20th Annual Scientific Meeting of the Society for Biological Therapy

Primer in Tumor Immunology Educational Course: November 10, 2005

Cancer Immunotherapy with T Cells: Vaccines and Adoptive Immunotherapy

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Outline: T Cell & Vaccine Therapy

- Cancers can be cured by immune T cells
  - Hematologic malignancy can be cured by allogeneic T cells
  - Solid tumors can also be treated with allogeneic T cells, but less effectively
- Cancer cells are immunogenic and can be recognized and killed by autologous T cells
- Autologous immune T cells can be used effectively in therapy
  - Transferred immune T cells are most effective
  - Vaccines that induce immune T cell responses can be effective, but less so
- Many new biological reagents are available as potential immunotherapeutic drugs to substantially increase the number and therapeutic function of immune T cells in vivo
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Probability of relapse after BMT for early leukemia varies according to type of graft and development of GVHD.

(Horowitz et al. BLOOD 75:555, 1990)
Complete Response to Donor Lymphocyte Infusion as Therapy for Relapse after HLA-Matched Hematopoietic Cell Transplant

<table>
<thead>
<tr>
<th>Chronic myeloid leukemia</th>
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<td>Cytogenetic/molecular relapse</td>
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<td>Hematological relapse</td>
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<td>Accelerated phase/blast crisis</td>
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<td>Acute myeloid leukemia/myelodysplastic syndrome</td>
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<td>Acute lymphoblastic leukemia</td>
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<td>Multiple myeloma</td>
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<td>Non Hodgkin lymphoma</td>
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(Baron & Storb, Semin Immun 26, 2004)
Major Problem of Allogeneic Transplant

• Donor T cells that mediate the graft vs. leukemia effect (GVL) commonly mediate severe and lethal GVHD
Tissue Targets of GVHD vs. GVL

• GVHD
  – Skin
  – Gut
  – Liver
  – Hematopoietic cells
    • Normal cells
    • Leukemia cells

• GVL
  – Hematopoietic cells
    • Leukemia cells
    • Normal cells
Molecular Targets of GVHD vs. GVL

- Peptides from segments of polymorphic proteins that differ between donor and host
  - AKA, minor histocompatibility Ag
- GVHD dominates, if dominant response is to polymorphic proteins expressed primarily by skin, liver and/or gut
- GVL dominates, if dominant response is to polymorphic proteins expressed primarily by hematopoietic cells
- Examples of potential dominant GVL targets
  - Polymorphic segments of hematopoietic differentiation Ag
  - Leukemia specific antigens
    - e.g. bcr-abl joining region segment
  - Aberrantly expressed leukocyte differentiation antigens
    - e.g., WT1, proteinase 3
Organ Targets of Graft vs. Host Disease & Graft vs. Leukemia

Epithelial tissues:
- Skin
- Stomach, intestines
- Liver
- Fibroblasts

Haematopoietic system:
- Neutrophil
- Antigen-presenting cell
- Macrophage
- T cell

Leukaemia

GVHD
T cell responding to broadly expressed minor histocompatibility antigen

GVL
T cell responding to haematopoietic-restricted minor histocompatibility antigen

(Bleakley & Riddell, Nat Rev 4:2004)
Standard vs. Mini-Transplant

• Standard Transplant (myeloablative)
  – High dose chemotherapy/radiation therapy
  • Eliminates hematopoietic cells (normal & leukemic)
  • Prevents rejection of transplant
  – Leukemia eliminated by both chemotherapy/radiation and GVHD/GVL

• Mini-Transplant: low intensity (non-myeloablative)
  – High dose immunosuppression
  • Prevents rejection of transplant
  – Leukemia eliminated exclusively by GVHD/GVL

• Results
  – Less chemotherapy/radiation therapy related deaths
  – Common GVHD deaths
  – GVHD/GVL is therapeutic in some patients
Mini-Transplants for Leukemia

- 305 patients
  - 46% acute GVHD
    • 15% grade III/IV
  - 43% chronic GVHD

- 45% 2-year mortality
  - 23% Relapse
  - 22% Non-Relapse Mortality

- 40% 2-year relapse free survival

(Baron & Storb, Semin Immun 26, 2004)
Rash of graft-versus-host disease
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Mini-Transplants for Renal Cell Cancer

- Cumulative data - 6 studies
- 70 patients
  - 6% CR (4 pts)
  - 29% PR (20 pts)
  - 35% Total Response
  - 24% Regimen mortality (17 pts)

(Lundqvist & Childs, J Immunother 28:281, 2005)
(Durable GVT Effect: Metastatic Renal Cell Cancer)

(Lundqvist & Childs, J Immunother 28:281, 2005)
Association of Response with Survival in RCC

(Takahashi & Childs, ClinCaRes 10:6353s, 2004)
Association of GVHD with Response in RCC (n=19)

(Takahashi & Childs, ClinCaRes 10:6353s, 2004)
Course of Breast Cancer Response to Hematopoietic Cell Transplant + Donor Lymphocyte Infusion

(Bishop et al JCO 22:3886, 2004)
Allogeneic Transplant Conclusions

• Cancers can be cured by immune T cells
  – Hematologic malignancy can be cured by allogeneic T cells
  – Solid tumors can also be treated with allogeneic T cells, but less effectively

• Highly toxic with a high proportion of treatment related deaths

• Major question for tumor immunology:

Can autologous tumor immune T cells reproduce the therapeutic efficacy of allogeneic transplant without the inordinate toxicity?
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Questions

• Is cancer immunogenic?

• What are the immunogenic targets?
Cancer

• Uncontrolled growth
• Progeny of a single transformed cell
• Multi-step process
• Multiple genetic alterations occurring over many years
• Cumulative effect of genetic alterations on control of cell growth and differentiation
Carcinogenic Polycyclic Hydrocarbons
Animal Studies: Tumors Can Elicit Immunity and Immunity Can Protect

• Methylcholanthrene (MCA) induces sarcomas which are progressive and fatal in primary host
  – Resection yields cures
  – Implant into secondary host yields progressive tumor.
  – Reimplant into primary host yields rejection:
    • Specific
    • T cell-mediated

• Major challenge: To manipulate the primary host to augment the existent but ineffective host response to promote tumor eradication
Tumor Antigen Classification

• Tumor-specific antigens
  – Expressed only on tumors
    • Unique
    • Shared

• Tumor-associated antigens
  – Expressed on normal cells
  – Qualitative or quantitative different on tumor
Tumor-Specific Antigens

• Products of genes mutated by chemical & physical carcinogens
  – Normal genes--random DNA mutations
  – Cancer-related genes--non-random DNA mutations
    • ras, p53, bcr-abl

• Antigen receptors
  – Surface immunoglobulin on B cell tumors
  – T cell receptor on T cell tumors

• Oncogenic viruses
  – MuLV, FeLV
  – HTLV, HPV, EBV
Tumor-Associated Antigens

• Normal cellular gene products
  – Oncofetal antigens
    • CEA, alpha-fetoprotein, p97
  – Cancer-testis antigens
    • MAGE-1,3

• Differentiation and lineage-specific antigens
  – MART-1, gp100, tryrosinase, TRP-2
  – PSA, PAP, PSCA, PSMA, Prostein
  – MUC1, EpCam, gangliosides, RBC antigens
  – Proteinase 3

• Overexpressed transformation related proteins
  – p53, HER-2/neu, WT1
Escaping the Immune System - a Model

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Cell-Transfer Therapy

Antitumor lymphocytes grown in culture

Cultured lymphocytes

Tumor excised

Lymphocytes reach tumor

Lymphocytes
“Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma”

- 35 pts
- Refractory to high dose IL2
- Regimen
  - Lymphodepleting chemotherapy
  - Autologous tumor-reactive culture expanded T cells
- 18 of 35 (51%) Responders
- 3 (9%) CR – all ongoing (7+, 14+, 24+ months)
- 15 (43%) PR
  - Median duration 11.5 months
  - 3 ongoing (13+, 16+, 30+ months)
- At least 50% of melanoma tumors cannot completely resist immune attack!

(Dudley JCO 23:2346, 2005)
Patient 31: Mart-1 Reactive TIL

Dudley et al. JCO (2005)
“Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma”

• Requires
  – Evident tumor
  – Multiple cultures/patient
  – 6-8 weeks of culture

• Most effective with high-dose toxic chemotherapy
  – 2 with Pneumocystis pneumonia
  – 1 with EBV lymphoma
  – 1 cortical blindness, progressive multifocal neuropathy

• TIL not uniformly available
  – Obtainable in 81% of patients attempted
  – Fewer than 81% treatable

• Effect on overall survival unknown

(Dudley JCO 23:2346, 2005)
Melanoma T Cell Therapy Lessons

• Antigens expressed by tumors can elicit immune responses.
  – Immune T cells can existent in cancer patients and co-exist with cancer cells
  – Cancers can grow despite existent immune T cells

• Antigen-specific T cells can treat established malignancy.
  – Ineffective T cells can be rendered effective by in vitro growth and treatment with increased numbers

• Tumor antigens need not be tumor specific
  – T cell targets can be tissue-specific differentiation antigens
Can Vaccines Increase the Number of Immune T Cells In Vivo and Thereby Reproduce the Therapeutic Effects of T Cell Therapy?
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Cumulative Results: NCI Trials of Solid Tumor Vaccines for Metastatic Disease

• Background
  – 440 patients
  – 96% had melanoma
  – All metastatic
  – Variety of vaccines- peptide, virus-vector, tumor cell, dendritic cell, heat shock protein

• Outcome
  – 1% CR - 4 pts
  – 2% PR - 9 pts
  – 97% NR - 428 pts
  – 2.6% Overall response - 13 pts

(Rosenberg et al; Nature Med,10:2004)
“Tumor Regression and Autoimmunity after Removal of a Functionally Tolerant State of Self-Reactive CD8+ T Cells”

- Pmel-1(gp100) TCR transgenic mice
- B16 melanoma grew normally in pmel-1 TCR TG mice
- Peptide vaccine resulted in only modest delay in subcut tumor growth
- Adoptive transfer of T cells plus vaccine induced T cell infiltration into tumors, but no marked tumor cell death
- Plus IL-2 - extensive tumor cell death and loss of tissue integrity

Overwijk (Restifo) JEM 189:569, 2003
Unimpeded Growth of Antigenic Tumor in TCR TG Mice

Overwijk (Restifo) JEM 189:569, 2003
Therapy with T Cells + Vaccine + IL-2

pmel-1 (fresh) + rFPVhgp100 + IL-2

Proportion Surviving

Days After Treatment

no treatment

Overwijk (Restifo) JEM 189:569, 2003
T Cells + Vaccine

hgp100 / Vβ13 mAb

T Cells + Vaccine + IL-2

hgp100 + IL-2 / Vβ13 mAb

Overwijk (Restifo) JEM 189:569, 2003
“Tumor Regression and Autoimmunity after Removal of a Functionally Tolerant State of Self-Reactive CD8+ T Cells”

- The presence of overwhelming numbers of Pmel specific T cells (>95% of CD8+ T cells) did not impact on tumor growth
- Large numbers of antigen specific T cells are necessary, but not sufficient
- One effective regimen employed T cell transfer + vaccine + IL-2
- Other regimens should be as or more effective

Overwijk (Restifo) JEM 189:569, 2003
“Human Tumor-Specific T Lymphocytes: Does Function Matter More Than Number?”

• Not a tight correlation between vaccine induced T cell response and detectable clinical benefit
• Some pts have a strong response without clinical benefit
• Some pts respond with few detectable anti-tumor T cells
  – Plausible model: anti-vaccine T cells, even at very low frequencies, modify an immunosuppressive environment within a tumor, opening a permissive window for the priming or restimulation of other anti-tumor T cells

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)
Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Tumor resistance
- Lymphocyte quiescence
- Too low lymphocyte: tumor ratio

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)
Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

• Tumor resistance
  – Environment not permissive to T cell infiltration
  – Decrease of loss or antigen expression
  – Resistance to lysis or to TRAIL- or Fas-induced apoptosis
  – Contact inhibition of T cells (NK inhibitory receptors)

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)
Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Lymphocyte quiescence
  - Shortage of soluble factors (tryptophan, arginine, IL-2, etc.)
  - Inappropriate co-stimulation
  - Immunosuppressive soluble factors (TGF-beta, galectin-1, IL-10, prostoglandins, etc.)
  - Regulatory T cells (Tregs)

(Coulié & Connerotte Curr Opin Imm 17:320, 2005)
Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

• Too low lymphocyte: tumor ratio
  – Insufficient expansion of anti-tumor T cell clones
  – T cell apoptosis within tumor

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)
Methods to Increase Efficacy of Cancer Vaccines

• Increase the number and/or function of effector T cells
• Treat smaller amounts of tumor
Vaccine Therapy of Minimal Residual Disease vs. Evident Disease

• Minimal residual disease
  – Increased effector/tumor ratio
  – Less tumor induced immunosuppression
  – Less chemotherapy/radiation therapy induced suppression
  – Increased time for immune response to function
  – Possibly less protection from established tumor stroma

• Proof of efficacy requires large randomized trials
Vaccine Therapy of Heme Malignancy vs. Solid Tumors

• Trials in hematologic malignancy might offer greater likelihood to develop effective vaccines
  – Lymphoma - anti-idiotype
  – Leukemia - proteinase 3 and WT1

• Possible reasons for better efficacy for heme malignancy
  – Susceptible Targets
    • Leukemia/lymphoma susceptibility to CTL
    • Leukemia/lymphoma susceptibility to Th cytokines
  – Compartment accessibility to T cells
“Complete molecular remissions induced by patient-specific vaccination (Idiotype protein) plus GM-CSF against lymphoma”

- B cell lymphoma
- Immunized to “self” Ig (idiotype determinants)
  - Chemotherapy induced remission
  - Vaccination beginning at 6 months
- Tumor-specific T cells elicited in 19 of 20 patients
- Lymphoma detectable by PCR in 11 patients
- Lymphoma cleared in 8 of 11 patients

(Bendandi et al: Nature Med. 5:1171, 1999)
Proteinase 3 Leukemia Vaccine

• Proteinase 3
  – Normal granulocyte protein; increased in leukemia
  – Peptide-base vaccine (PR1)
• 42 patients were enrolled,
  – 25 AML, 10 CML, 7 MDS
• 22 patients (49%) had an immune response
  – 4 CR
    • 3 AML
    • 1 CML
  – 2 partial remissions
    • 1 MDS
    • 1 CML

(Molldrem ASH Abstract 259. Presented Dec. 6, 2004: Medscape)
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Multiple Points of Intervention to Engender Successful Cancer Immunotherapy

- Antigen-specific engineered vaccines
  - Incorporation of dendritic cells, differentiators or activators into vaccines
  - Enhanced antigen presentation by dendritic cells
    - Antigen coupled to DC targeting molecules
    - Incorporation of B7 family costimulatory molecules
    - Mobilization of dendritic cells (Flt3L, CD40L, TLR agonists)

- Blockade of immunologic checkpoints
  - CTLA-4 blockade
  - PD-1 blockade
  - Stat3 inhibition

- Enhanced traffic and activity of tumor specific T cells at sites of metastases
  - IL-15
    - B7-H1 blockade
    - B7-H4 blockade
  - Target proinflammatory signals to neovascular endothelium
  - Immunotherapy + blockade of anti-apoptosis pathways in tumors
Examples of potential points of intervention and potential immunotherapeutic drugs to increase the number & therapeutic function of immune T cells in vivo

• Co-stimulatory molecules
  – CD28 & CTLA4
  – Extended B7 family

• Regulatory T cells (CD4+CD25+ Treg)

• T cell growth factors
  – IL-7
  – IL-15
CD28 and CTLA4: Positive & Negative Co-stimulatory Molecules

- Two receptors are necessary for T cell activation
  - TCR
    - Binds to peptide/MHC complex
  - CD28
    - Expressed constitutively on T cells
    - Binds to B7-1 and B7-2 on APC

- TCR + CD28 engagement promotes T cell activation, proliferation, IL2 production
- Subsequent CTLA4 up-regulation and engagement dampens T cell activation
CD28 and CTLA4: Positive & Negative Co-stimulatory Molecules

- **CTLA4**
  - Not expressed on resting T cells
  - Up-regulated following T cell activation
  - Binds to B7-1 and B7-2 on APC
    - Higher affinity than CD28
  - Antagonizes T cell activation
    - Interferes with IL2 production, IL2 receptor expression and T cell cycle progression
“Combination Immunotherapy of B16 Melanoma Using CTLA-4 and GM-CSF-producing Vaccines Induces Rejection of Subcutaneous and Metastatic Tumors Accompanied by Autoimmune Depigmentation”

• Highly tumorigenic, poorly immunogenic murine melanoma B16-BL6
• Anti-CTLA-4 blockade and vaccination
  – Eradicated established tumors 80% (68/85)
  – Each treatment alone showed little or no effect
• Tumor rejection was dependent on CD8+ T cells
  – Depigmentation occurred in CD4-depleted mice

(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)
Control IgG

Anti-CTLA4

Control IgG + Vaccine

Anti-CTLA4 + Vaccine x1

Anti-CTLA4 + Vaccine x2

Anti-CTLA4 + Vaccine x3

(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)
T cell infiltration of pulmonary metastasis

Vaccine alone       Vaccine + anti-CTLA4

(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)
(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)
“Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti–Cytotoxic T-Lymphocyte Antigen-4”

- 56 patients with progressive stage IV melanoma
  - Anti–CTLA-4 every 3 weeks,
  - Concomitant vaccination with gp100 HLA-A*0201-restricted peptides
- 2 CR (30+ 31+ months)
- 5 PR (4, 6, 25, 26, & 34 months,
- 13% overall objective response
  - Tumor regression seen in lung, liver, brain, lymph nodes, & subcutaneous sites

“Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti–Cytotoxic T-Lymphocyte Antigen-4”

- 14 of 56 (25%) experienced grade 3/4 autoimmune toxicity
  - 7 colitis
  - 4 dermatitis
  - 1 uveitis
  - 1 enterocolitis
  - 1 hepatitis
  - 1 hypophysitis

- 5 of 56 experienced grade 1/2 autoimmune toxicity (vitiligo, antinuclear antibodies and pulmonary infiltrates)

- Correlation of autoimmunity with anti-tumor response
  - 36% with autoimmunity had clinical response
  - 5% without autoimmunity had clinical response

C: Uveitis with posterior synechiae (iris adhesions to the lens) causing irregular pupils
D: The same patient, 4 days later, after treatment with topical corticosteroids.

Extended B7 Family and Regulatory T cells

• B7-1/B7-2 & CD28/CTLA-4 regulate clonal composition of naive T cells that become activated by antigen-bearing DCs migrating into lymphoid organs from peripheral tissues

• B7h & inducible costimulatory molecule (ICOS) promotes T-dependent antibody isotype switching and expansion of effector T cells after clonal expansion of naive T cells, when the differentiated T helper cells (Th) migrate into the follicles

• Programmed death ligands (PDLs) & (PD)-1 regulate effector T cells trafficking into inflamed tissues

• B7-H3 & B7x and BTLA (B and T lymphocyte attenuator) could be last-ditch regulators and control the interaction between effector T cells and the peripheral tissues

Regulatory T cells: (CD4+CD25+ Treg)

- Naturally occurring
- Control immunologic tolerance to self antigens
- Approximately 5-15% of normal CD4+ T cells
- Constitutively express high levels of cell surface
  - CD25 (IL-2Ra)
  - GITR (glucocorticoid-induced THF receptor)
  - CTLA-4
- Absence is associated with severe autoimmunity
Regulatory T cells: (CD4+CD25+ Treg)

- Functionally competent when isolated ex vivo
- Upon TCR cross-linking
  - Suppress proliferation and IL2 production of responder CD25-CD4+ or CD8+ T cells
    - Contact-dependent manner
- Suppress autoimmunity, tumor immunity, allergy and immunity to chronic infection
  - Carefully timed depletion of CD25+ T cells enhances tumor immunity and autoimmunity
“Intratumor depletion of CD4+ cells unmasks tumor immunogenicity leading to the rejection of late-stage tumors”

- C3B6F1 mice inoculated s.c. with fibrosarcoma cells
- Identified intratumor growth of CD4+CD25+ T cells

(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)
In vivo Deletion of CD4+ or CD25+ T cells Unmasks Tumor Immunogenicity Leading to the Rejection of Late-stage Tumors

(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)
Intra-Tumor Deletion of CD4+ or CD25+ T cells Unmasks Tumor Immunogenicity Leading to the Rejection of Late-stage Tumors

(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)
“Cytokine Signals in T-Cell Homeostasis”

- **IL7 therapy** (normal mice & primates)
  - Increases CD4+ and CD8+ cells
  - Greater effect on the CD8+
- **IL15 therapy**
  - Selectively expands CD8+ cells
  - More potent than IL7
  - Selectively expands CD8+ memory cells

(Guimond, Fry & Mackall J Immunother 28, 2005)
“Adjuvant IL-7 or IL-15 Overcomes Immunodominance and Improves survival of the CD8+ Memory Cell Pool”

- Day 0: female mice immunized against male minor histocompatibility antigen complex (HY)
- Days 0-27: rhIL-7 rhIL-15
- Day 28: Quantified male antigen (Uty) tetramer binding T cells

(Melchionda et al (Mackall) JCI 115 2005)
Conclusions

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