

Gene Therapy: Melanoma Theory to Practice

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Melanoma: Targeting the Immune System

Melanoma is one of the most immunogenic of all solid tumors:

- **spontaneous regression**
- **identification of tumor associated antigens, tumor antigen-specific antibodies, tumor-specific cytotoxic T cells**
- **CD8 T cells has been shown to prevent tumor formation in vivo and in vitro, and the presence of infiltrating CD8 T cells within tumors is positively correlated with better prognosis in cutaneous melanoma**
- **many immunotherapy strategies have been evaluated to increase tumor control and patient survival**

Fang L, et al. J Invest Dermatol 2008;128:2956-2605

Melanoma: Vaccine Therapy

- **Whole-cell vaccines**
- **Dendritic cell vaccines**
- **Peptide vaccines**
- **Ganglioside vaccines**
- **DNA vaccines**
- **Viral vectors**

Lens M. Expert Opin Biol Ther 2008

Melanoma: Whole-Cell Vaccines

- **Autologous whole-cell vaccines**
- **Heat-shock proteins**
- **Allogeneic whole-cell vaccines**
 - **Canvaxin™**
 - **Melacine®**
- **Allogeneic vaccines prepared from vaccinia melanoma lysates**

Melanoma Vaccines: Heat Shock Proteins

- Heat-shock proteins (HSP) expression is increased when cells are exposed to stressful conditions and act as “chaperones” to upregulated antigens on antigen-presenting surfaces
- Patients with metastatic melanoma vaccinated after surgery with autologous tumor-derived HSP peptide complexes gp96 have been shown to develop class I HLA-restricted tumor-specific T cell immunity
Belli F, et al. JCO 2002
- Phase II trial combined GM-CSF given at the site of the HSPPC-96 injection in combination with interferon alfa
Pilla L, et al. Cancer Immunol Immunother 2006

Melanoma: Autologous Tumor-Derived Heat Shock Protein gp96 Peptid Complex Vaccine (Vitespen)

- Aim: Assess antitumor activity of autologous, tumor-derived HSP gp96 peptide complex in patients with stage IV melanoma
- Method:
 - Phase III multinational study
 - Patients randomized 2:1 to receive vaccine versus physician’s choice (PC)*
- Endpoint:
Primary: overall survival

* PC = dacarbazine or temozolomide or IL2 or resection
Testori A, et al. JCO 2008

Melanoma: Autologous Tumor-Derived Heat Shock Protein gp96 Peptid Complex Vaccine (Vitespen)

- **Patient treatment:**
 - Physician choice:**
 - 107 assigned ⇒ 79.8% received
 - Vitespen**
 - 215 assigned ⇒ 61.9% received
 - number of injections ranged 0 to 87; median 6
- **Results:**
 - ITT analysis no statistical difference in OS
 - Patients in the M1a and M1b substages receiving a larger number of immunization survived longer than those receiving fewer treatments

Testori A, et al. JCO 2008

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Dendritic Cells (DC)

- **Most effective antigen presenting cells (APCs) capable of capturing, processing and presenting antigens to T-and B- lymphocytes.**
- **Catagories of DC:**
 - **plasmacytoid DC**
 - **myeloid DC**
 - **inflammatory DC**
- **DC vaccination**
 - **development of techniques to generate large number of these cells *in vitro* from blood monocytes or CD34+ progenitor cells**

Dendritic Cell Vaccination Trials

- **Proof of principle studies performed in 1990s**
- **Clinical studies:**
 - **DC-vaccination with non-matured DC**
 - **DC-vaccination with mature DC**
- **Responses**
 - **Objective responses: 5- 10%**
 - **Type of responses: stabilization of disease, mixed responses**
- **Changing the way we look at results:**
 - **Immunologic responses**
 - **Conventional RECIST criteria may not be appropriate**
 - **Redefining dose**

Lesterhuis WJ, et al. Critical Rev Oncol Hematol 2008

Melanoma: Dendritic Cell Vaccine

- Phase III evaluation of autologous peptide-loaded dendritic cell vaccine vs dacarbazine in patients with metastatic melanoma
- Treatment:
 - Dacarbazine 850 mg/m² IV q 4 weeks
 - DC vaccines loaded with MHC class I and II – restricted peptides applied SQ every 2 weeks x 5, then q 4 weeks
- Endpoints:
 - primary: objective response
 - Secondary: toxicity, overall survival, progressive free survival

Schadendorf D, et al. Ann Oncol 2006

Dendritic Cell-Based

Therapy	No	OR	CR	PR + SD	
Peptide or tumor lysate	32	8	2	6	Nestle, 2006
Peptide vs peptide +GMCSF	13	1	0	2	Slingluff, 2003
Peptide/lysate vs DTIC	53	3	0	10	Schalendorf, 2006

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Schadendorf D, et al. Ann Oncol 2006

Melanoma: Dendritic Cell Vaccine

- Phase III evaluation of autologous peptide-loaded dendritic cell vaccine vs. dacarbazine in patients with metastatic melanoma from the Dermatologic Cooperative Oncology Group
- Results:
 - at time of first interim analysis 108 patients enrolled
 - OR was low: VAC 3.8 % vs. dacarbazine 5.5%
 - Data Safety & Monitoring Board recommended closure of the study
 - Unscheduled subset analyses: patients with normal LDH and/or stage M1a/b survived longer in both arms
 - Observed association of performance status and HLA haplotype and survival in patients treated with vaccine

Schadendorf D, et al. Ann Oncol 2006

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Melanoma: Peptide Vaccines

- Immunogenic peptides
 - tissue specific antigens
 - cancer testis antigens
 - mutated cancer-specific antigens
- A peptide derived from tissue specific antigen (gp100) has been synthesized in a mutated form to enhance HLA-A2.1 binding ⇒ T cell stimulation
 - initial small clinical trials demonstrated increase immune response but no antitumor response
 - Rosenberg SA, et al. Nat Med 1998**
 - Miller AM, et al. Cancer 1981**
 - combination therapy with interleukin-2 is a method that may increase antitumor effects

Combination Therapy for Advanced Melanoma: gp100 Peptide and Interleukin-2

- Three separate Phase II trials evaluating the combination of high-dose interleukin-2 (HD IL2) and gp100 peptide vaccine in patients with advanced melanoma
- Treatment:
 - gp100 (210M) peptide SQ during week 1,4,7, 10
 - HD IL-2
 - Trial 1: week 1 and 3
 - Trial 2: week 7 and 9
 - Trial 3: week 1, 4, 7 and 10

Sosman JA, et al. JCO 2008

Combination Therapy for Melanoma: gp100 Peptide and Interleukin-2

- N= 130 patients (Sept 1998 – Nov 2003)
- Median follow-up time of 60 months

<u>Cohort</u>	<u>No.*</u>	<u>CR</u>	<u>PR</u>	<u>RR</u>	<u>95% CI (%)</u>
Trial 1	42	6	4	23.8	12 to 40
Trial 2	40	4	1	12.5	4 to 27
Trial 3	39	1	4	12.8	4 to 27
Overall	121	11	9	16.5	10 to 26
HD IL database	270	17	26	15.9	12 to 21

* number assessed

Sosman JA, et al. JCO 2008

Combination Therapy for Melanoma: gp100 Peptide and Interleukin-2

Immune Correlates for Response:

- Paired samples from peripheral blood obtained prior to treatment and on week 12 (n=53)
- There was insufficient power to detect differences between responders and non-responders in any single trial.
- Limitation of immune testing is the amount of intra subject variation inherent in the assays.

Sosman JA, et al. JCO 2008

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Melanoma: Adjuvant Therapy EORTC Study 18961

- **Aim:** Detect difference in disease free survival (DFS) at 5 years between patients receiving adjuvant vaccine (ganglioside GM2-KLH21) treatment versus observation
- **Methods:**
 - Phase III trial
 - Stage II melanoma post resection of melanoma
 - Stratification by sentinel lymph node staging, depth, ulceration, gender, treatment center
 - Recruited from March 2002 – Dec 2005

Eggermont AM, et al. JCO 2008 (abst)

Melanoma: Ganglioside Vaccines

- **Aim:** Detect difference in disease free survival (DFS) at 5 years between patients receiving adjuvant vaccine (ganglioside GM2-KLH21) treatment versus observation
- **Treatment strategy:**
 - Ganglioside GM2-KLH/Q3-21 vaccine subcutaneously weekly x 4, then q 3 months from week 12 for 2 years, then q 6 months during 3rd year (#14)
 - Observation
- **Endpoint:**
 - Primary: DFS
 - Secondary: survival, toxicity

Eggermont AM, et al. JCO 2008 (abst)

**Melanoma: Adjuvant Therapy
EORTC Study 18961**

From randomized ITT population (n=1314):

■ **Disease Free Survival**

	HR (98% CI)	p value
Obs	1.02 (0.77, 1.36)	0.85
VAC	1.0 (0.75, 1.34)	0.99

■ **Distant Metastatic Free Survival**

	HR (98% CI)	p value
Obs	1.33 (0.77, 2.28)	0.08
VAC	1.32 (0.76, 2.30)	0.10

Eggermont AM, et al. JCO 2008 (abst)

**Melanoma: Adjuvant Therapy
EORTC Study 18961**

- **EORTC IDMC reviewed safety and efficacy data and recommended that the trial be stopped and vaccinations be halted in patients receiving VAC.**
- **Conclusion: This strategy of vaccine was ineffective and may even be detrimental in patients with stage II melanoma.**

Eggermont AM, et al. JCO 2008 (abst)

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T-Cell Activation

T cells require two signals from dendritic cells for full activation:

- binding of major histocompatibility complex – antigen to the T cell receptor
- binding of co-stimulatory molecules expressed on mature dendritic cells

Melanoma: CD8 T-Cell Response

Criteria for antitumor response:

- **generation of sufficient quantity of antitumor specific CD8 T cells**
- **CD8 T cells must be able to infiltrate into the tumor**
- **activation of CD8 T cells within the tumor ⇒ cell death**

Melanoma: CD8 T-Cell Response

Strategies to optimize CD8 T-cell response for treatment:

- **Non-specific stimulation of anti-tumor immune responses**
 - **stimulation of endogenous effector cells**
 - **removing inhibitory signals for T cell activation**
- **Active immunization to enhance endogenous anti-tumor responses in vivo**
 - **vaccines**
- **Adoptive cell-transfer therapy**

Melanoma: Adoptive Cellular Therapy

- **Cytotoxic T lymphocyte therapy (CTL)**
- **Tumor infiltrating lymphocyte therapy (TIL)**
 - **TILs and interleukin-2**
 - **non-myeloablative lymphodepleting preconditioning ⇒ TILs and interleukin-2**
 - **generate and adoptively transfer engineered autologous T cells that express high affinity for melanoma-specific antigens**

Melanoma : Options for Pharmacotherapy

- **Chemotherapy**
- **Immunotherapy**
 - **cytokine (IL-2, interferon)**
 - **cytotoxic T-lymphocyte antigen-4 antibodies**
 - **vaccines**
- **Targeting signal transduction pathways**
- **Apoptotic therapy**
- **Antiangiogenic therapy**

Melanoma : Options for Pharmacotherapy

- **Melanoma vaccines can induce cellular immune and/or antibody responses**
- **The science of melanoma vaccines:**
 - **Best target(s)**
 - **Best delivery**
- **Clinical trials with melanoma:**
 - **Small numbers**
 - **Endpoints: immune response vs. clinical response**
 - **Strategy: vaccine vs. vaccine + adjuvant vs. combination**
 - **Timing: early disease vs. late disease**