Cancer Immunotherapy with T Cells: Vaccines and Adoptive T Cell Therapy

I. T cells and tumor immunity

II. Vaccines: generate T cell response

III. T cell therapy: augment T cell response
T Cell Infiltration Predicts Survival in Ovarian Cancer

Intratumoral

Stromal

74 advanced stage ovarian

Zhang et al, NEJM, 2003
Infiltrating Memory T Cells Predict Outcome in Colorectal Cancer

Factors Predicting Outcome:
- Th1
- $T_{EM}$
- Central
- Dense

>400 samples

Pages F et al, NEJM, 2005

Cancer Antigens Recognized by the Immune System

<table>
<thead>
<tr>
<th>Tumour-associated antigen</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS3</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>KRAS2</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>APC</td>
<td>Colorectal carcinoma</td>
</tr>
<tr>
<td>TGFβ receptor II</td>
<td>Colorectal carcinoma</td>
</tr>
<tr>
<td>Caspase 8</td>
<td>Head and neck tumours</td>
</tr>
<tr>
<td>β-catenin</td>
<td>Melanoma</td>
</tr>
<tr>
<td>CDK4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>GrTV</td>
<td>Melanoma</td>
</tr>
<tr>
<td>SYT-SSX fusion protein</td>
<td>Soft-tissue sarcoma</td>
</tr>
<tr>
<td>SP100</td>
<td>Melanoma</td>
</tr>
<tr>
<td>MART1</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>Melanoma</td>
</tr>
<tr>
<td>TRP1</td>
<td>Melanoma</td>
</tr>
<tr>
<td>TRP2</td>
<td>Melanoma</td>
</tr>
<tr>
<td>PSA, PAP, PSA A</td>
<td>Prostate carcinoma</td>
</tr>
<tr>
<td>Melanoma antigen family (MAGE)</td>
<td>Several types</td>
</tr>
<tr>
<td>G antigen family (GAGE)</td>
<td>Several types</td>
</tr>
<tr>
<td>B melanoma antigen (BAGE)</td>
<td>Several types</td>
</tr>
<tr>
<td>SSX2</td>
<td>Several types</td>
</tr>
<tr>
<td>SAGE1</td>
<td>Several types</td>
</tr>
<tr>
<td>LAGE1</td>
<td>Several types</td>
</tr>
<tr>
<td>Cancer/testis antigen NY-ESO1</td>
<td>Several types</td>
</tr>
<tr>
<td>CEA</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>GA73-1</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>Mucin 1</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>Survivin</td>
<td>Several types</td>
</tr>
<tr>
<td>Telomerase</td>
<td>Several types</td>
</tr>
<tr>
<td>CD55</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>PFRAME</td>
<td>Several types</td>
</tr>
<tr>
<td>Chronic gonadotrophin β</td>
<td>Several types</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Global H, transcription factor α, and αδTf-Tn</td>
<td>Several carcinomas</td>
</tr>
<tr>
<td>Gangliosides</td>
<td>Melanoma</td>
</tr>
<tr>
<td>SAF71, SAF72</td>
<td>Some carcinomas</td>
</tr>
<tr>
<td>E6, E7 (human papillomavirus)</td>
<td>Cervical carcinoma</td>
</tr>
<tr>
<td>LMP2, EBNA1 (Epstein-Barr virus)</td>
<td>Nasopharyngeal carcinoma</td>
</tr>
</tbody>
</table>

adapted from Mocellin S et al, Lancet Oncol, 2004
Pre-Existent Tumor T Cell Immunity is Low Level

Minority of the inflammatory infiltrate in tumors

Effector cells at the site of the tumor

<table>
<thead>
<tr>
<th>Frequency CD8+</th>
<th>Functional State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volunteer donors (blood)</td>
<td>0.07%</td>
</tr>
<tr>
<td>(65% ± 4%)</td>
<td></td>
</tr>
<tr>
<td>(65% ± 29%)</td>
<td></td>
</tr>
<tr>
<td>(35% ± 29%)</td>
<td></td>
</tr>
<tr>
<td>Melanoma patients (blood)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Melanoma patients (tumor)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Romero et al, Immunol Rev, 2002
Cancer Immunotherapy with T Cells: Vaccines and Adoptive T Cell Therapy

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Mechanisms of Ineffective Tumor Immunity

- T regulatory cells
- Tolerance to self antigens
- Non functional APC
- Macrophage APC w/o co-stim
  - Suppressive DC
  - Lack of DC
- Chronic inflammation
- Inhibitory cytokines
- Tumor microenvironment
- Limited response

adapted from Smyth et al, Nat Immunol, 2001
Circumventing Tolerance via Treg Depletion

Knutson et al, JI, 2006

Increased tumor antigen specific immunity
T cell and antibodies
Depletion of Tregs Prior to Vaccination Enhances Immunity

XCD25-Immunotoxin enhances MR

3 id injections of tumor RNA transfected DC +/- XCD25 Immunotoxin

RENAL CELL CA

Dannull, J et al, JCI, 2005
Activating APC for Vaccination

Intradermal injection of cytokines: trafficking to dermis/activation

Resting

Activated

Green: CD11c
Red: CD86
Toll-Like Receptor Ligands

Medzhitov, R. Nat Rev Immunol, 2001
Activation of Skin APC

Baseline
H&E
PBS
GM-CSF
Dermis
TLR-7 Agonist
Imiquimod
10-fold
TNTC
Wagner et al, 2006
Stimulating Dendritic Cells *in situ* with CpG via TLR-9

8 melanoma patients

**Patient 1**

**Patient 2**

- Standard adjuvant IFA
- Standard adjuvant IFA

\[ \text{T}_{EM} \text{ with lytic activity} \]

Speiser et al, JCI, 2005
Manipulating the Antigen for Vaccination

Limited response

Effector
CTL

TCR

MHC class I/B2-m

Tumor Peptide

Tumor cell

CD8

CD4

CD28

CD40

CD40L

TCR

MHC I

MHC II

DC
Peptide Modified to Increase Class I Binding

Modified gp100 Peptide
- Stage I-III melanoma: adjuvant setting
- Modified gp100 peptide
  - HLA-A2
  - p209-2M
- Given sq in IFA q 2 or 3 weeks
- HLA-tetramer to assess immunity
- Increased peptide specific CD8+ in 28/29
- 28% of patients >1%

Smith et al, JCO, 2003
Intermediate Binding Altered Peptides are Optimal Vaccine Candidates

AH1 epitope/CT26 tumor/BLAB/c: libraries screened by T cell clone

McMahan, R et al JCI, 2006
Xenoantigen Immunization

**Mouse PAP in Man**
- DC pulsed with mouse PAP protein
- Highly homologous foreign protein
- 21 patients with metastatic prostate cancer
- 2 monthly vaccinations
- All patients = immunity to mouse PAP
- 50% immunity to human PAP
- 6/21 with clinical stabilization
- Stabilization associated with human PAP immunity

Fong et al, JI, 2001
Vaccinating to Induce CD4\(^+\) T Cell Immunity

**HER2 Peptide Immunity**
- HER2 Th peptides in GM-CSF given i.d.
- 3 peptides/vaccine
- Stage III/IV breast, ovarian, or NSCLC
- 38 patients completed all 6 immunizations
- >90% developed immunity to HER2 peptides
- >60% developed immunity to HER2 protein
- Immunity could persist >1 year
- Epitope spreading in majority = protein response

**HER2 Protein Immunity**

Definition of Class II Epitopes
- HER2 Th peptides in GM-CSF given i.d.
- 3 peptides/vaccine
- Stage III/IV breast, ovarian, or NSCLC
- 38 patients completed all 6 immunizations
- >90% developed immunity to HER2 peptides
- >60% developed immunity to HER2 protein
- Immunity could persist >1 year
- Epitope spreading in majority = protein response

*Disis et al, JCO, 2002*
Evolving Immunity with Immunization

Intramolecular epitope spreading

Intermolecular epitope spreading

HER2-neu Peptides

% with T cell Immunity

Disis et al, JCO, 2002

Disis et al, J Clin Immunol, 2004
Productive Immunity Modulating the Microenvironment

Vanderlugt et al, Nat Rev Immunol, 2002
DC-MUC-1 Vaccine + LD IL-2 in RCC Elicits Epitope Spreading

15% RR (PR+CR), 1 CR
Induced immunity associated with response \((r=0.79)\)
\((n=20)\)

Wierecky J et al, Ca Res, 2006
# Vaccinating Established Disease

## Clinical Outcomes: Cancer Vaccines in Melanoma Patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total Patients</th>
<th>Responding Patients</th>
<th>RR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td>410</td>
<td>11</td>
<td>2.7</td>
</tr>
<tr>
<td>Viral Vector</td>
<td>160</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Tumor Cells</td>
<td>43</td>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>Dendritic Cells</td>
<td>116</td>
<td>11</td>
<td>9.5</td>
</tr>
</tbody>
</table>

*adapted from Banchereau et al, Nat Rev Immunol, 2005*
Therapeutic Immunization

Antigen Specific T cell Activation

Minimal Tumor Cell Death

Suppressive tumor microenvironment

Continued Tumor Growth

Tumor Overwhelms Immune System

Adapted from Finn, Nat Rev Immunol, 2003
Cancer Vaccines in the Adjuvant Setting

**Table 4. Survival and Recurrence Rates for the Vaccinated and Prospectively Observed Control Groups of Patients With Node-Positive Breast Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated, HLA-A2+ (n = 24) (%)</th>
<th>Observed, HLA-A2- (n = 29) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>85.7</td>
<td>59.5</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>8.3</td>
<td>20.7</td>
</tr>
</tbody>
</table>

* Median follow-up was 22 months (range, 6 to 48 months).
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Intervention Based on Tumor Burden

<table>
<thead>
<tr>
<th>Disease Burden</th>
<th>Vaccine Prevention</th>
<th>Therapeutic Vaccines</th>
<th>Alternative Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Disease</td>
<td>≥ 1:10,000 T cells</td>
<td>&gt;1:10,000 T cells</td>
<td>&gt;1:100 T cells?</td>
</tr>
<tr>
<td>Microscopic Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Long Term Survival after Transplant Relapse with DLI

Collins et al, JCO, 1997
Transfer of Tumor Competent T Cells

Clones
Enriched PBMC
TIL
Gene Modified Cells

Gattinoni L et al Nat Rev Immunol, 2006
Adoptive T Cell Therapy with CD8+ T Cell Clones

Infusion of MART-1 CD8+ T Cell Clones

Yee, C et al, PNAS, 2002
Adoptive Transfer of Expanded TIL After Induction of Lymphopenia

- 35 patients with MM
- Cytoxan/Fludarabine
- TIL + HD IL-2
- 18/35 (51%) had objective clinical response
  - 3 CR
  - 15 PR
- 1 patient: EBV lymphoma

Dudley M et al, JCO, 2005
Lymphodepletion Will Enhance T Cell Expansion \textit{in vivo}

- Removal of cells (e.g. NK) that consume critical cytokines, IL-7, IL-15
- Preferential depletion of T regulatory cells
- Homeostatic proliferation

\textit{Klebanoff CA et al, Trend Immunol, 2006}
T Cells Genetically Engineered to Express Functional MART-1 TCR

MART-1 TCR from CR TIL

Transduced PBMC

12% Partial Response Rate

Cohorts based on cell doubling time
Infused when actively dividing

Tumor regression

Morgan RA et al, Science, 2006
Effect of Adoptively Transferred T Cells in vivo

Persistence

Immune Escape

Dudley M et al, JCO 2005
Successful Immunity Leads to Immunoediting

- Functional and Effective Immunity
- Persistent and Ongoing Immune Response: Selective Pressure
- Tumor that has been “Immunologically Sculpted”

Eradication of Tumor Cells → Outgrowth of Cells that Survive Immune Attack → Uncontrolled Tumor Growth

Dunn et al, Nature Immunol, 2002
Generating Anti-Tumor T Cell Immunity: Effectors and the Environment

Productive Inflammation
- GM-CSF, IL-12, IL-18, IFNγ, IL-4

Non-Productive Inflammation
- VEGF, IL-6, IL-10, TGFβ, M-CSF, NOS, arginase, IDO, PGE2, COX2, gangliosides

Tumour microenvironment

Supportive of T cell activation and expansion

adapted from Zou, Nat Rev Ca, 2005