The following relationships exist related to this presentation:

<No Relationships to Disclose>
Cancer vaccines 2007

Carmen Scheibenbogen
Institut für Medizinische Immunologie, CCM
Charité, Berlin
Anti-cancer vaccines

Preventive vaccination

Anticancer-causing Viral Vaccine

antibodies

Therapeutic vaccination

Anticancer Vaccine

T cells
Preventive cancer vaccines

- Prevention of hepatocellular carcinoma by hepatitis B vaccination (Chang MH, NEJM, 1997)

- Prevention of cervical cancer by HPV16/18 vaccine (Ault KA, Lancet, 2007)
Therapeutic cancer vaccines

1. Principles

2. Clinical trials - current status

3. Future directions
Tumor cells can be recognized and destroyed by CD8+ T cells, thus a therapeutic vaccine needs to activate T cells recognizing tumor antigens.

**Diagram:**
- CD8+ T-cell
- Tumor cell
- T-cell-receptor
- Cytotoxic granules
- MHC I
Hierarchy of tumor antigens as suitable treatment targets

- WT1
- Mutations
- Fusion proteins
- Tyrosinase
- gp100
- MAGE

Essential for tumor cell proliferation

Immunogenic

Specific
Cancer vaccine - Composition

1. Tumor antigen
   • whole cell
   • synthetic +/- dendritic cells
2. Adjuvants
3. Antigen delivery
Strategies to induce tumor-specific T cell responses
- MHC class I peptides -
Strategies to induce tumor-specific T cell responses
- protein -
Strategies to induce tumor-specific T cell responses
- peptide + protein -

Costimulatory signals

Antigen

Dendritic cell

MHC I

CD 8+

MHC II

CD 4+
Cancer vaccines - Adjuvants

- GM-CSF
- TLR-ligands
  - CpG
  - Imiquimod
  - MLP

- IL-2
- IL-12

- KLH
- PAN-DR

Dendritic cell

CD 4+

CD 8+
Cancer vaccines- Antigen delivery

- Water/DMSO
- Montanide (IFA)
- Liposomes
Therapeutic cancer vaccines

1. Principles

2. Clinical trials - current status

3. Future directions
Cancer vaccines
A decade of vaccination trials in metastatic melanoma

Vaccination is:
• immunogenic - induction of T cells
• can induce tumor regression

however:
• Objective response rates „RECIST“ < 10%
• Weak association between quantitative T cell responses and tumor responses
Cancer vaccines - Current trials
- High risk melanoma -
Tyrosinase vaccination of patients with relapsing melanoma - cessation of relapses in a subset of patients

Letsch et al, unpublished
**E4697- Adjuvant trial for high risk resected stage III-IV melanoma**

*Hypothesis: GM-CSF and/or multi-epitope peptide vaccine will be of therapeutic benefit, acting upon T-cells or through dendritic cells in resected stage III-IV melanoma*

**E4697 Intergroup Trial:** A randomized, placebo-controlled phase III trial of yeast derived GM-CSF vs peptide vaccination vs GM-CSF plus peptide vaccination vs placebo in patients with “no evidence of disease” after complete surgical resection of “locally advanced” and/or stage IV melanoma

<table>
<thead>
<tr>
<th>Stratification</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
<th>Arm E</th>
<th>Arm F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA-A2 Status</strong></td>
<td>GM-CSF + Peptide vaccination</td>
<td>GM-CSF placebo + Peptide</td>
<td>GM-CSF + Peptide Placebo</td>
<td>GM-CSF placebo + Peptide placebo</td>
<td>GM-CSF</td>
<td>GM-CSF placebo</td>
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<tr>
<td>Positive</td>
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<td>Negative</td>
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<tr>
<td><strong>Site of Metastases</strong></td>
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<tr>
<td>Visceral</td>
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<tr>
<td>Non-visceral</td>
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<tr>
<td><strong>Number of Metastases</strong></td>
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<td>2–3</td>
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<td>4 or more</td>
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</tbody>
</table>

Provided by Kirkwood J.
Cancer vaccines- Current trials

ASCO 2007:

51 abstracts related to vaccination
Vansteenkiste J. et al. Final results of a multi-center, double-blind, randomized, placebo-controlled phase II study to assess efficacy of MAGE-A3 as adjuvant therapy in stage IB/II NSCLC

D. Soulieres et al. A multicentre open-label study to assess safety of Stimuvax (BLP25 liposome vaccine or L-BLP25) in NSCLC with unresectable stage III disease.
Vansteenkiste J. et al., MAGE-3 in resected NSCLC, ASCO 2007
Kaplan-Meier curve for Disease-Free Survival

DFS Distribution

Time from Surgery [months]

HR=0.73 (95% CI = 0.45 - 1.16)
one-sided logrank p= 0.093

Number at risk
MAGE-A3 122
Placebo 60

DFS: Interval from the date of surgical resection to the date of recurrence OR death, irrespective of cause of death
HR: Hazard ratio calculated by Cox analysis
Phase III study – MAGRIT (Vansteenkiste J. et al. ASCO 2007)
MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer ImmunoTherapy

Resectable NSCLC

Surgery

Pathological stage IB, II, IIIA

No chemo

Randomization

MAGE-A3 ASCI

Placebo

Up to 4 cycles of platinum-based chemo

Randomization

MAGE-A3 ASCI

Placebo

2,270 patients – double-blind, randomized trial
Vansteenkiste J. et al. Final results of a multi-center, double-blind, randomized, placebo-controlled phase II study to assess efficacy of MAGE-A3 as adjuvant therapy in stage IB/II NSCLC

D. Soulieres et al. A multicentre open-label study to assess safety of Stimuvax (L-BLP25 vaccine*) in NSCLC with unresectable stage III disease.

*L-BLP25 = synthetic MUC1 lipopeptide liposome vaccine
Multi-center phase IIIB randomized controlled study of L-BLP25 liposome vaccine for vaccination of stage IIIb/IV NSCLC (D. Soulieres et al, ASCO 07)

Overall Kaplan–Meier Survival: ITT

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>Stimuvax + BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>56 mo</td>
<td>51 mo</td>
</tr>
<tr>
<td>Median survival [95% CI]</td>
<td>13.0 mo [11.2–16.2]</td>
<td>17.2 mo [12.9–24.2]</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]; p value</td>
<td>0.745 [0.533–1.042]; p=0.085</td>
<td></td>
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<tr>
<td>1-year survival rate</td>
<td>55%</td>
<td>63%</td>
</tr>
<tr>
<td>2-year survival rate</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>3-year survival rate</td>
<td>17%</td>
<td>31%</td>
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</table>
Randomised phase III trial of L-BLP25 versus placebo in patients with stage III non-small cell lung cancer after response to primary chemoradiotherapy (D. Soulieres et al, ASCO 07)

- **Unresectable Stage IIIA/IIIB**
  - **STRATIFY**
  - **RANDOMIZE**

- **Placebo + BSC**
  - L-BLP25 + BSC Arm
  - Placebo Cyclo Day – 3 x 1
  - Placebo s.c. qW x 8
  - Placebo s.c. q6W Until progression

- **L-BLP25 s.c. qW x 8**
  - L-BLP25 s.c. q6W Until progression

- **Cyclo 300 mg/m^2 Day – 3 x 1**
  - Week 4 Evaluation

- **Evaluation Week 8**
  - Q 12W Evaluation

- **Evaluation Q 12W**
  - Placebo s.c. q6W Until progression
Cancer vaccines- Current trials - ASCO: AML -

Letsch A et al. Phase II trial of vaccination with WT1 peptide, GM-CSF, and KLH in patients with acute myeloid leukemia and myelodysplasia: Final immunological, molecular, and clinical results

Qazilbash MH et al. PR1 peptide vaccination for patients with myeloid leukemias
WT1 vaccination in AML: WT1-Tetr+ T cells in PB and BM
(Letsch et al. ASCO 2007)

Peripheral blood
(without preexisting response)

Bone marrow
(without preexisting response)
### WT1 vaccination - Clinical efficacy (Letsch et al. ASCO 2007)

<table>
<thead>
<tr>
<th>Status at study onset</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated AML or sAML</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blasts med 70%, range 40 - 85%</td>
<td>8</td>
<td>SD 2, 3, 3, 4, 4, 5, 7, 15+ months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4 pts. &gt; 50% blast reduction,</td>
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<tr>
<td></td>
<td></td>
<td>1 reduction of peripheral blasts, 1 erythroid response)</td>
</tr>
<tr>
<td><strong>RAEB I/II</strong></td>
<td>2</td>
<td>2 pts. with major neutrophil response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1 with 50% blast reduction, initial PD)</td>
</tr>
<tr>
<td><strong>No CR following chemo:</strong></td>
<td></td>
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<tr>
<td>- PR</td>
<td>4</td>
<td>1 CR at week 10 for 12 mo (initial PD)</td>
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<tr>
<td></td>
<td></td>
<td>1 SD 4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 PD</td>
</tr>
<tr>
<td>- no response</td>
<td>1</td>
<td>SD 4+ mo with 50% blast reduction</td>
</tr>
<tr>
<td>- PD, relapse</td>
<td>3</td>
<td>1 SD for 2 mo, 2 PD</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>1 CR, 12 SD &gt; 2 months</td>
</tr>
<tr>
<td><strong>High - risk CR</strong></td>
<td>8</td>
<td>TTF 2, 2, 4, 5, 10, 14+, 16+, 38</td>
</tr>
</tbody>
</table>
Cancer vaccines - Current trials - ASCO: AML -

Letsch A et al. Phase II trial of vaccination with WT1 peptide, GM-CSF, and KLH in patients with acute myeloid leukemia and myelodysplasia: Final immunological, molecular, and clinical results

Qazilbash MH et al. PR1 peptide vaccination for patients with myeloid leukemias
PR1 peptide vaccination for patients with myeloid leukemias
Qazilbash MH et al., ASCO 2007

66 patients with AML (42), CML (13) or MDS (11)

59 evaluated

34 T cell responder 25 T cell non-responder

21 + 3
Clinical responses (3 CR, 3 PR, 6 Mol. Response, 12 cCR)
Therapeutic cancer vaccines

1. Principles

2. Clinical trials - current status

3. Future directions
How to improve cancer vaccines?
Tumor Dysbalance
Immune stimulation - Immunosuppression

Danger signals
T cell cytokines

Regulatory T cells
T cell inhibitory receptors
Inhibitory cytokines
Metabolic dysfunction

• T cell anergy
• T cell apoptosis
• Failure of immunotherapy
Cancer vaccines
- New developments -

<table>
<thead>
<tr>
<th>Target</th>
<th>Interventions (clinical trials ongoing or to be activated soon*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunostimulation</strong></td>
<td></td>
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<tr>
<td>- Dendritic cell activation</td>
<td>TLR-Ligand: MLP (TLR4), Resiquimod (TLR 7), CpG (TLR9), Poly I:C (TLR3)</td>
</tr>
<tr>
<td>- T cell proliferation, inhibition of AICD, reversal of anergy, memory</td>
<td>(IL-15), IL-7, IL-21</td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td></td>
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<tr>
<td>- blockade of T cell receptors for negative regulation</td>
<td>Anti-CTLA-4, Anti-PD-1*</td>
</tr>
<tr>
<td>- Depletion of regulatory T cells</td>
<td>Anti-CD25, anti-GITR*</td>
</tr>
<tr>
<td>- Restoration of metabolic dysregulation (IDO)</td>
<td>1-Methyltryptophan*</td>
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</tbody>
</table>
LMB-2, a CD25-directed immunotoxin, causes a selective, transient elimination of circulating CD25+ Treg cells in vivo

Antibody blockade of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4): Association of tumor response with autoimmunity

• 137 melanoma, 61 renal cell pts treated
• 21% rate of GI toxicity (90% colitis); 5% mortality
• Response rates in patients
  with colitis: 36% / 35%,
  without colitis: 11% / 2%

Beck KE et al J Clin Oncol 24, 2006
CTLA-4 antibody with multipeptide vaccine for resected stages III/IV melanoma

• Total of 44 patients treated with CTLA-4 antibody with a multipeptide vaccine
• 20 IBEs (grades II/III)
• 4/20 patients with IBEs had a relapse, versus 13/24 without an IBE, p<0.03 (Fisher’s exact)
• 3 deaths in 20 patients with IBE versus 9/24 without an IBE

Ongoing randomized study of CTLA-4ab and gp100 peptide

Cancer vaccines
- New developments -

Biomarker/Immunomonitoring:

• Multifunctional Th1 cells define a correlate of vaccine-mediated protection against Leishmania (Darrah, Nat Med, 2007)
  \[ \text{IFN} \gamma/\text{TNF} \alpha/\text{IL-2}^+ \]

• HIV controllers exhibit ... a peculiar CD8 T cell activation phenotype (Saez-Cirion A, PNAS, 2007)
  \[ \text{HLA-DR high CD38 low} \]
Cancer vaccines 2007 - Conclusion

- Proof of immunogenicity
- Proof of clinical efficacy
  - therapeutic:
    frequent tumor stabilization, rare tumor regression
  - adjuvant: ongoing phase III trials
- Promising new strategies to enhance immunostimulation and revert tumor-induced immunosuppression
- Refined T-cell monitoring (quality) to define correlates of clinical efficacy
Thank you - Questions ??
Strategies to induce tumor-specific T cell responses
- genetic approaches -

Costimulatory signals

Antigen

DNA-plasmid

MHC I

CD 8+

MHC II

CD 4+