Will Dendritic Cells Help Us Address the Challenge of Cancer Vaccines?

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How to exploit the immune system for cancer therapy

ADOPTIVE T CELL TRANSFER
Expand T cells ex vivo

VACCINES
Expand T cells in vivo

ADOPTIVE T CELL TRANSFER

VACCINATION
After many disappointments....

CancerVax Canvaxin, CellGenesys GVAX, Corixa Melacine

Cancer vaccines are on the move

• Provenge: FDA approval for metastatic prostate cancer
  Improved overall survival in phase III
  (4.1 months), Dendreon (PBMCs plus GM-CSF-Antigen)

• BiovaxID in follicular lymphoma:
  Improved median time to relapse in phase III
  (13.6 months), Kwok et al

• Peptide plus Montanide and IL-2 in melanoma:
  Improved progression free-survival in phase III
  (2.9 months), Hwu et al
Next Generation of Therapeutic (Cancer) Vaccines:

Designing Vaccines Based On Immunology

Immunology has the potential to identify vaccines, i.e., antigen-specific, durable, non-noxious preventions and therapies for infections, cancer, allergy, autoimmunity, transplantation

Quoted from Ralph Steinman

REPROGRAMMING THE IMMUNE SYSTEM
Dendritic Cells are central to vaccination

ANTIGEN
CAPTURE: Fc, TLR, Fr-R
PROCESSING

IMMATURE DC

ACTIVATORS
pathogens, cytokines

MATURE DC

IMMUNE RESPONSE
T CELL ATTRACTION
CHEMOKINES

THE IMMUNOLOGIC SYNAPSE
MHC/peptide: TCR
CD40/CD40L, B7 family
Cytokines

DC/T CELL
BINDING
DC-SIGN/ICAM-3
Desired features of DC vaccines

• Induce high avidity CTLs

• Induce long term memory CD4\(^+\)/CD8\(^+\)T cells

• Do not induce regulatory T cells

• Induce CD4\(^+\) T cells that help CD8\(^+\) T cells

Our two paths to therapeutic DC-based HIV and cancer vaccine
First generation DC vaccines

Antigen:
- Short 9-10aa peptides
  - KLH
- Killed allogeneic tumor cells

DC vaccine:
- CD34-DCs
- Activated CD34-DCs
- GM/TNF MoDCs
- Activated GM/IL4 MoDCs
- GM/IFNa MoDCs

Conclusions:
- Immunogenicity
  - Clinical responses
- The quality of activation signal
- Immunogenicity
  - Clinical responses
- Improved DCs
  - Closed system
  - Frozen vaccine
DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses (2+1/20 patients)

1992
Melanoma Diagnosis
Surgery

10 years

09/02
Biopsy
Proven
Metastatic
Melanoma
M1b

12/02
Progressive
Disease

11/03
PR>
60 months
CR
without any additional treatment

02/03
Progression
Current
DC Vaccine trial

10/03
Progression
Current
DC Vaccine trial

Baseline

After 8 vaccines

October 2005

Palucka et al. J Immunotherapy 2006
EPIMAX: Comprehensive high throughput assessment of antigen-specific T cell repertoire

Cluster analysis
48hrs cytokines

Peptide analysis
48hrs cytokines

7d Proliferation

Tetramer
Distinct MART-1 CD8+ T cell epitopes elicit distinct transcriptional responses (and Immune Responses?)
DC vaccines can expand high avidity polyfunctional MART-1 melanoma-antigen specific CD8+ T cells

PBMCs + Peptides
D7 4hrs Restimulation
Tetramer Assay ICS CTL assay

1uM
100nM
10nM
1nM

MART-1 tetramer
MART-1 tetramer
MART-1 tetramer
MART-1 tetramer

CD107
Gr B
CCR7

IFNγ

Chun, Israyleyan, Goldberg
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
Human Dendritic Cell Subsets In Vivo and In Vitro

Human Dermal DCs – DC-SIGN positive

CD14+

CD1a+

NSE

T cell activation

IL10

B cell diff

Human Langerhans Cells – Langerin positive

Langerhans Cells are More Efficient than Interstitial-DCs in CD8+T Cell Priming

Klechevsky, Ueno
LCs efficiently prime effector CD8$^+$ T cells

Klechevsky, Ueno et al, Immunity, 2008
IL-15 might explain the biological functions of LCs on CD8+T cells

CD8+ T cells primed by dermal DCs in the presence of IL-15

Eynav Klechevsky
LCs Preferentially Control Cellular Immunity While intDCs Preferentially Control Humoral Immunity

Kissenpfennig et al
*Immunity* 2005; 22, 643

CD34+ HPC

Interstial DC
B cell priming
Tfh priming

Langerhans DC
CD4+CD8+ T cell priming

HUMORAL IMMUNITY

CELLULAR IMMUNITY

**IL12**

**IL15**

Activation of memory T and B cells
LANGERHANS CELLS PREFERENTIALLY CONTROL CELLULAR IMMUNITY
WHILE DERMAL DC PREFERENTIALLY CONTROL HUMORAL IMMUNITY

Klechevsky, Ueno et al Immunity 2008
Which DC Receptors can target Antigens?

Gerard Zurawski, Sandra Zurawski, Sangkon Oh
Are All DC Receptors Equal?

Gerard Zurawski, Sandra Zurawski, Sangkon Oh
Mature dendritic cells in breast cancer co-localize with T cells

Bell et al JEM 1998
Breast tumor tissue can be induced to produce a wide range of T cell cytokines.

**Diagram:**
- Tumor (T)
- Surrounding tissue (ST)
  - Activate in PMA/inomycin for 18 hrs
  - Collect supernatant
  - Luminex assay

**Graph:**
- Log pg/mL of various cytokines (IL-2, IL-4, IL-13, IFN-γ, TNF-α) with different samples and statistical significance (p=0.0221, n=73).
Tumor infiltrating T cells produce type 2 cytokines, particularly IL-13

Cell gating: Live/CD45+/CD3+/CD4+
Breast cancer cells show IL-13 staining and display an IL-13 signature (pSTAT6)

IL-13/Cytokeratin

pSTAT6

Aspord, Pedroza et al JEM 2007

The IL-4/IL-13/Stat6 signalling pathway promotes luminal mammary epithelial cell development
CD4+ T cells promote early tumor development

... which can be prevented by IL-13 antagonists

Aspord, Palucka et al. J.Exp.Med. 2007 Vol.204: 1037
Breast tumors are infiltrated with OX40L+ HLA-DR+ CD11c+ DCs

Ito et al. JEM 2005
OX40L\(^+\) mDCs drive pro-inflammatory type 2 CD4\(^+\) T cell response in breast cancer in vitro
OX40L drives pro-inflammatory type 2 CD4+ T cell response in breast cancer in vivo

![Graph showing tumor size over days with different treatments: PBS, Isotype, a-OX40L.

- Tumor size mm³
- XYZ plots for IL-13 and IFNγ with values: 0.49, 2.13, 44.1, 0.19, 0.42, 32.8]
Factors that can up-regulate OX40L on DCs

- Thymic stromal lymphopoietin (TSLP)

TSLP is present in breast cancer microenvironment

<table>
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Fresh sonicated human breast tumors

TSLP / IL-13

Cytokeratin / TSLP

Primary tumors
OX40L induction on mDCs can be abolished by TSLP blockade

TSLP

Sonicated Breast Cancer + anti-TSLP Ab

OX40L staining

TSLP

FL2-H: OX40L PE

% of Max

0 20 40 60 80 100

10^0 10^1 10^2 10^3 10^4

T97 a-TSLP

T97
TSLP is critical for induction of OX40L on DCs and their capacity to generate IL-13 secreting CD4+ T cells.
TSLP is involved in tumor development

PBS

T cells + PBS

T cells + isotype

T cells + α-TSLP

![Graph showing tumor growth over days with different conditions: PBS, T cells + PBS, T cells + isotype, T cells + α-TSLP.](image)

IL-13

* *p=0.022

![Bar graph showing IL-13 levels in different samples: Tumor, dLN, cLN.](image)
Next generation DC vaccination trials: Patient selection
Combined therapies

- modulation of inflammation and tumor environment

Diagram:
- CTL
- T helper
- Tregs
- Th2
- Block regulatory molecules
- Block suppressive cytokines
- Block inhibitory receptors
- Improved cancer vaccines
- Breakdown suppressive tumor environment
Thanks to our patients

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JACQUES BANCHEREAU

AND MANY BIIR MEMBERS.....