dose Cohort (n=13) 150µg PRAME 300µg PSMA Fixed dose plasmid (2,400µg)	High peptide dose Cohort (n=11) 300µg Melan A 300µg Tyrosinase Fixed dose plasmid (2,400µg)
Endpoints: Safety and tolerability, Immune response, Clinical outcome	