THERAPEUTIC VACCINES: their Immunological Basis and their Bright Future

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THE IMMUNE SYSTEM AT THE CENTER OF HEALTH AND DISEASES

HYPO

INFECTIOUS DISEASES

NORMAL

DEFENSE
Resistance to microbes

HOMEOSTASIS
Removal of damaged cells

SURVEILLANCE
Removal of tumor cells

HYPER

ALLERGY

AUTOIMMUNITY

INCREASE IMMUNITY

INCREASE TOLERANCE

GRAFT REJECTION
Vaccines represent a major success of Medicine

Prophylactic Vaccines:

• Prevent diseases
• Multiple Examples
• Mostly based on Humoral Immunity though Cellular Immunity is observed in vaccines based on live attenuated microbes

Therapeutic Vaccines:

• Treat diseases
• Few examples
• Based on Cellular Immunity
Therapeutic 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
Bringing Dendritic Cells Into Medicine

Antigen uptake receptors and processing pathways for presentation of peptide–MHC complexes

Location at body surfaces and in the T-cell areas of lymphoid organs

Maturation or differentiation in response to microbial and other stimuli

Subsets with distinct pattern recognition receptors and functions

1973-2013

Dendritic cells: Ralph M. Steinman, MD
2011 Nobel Prize in Medicine or Physiology

Steinman & Banchereau
Nature 2007
Autoimmunity

Cancer

Infectious diseases

Transplantation/Allergy

Dendritic Cells

Pathophysiology

Therapy

VACCINES

CYTOKINE BLOCKADE

CHECKPOINT BLOCKADE
Launching immunity
Cancer vaccines are designed to treat cancers that have already developed.

They are intended to:

1. delay or stop cancer cell growth;
2. cause tumor shrinkage;
3. prevent cancer from recurring;
4. eliminate cancer cells that have not been killed by other forms of treatment.
Novel Approaches to Treat Cancer

ADOPTIVE T CELL TRANSFER

Expand T cells ex vivo

VACCINES

Expand T cells in vivo

• June et al. Sci Transl Med 2011
• Rosenberg et al. Science 2002
• Greenberg et al PNAS 2002
• Heslop & Brenner N Eng J Med 1994

• Provenge: FDA approval for metastatic prostate cancer
  • Oncovex
• BiovaxID in follicular lymphoma
  • Prostvac: Improved overall survival in prostate cancer in phase II
  • GVAX
• Endogenous vaccination: targeted therapy or chemotherapy
Cancer therapy via DCs

- **Endogenous vaccination**
  - Immunogenic chemotherapy
  - Radiotherapy
  - Anti-tumour antibodies
  - T cell immune checkpoint blockade

- **Ex vivo-generated cytokine-driven DCs**
  - Ex vivo instruction to generate and maintain cytotoxic effector and helper T cells

- **Reprogramming inflammation**
  - Targeting DCs with TLR ligands
  - Cytokine blockade

- **Targeting antigens to DC subsets in vivo**
  - DC antibody linked to pathogen and/or cancer-specific antigens and DC activators
Some key challenges for vaccines in immunological science and medicine

- What antigens can be protective in microbial and other diseases?

- Can defined adjuvants substitute for complex and replicating microbial vectors?

- How do adjuvants work to facilitate antigen presentation and immune responsiveness?

- What types of lymphocytes provide protection?
The complexity of therapeutic vaccines: which antigens, which dendritic cells, which immune responses?
Cancer vaccine platforms

1. Peptides and Proteins
   - GSK1572932
   - GV1001
   - CDX-100
   - V503
   - PR1
   - BLP25
   - Vitespen
   - BiovaxID

2. Xenoantigens
   - TIMUS: Negative Selection
   - TIMUS: Break Tolerance
   - T cell clonal expansion
   - Ag-specific T cell
   - Self-antigen
   - Tumor cell
   - Xenoantigen
   - Hb(64-76)/1Ek

3. Engineered DNA Plasmids
   - gene encoding for TAA or TSA
   - Amollimogene
   - MVA-MUC1-IL12
   - MVA 5T4

4. Virus and Bacteria

Cancer Vaccines in Phase II/III Clinical Trials: State of the Art and Future Perspectives

S. Ceccò, E. Muraro, E. Gaiaconin, D. Martorelli, R. Lazzarini, P. Baldo, and R. Dolcetti

Current Cancer Drug Targets, 2011, Vol. 11, No. 1
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
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<tbody>
<tr>
<td>abagovomab (anti-idiotypic mAb vaccine)</td>
<td>ovarian</td>
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<tr>
<td>astuprotimumut-R (MAGE-A3 recombinant antigen-specific cancer immunotherapy)</td>
<td>malignant melanoma, non-small-cell lung (NSCLC)</td>
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<td>BiovaxID® B-cell lymphoma vaccine (personalized lymphoma vaccine)</td>
<td>indolent follicular lymphoma (Fast Track)</td>
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<td>CVac™ cancer vaccine MUC-1</td>
<td>ovarian</td>
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<td>DCVax®-Prostate dendritic cell-based vaccine</td>
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<td>GVAX® Prostate</td>
<td>prostate (Fast Track)</td>
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<td>HyperAcute® Pancreas algenpantucel-L (Orphan Drug)</td>
<td>pancreatic (Fast Track)</td>
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<td>IMA901 (multiple tumor-associated peptides cancer vaccine)</td>
<td>kidney</td>
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<tr>
<td>Lucanix® belagenpumatucel-L (cell-based therapeutic vaccine)</td>
<td>NSCLC (Fast Track)</td>
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<td>Vaccine/Drug Description</td>
<td>Indication</td>
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<td>M-200 prophage cancer vaccine</td>
<td>metastatic melanoma (fast track)</td>
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<td>MVax® autologous cell vaccine</td>
<td>malignant melanoma</td>
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<td>NeuVax™ E75 cancer vaccine</td>
<td>early-stage breast (prevention of relapse)</td>
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<td>polyclonal antibody stimulator (Orphan Drug)</td>
<td>gastric, pancreatic</td>
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<td>Prostvac™ prostate cancer vaccine</td>
<td>metastatic prostate (Fast Track)</td>
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<td>Provenge® sipuleucel-T</td>
<td>recurrent early-stage prostate</td>
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<tr>
<td>Rindopepimut (Orphan drug)</td>
<td>glioblastoma (first-line therapy) (Fast Track)</td>
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<tr>
<td>Stimuvax® emepepimut-S</td>
<td>NSCLC (Fast Track)</td>
</tr>
<tr>
<td>V503 (virus-like particle [VLP] vaccine)</td>
<td>prevention of cervical, prevention of vulvo-vaginal</td>
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</tbody>
</table>

Adapted with permission from Pharmaceutical Research and Manufacturers of America (PhRMA). Medicines in Development. Vaccines. 2012
IMPACT Overall Survival: Primary Endpoint
Intent-to-Treat Population

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 Mos.

- PROVENGE (n = 341)
  Median Survival: 25.8 Mos.
- Placebo (n = 171)
  Median Survival: 21.7 Mos.
Immunotherapy via antibodies: Anti-CTLA4 plus peptide vaccine

Generation and Regulation of Anti-Tumour Immunity

I Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673
Chemotherapy and targeted therapy meet immunology: immuno-oncology

Cancer immunotherapy – revisited

W. Joost Lesterhuys *, John B. A. G. Haanen * and Cornelis J. A. Punt *

NATURE REVIEWS | DRUG DISCOVERY | VOLUME 10 | AUGUST 2011
Our two paths to therapeutic DC-based vaccines

Ex vivo DCs

MHC class I

MHC class II

Targeting DCs in vivo
DC vaccine loaded with killed allogeneic melanoma cells can induce durable clinical responses (2+1/20 patients): IND #10649, Baylor IRB #002-094

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

CD8

MART-1

Pre

Post

8 DC vaccines

2.5 years later

Tetramer

Pre

Post

8 DC vaccines

2.5 years later

IP-10 (ng/ml)

0
1
2

Pre

Post

0.17

0.63

0.98

30.0

CD8

CD8

MART-1

0.01

1.05

0.94

0.63
Distinct MART-1 CD8+ T cell epitopes elicit distinct transcriptional responses

Peptide analysis
48hrs cytokines

1519 genes

Microarray

18 h

PBMCs

Identified peptide

Confidential

Ueno & Chaussabel
Assessing DC vaccine immunogenicity in HIV-infected person under HAART

19 pts
HAART plus DC-HIV lipo 5 vaccine

Vaccinations
weeks 0 4 8 12 16 22 24

Primary endpoint
Safety

Secondary endpoint
Immunogenicity

Follow up
Immune status
Viral status

Interrupt HAART

Cobb, Palucka, Levy, Sloan
Lipo5-DC Vaccination Increases Specific IFN-g Secreting CD4+ T Cells In Patient D1-11

A1                   A2
CD4+ T cells
IFNg
TNFa
LP-MIX
G17
G253
N66
N116
P325
DC as Cancer Vaccines: What we have learned (1\textsuperscript{st} decade)

- DC vaccines are safe
- DC vaccines can elicit tumor antigen-specific T cell immunity
- Vaccination with DCs can lead to durable (several years) tumor regression and clinical benefit in a small fraction of patients.

\textbf{THUS GET BACK TO WORK!}

Palucka et al (2010). Immunity
Human Dendritic Cell Subsets In Vivo and In Vitro

Human Dermal DCs – DC-SIGN positive

Human Langerhans Cells – Langerin positive

CD14+ CD1a+

NSE

T cell activation

IL10

B cell diff

Langerhans Cells are More Efficient than CD14+Dermal-DCs in CD8+T Cell Priming

Klechevsky, Ueno, Immunity, 2008

HLA-A*0201+ 
melanoma cells

Specific lysis
E:T

Peptide-pulsed T2 cells

LCs-T
intDCs-T

E:T

30:1 15:1 7.5:1 3.5:1
0
20
40
60
80

LCs-T
intDCs-T

LCs-T
intDCs-T

α CD8

γδ TCR

p/MHC

Tetramer

9 days

p/MHC

TCR

p/MHC

TCR

α CD8

γδ TCR

p/MHC

Tetramer

α CD8

γδ TCR

p/MHC

Tetramer

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LCs efficiently prime effector CD8$^+$ T cells

Banchereau, Klechevsky: Blood, 2012
Blocking ILT-4 receptor* on dermal CD14+ DCs enhances CTL-priming

Dermal CD14+ DCs + Naïve CD8+T cells

Anti-ILT4 (#20F3)  mlG1  No Ab

*LILRB2 or CD85d. Three ITIM Motifs

Banchereau, Klechevsky: PNAS, 2012
**CD14+ Dermal DCs Induce Naïve CD4+ T cells to become B-helper T cells (Tfh)**

Sorted activated CD4+ T cells

Allogeneic naïve CD4+ T cells

Autologous naïve B cells

\[ \alpha \text{IgM} + \text{CpG} \]

Ig ELISA

(Klechevsky et al: Immunity 2008)
For HIV vaccine, gag/nef will be delivered to LCs and env to interstitial DCs.
Our vision of therapeutic vaccine in cancer

- Potent Vaccine plus TEM targeting
- Potent vaccine
- Combination therapy

Primary tumor

Metastatic disease

Surgery
Chemotherapy
Radiotherapy

Residual disease
Which DC Receptors can target Antigens?

- MMR
- DEC-205
- DC-SIGN
- Langerin
- DCIR
- LOX-1
- ASGPR
- CLEC-6
- Dectin-1
- MARCO

Zurawski, Oh, Palucka, Klechevsky, Flamar, Li, Ni, Zurawski et al
Not All DC Receptors are Equal!

Viruses
Bacteria
Fungi

Dendritic cell
DC-surface receptors

Naïve CD4

Th1
Th2
Th17
Th21
Treg
Construction of the aCD40.HIV5pep vaccine

A.L.Flamar; G.Zurawski
Antigens targeted to DCs via LOX-1 and DC-ASGPR Induce increased CD4+ T cell proliferation

Li, Flamar, Oh, Zurawski
Targeting DCs via distinct lectins leads to distinct types of immune responses

Li, Flamar, Oh, Zurawski
CD4⁺ T cells induced by anti-DC-ASGPR-PSA suppress the proliferation of allogeneic CD4⁺ T cells

Li, Flamar, Oh, Zurawski
Anti-LOX-1-PSA and anti-DC-ASGPR-PSA, respectively, generate IFNγ- and IL-10-producing HA1-specific CD4⁺ T cells in vivo.

Restimulation of PBMC with peptide pools after 2nd boosting with vaccines

ELISA for IFNγ & IL-10

R. Legrand, CEA, France