Determining Potency of Immunologic Therapy:
Assessing Dendritic Cell Vaccines

Karolina Palucka, MD, PhD
Assessing Dendritic Cell Vaccines: Ten years of experience with ex vivo generated DC vaccines

- cGMP Vaccine manufacture core
- cGMP Cell and Tissue Procurement Core
- GLP Immunomonitoring Core including polychromatic flow and genomics
Baylor closed system for DC vaccines

Apheresis

Lymph Freezing Long-term storage LN2

Monocytes

DC Freezing Storage LN2

Culture

Monocyte Freezing Long-term Storage LN2

Roberts, Burkeholder, Taquet, Walters, Finholt
Assessing Dendritic Cell Vaccines:

Ten years of experience with ex vivo generated DC vaccines

• Immune and clinical outcomes
• Assessing potency of vaccine products
• Predictive biomarkers of vaccine efficacy
Distinct DC subsets induce distinct type of immune responses

Banchereau & Palucka, 2005
DENDRITIC CELL MATURATIONS
The control point of cellular immunity

**Microbial Products:**
- TLR, NOD and lectin ligands
- LPS, DNA, RNA

**Tissue damage:**
- Uric acid, HSPs

**Cells of innate immunity**
- pDC, NK, NK T, Neutrophils
- IFN, TNF, GM-CSF

**Cells of adaptive immunity**
- T and B cells
- CD40 L, RANK

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Immature DC  →  Mature DC

*Steinman & Mellman*
BIIR DENDRITIC CELL VACCINE TRIALS:
FIRST GENERATION TRIALS IN METASTATIC MELANOMA

<table>
<thead>
<tr>
<th>TAA short peptides</th>
<th>Allogeneic killed tumor cells</th>
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<tbody>
<tr>
<td>#1: CD34-DCs KLH</td>
<td>#5: GM/IFN-MoDCs</td>
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<tr>
<td>#2: IFNA activated CD34-DCs</td>
<td>#4: GM/IL4-MoDCs TNF/CD40L, KLH</td>
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<tr>
<td>#3: GM/TNF-MoDCs KLH</td>
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</table>

- Activation
- Feasibility no G-CSF
- Broad TAA repertoire no HLA restriction cognate CD4+ T cell help
- Improved DCs Closed system Frozen vaccine
Peptide & KLH-pulsed CD34-DCs

Progressive patients do not mount TAA-specific responses

Boosting vaccinations can maintain long-lived melanoma-specific memory T cells

Melanoma-specific ELISPOTS / $2 \times 10^5$ PBMC

$P = 0.0032$

Palucka et al. J Immunotherapy 2003
Palucka et al J Immunotherapy 2005
DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses (2+1/20 patients)

Palucka et al. J Immunotherapy 2006
DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses (2+1/20 patients)

Palucka et al. J Immunotherapy 2006
Clinical Responders and Long term survivors: the key to design of efficient therapeutic cancer vaccine

Median Survival: 17 months

(n=66)
DC vaccines can expand long-lived melanoma-antigen specific CD8+ memory T cells

Ueno, Palucka
DC vaccines can expand high avidity polyfunctional MART-1 melanoma-antigen specific CD8+ T cells

**IFNγ**

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<th>Flow Cytometry Representation</th>
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**CD107**

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**Gr B**

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**CCR7**

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**DC vaccines can expand high avidity polyfunctional MART-1 melanoma-antigen specific CD8+ T cells**
EPIMAX: Assessment of Antigen-specific T cell repertoire ex vivo

Overlapping Peptides

CFSE-labeled PBMC

48 h

8 d

Cytokines / Luminex

Determination
- T cell epitopes
- Type of responses

CFSE-dilution analysis

Determination
- Proliferation
- CD4/CD8

Ueno
Patients with metastatic melanoma have circulating melanoma antigen-specific IL10-producing T cells at baseline.
Patients with Metastatic Melanoma Display Circulating Tumor Antigen-specific T regs

Determination of IL-10-inducing peptide

Proliferation of peptide-specific T regs

Suppressive function of specific T regs

Vence et al. PNAS, 2007
Breast cancer tumors are infiltrated by CD4+ T cells secreting IL-13.
Breast cancer cells show IL-13 staining and display an IL-13 signature (pSTAT6)

Aspord et al. J.Exp.Med. 2007 Vol.204: 1037
Assessing Dendritic Cell Vaccines:

- Immune and clinical outcomes to define biomarkers of efficacy:
  - Which patient populations to assess immunogenicity:
    MRD vs metastatic disease
Assessing Dendritic Cell Vaccines: Multivariate analysis

<table>
<thead>
<tr>
<th>Cells</th>
<th>Antigens</th>
<th>Activators</th>
<th>Route of injection</th>
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<tr>
<td>CD34-DCs</td>
<td>Peptides</td>
<td>Cytokines</td>
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<tr>
<td>GM/IL4-DCs</td>
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Mechanism/Infrastructure for analysis from many trials to draw statistically meaningful conclusions
Thanks to our patients
SUPPORT: BUMC FOUNDATION, SAMMONS CANCER CENTER, NCI, NIAID, INSERM, ANRS,
Dr M. Ramsay

- Vaccine:
  S. Burkeholder
  M. Leogier
  F. Kerneis
  M. Michnevitz
  J. Finholt-Perry

- Clinical Core:
  Joe Fay
  S. Hicks
  B-J. Chang
  D. Wood

- Cell and Tissue Core:
  L. Walters

- cGMP Lab:
  L. Roberts
  N. Taquet

- Post-docs/Students:
  C. Aspord
  F. Berard
  P. Blanco
  P. Dubsky
  D. Frleta
  E. Klechevsky

- Targeting:
  G. Zurawski
  S. Zurawski
  AL. Flamar
  E. Klechevsky
  SK. Oh

- Immunomonitoring:
  Hide Ueno
  J-P. Blanck
  L. Boudery
  J. Shay

- Microarrays:
  D. Chaussabel
  N. Baldwin
  R. Steinman
  M. Dhodapkar
  Y. Reiter

JACQUES BANCHEREAU
AND MANY BIIR MEMBERS.....