Cancer Immunotherapy: Can Your Immune System Cure Cancer?

Steve Emerson, MD, PhD
Herbert Irving Comprehensive Cancer Center
Bodnar’s Law

• Simple Things are Important

• Very Simple Things are Very Important

• Not Everything Important is Simple
Why is Tumor Immunotherapy Essential?

• Except for Rare/Localized Tumors, all Curative Treatment is Systemic

• Traditional Chemotherapy is Based on Killing Rapidly Dividing Cell
  
  – Underlying Hypothesis: Cancer Cells Divide more Rapidly than Normal Cells.
  
  – False. Many Normal Cells Divide as Rapidly as Tumor Cells

  • We Need Therapies that are not Cell Cycle Specific
Tumors Rejection is “Routine,” and Genetically Controlled

“Essentially, the facts are these: When the growth of a transplantable tumor is adequately observed in inbred stocks of mice and in the various hybrid generations between them it is found, with rare exceptions, that the tumour (1) grows progressively in 100% of the animals of the strain in which it originated, (2) fails to grown, or grows temporarily and then regresses, in unrelated strains, (3) grows in 100% of F1 strains in which one parent is from the susceptible strain (strain of origin)…”

G. D. SNELL J Genetics 49:2:87;1948
Tumor Rejection begat Transplantation Immunology

• Sophisticated Mouse Genetics—Crosses, Backcrosses and Recombination, lead to the Identification of the Major Histocompatibility

• Genetics and Biochemistry honed down on H-2 and DR (HLA A,B,C,DR), then

• MHC-Restricted Antigen Presentation.

  - Beautiful Model of Antigen-Specific Recognition, for both Soluble and Membrane Bound Pathogenic Antigens

• But Whatever Happened to Tumor Immunity?!
Molecular Immunology Implies Tumor Immunity

• Mutations and Translocations create Neo-Antigens

• All Proteins, cell surface and intracellular, are degraded and presented on the cell surface via Class I MHC (HLA A,B… H2K,D)

• Ergo, Tumor Cells Must (Should?) Present Neo-Antigens to their own T Cells

• If (since) tumors exist, there must be mechanisms that subvert normal immune recognition
Tumor Immunology Re-Emerges, with Allogeneic Bone Marrow Transplantation

Replacing Missing, Dysfunctional or Leukemic Bone Marrow Stem Cells
After Bone Marrow Transplantation, Allogeneic Donor T Cells Recognize and Kill Host Leukemia Cells

Fig 1. Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.
Survival after chemotherapy and donor leukocyte infusions (DLIs) for patients with relapsed acute myelogenous leukemia (AML).
Preemptive donor lymphocyte transfusions in high-risk AML; evaluation in a matched pair analysis.
Pathophysiology of GVHD

- activation
- radiation
- Chemotherapy
- Virus...TLR9
- LPS...CD14
- HSP70...TLR4

Host: monocyte / dendritic cell

- CD40
- ICAM
- B7.1
- MHC II
- TNF-α
- IL-6

Donor: T-cell

- GM-CSF
- CD40L
- LFA3
- mHA
- TCR
- CD4
- CD28
- IL-2
Adoptive Immunotherapy in Chimerism
GVL-Reaction

T-cell

Costimulation:
CD80, CD86 - CD28
TNF-α, IL-6

epithelial cell

leukemia cell / dendritic cell

On all cells

Restricted to hematopoietic cells
T Cells Survey and Delete Antigen-Specific Tumors, in Syngeneic Mice

Expression of tumour-specific antigens underlies cancer immunoediting

Michel DuPage, Claire Mazumdar, Leah M. Schmidt, Ann F. Cheung & Tyler Jacks

16 February 2012 | Vol 482 | Nature | 405

Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting

Hirokazu Matsushita1*, Matthew D. Vesely1, Daniel C. Koboldt2, Charles G. Rickert1, Ravindra Uppaluri1, Vincent J. Magrini2,4, Cora D. Arthur1, J. Michael White1, Yee-Shiu Chen1, Lauren K. Shea1, Jasreet Hundal2, Michael C. Wendl2,4, Ryan Demeter2, Todd Wylde2, James P. Allison5,6, Mark J. Smyth7,8, Lloyd J. Old9, Elaine R. Mardis2,4 & Robert D. Schreiber1

400 | Nature | Vol 482 | 16 February 2012
Modifying Bulk T Cells to Make Large Numbers of Antigen-Specific T cells

CD19 CAR T Cells are Manufactured in 11 Days

- T Cells collected directly from the patient
- Genetically engineered to express the CD19 CAR
- Expanded ex vivo before infusion
CAR-Modified T Cells Can Massively Expand after IV Infusion
Other Barriers to Effective T Cell Anti-Tumor Therapy

- Costimulatory Inhibition
- Failure to Present Internal Antigens
- Myeloid Suppressor Cells
- Regulatory T Cells
APC-T Cell Co-Stimulatory or Co-Inhibitory Ligand-Receptor Pairs

Antigen-presenting cell:
- PDL1 or PDL2
- PDL1 or PDL2
- CD80 or CD86
- CD80 or CD86
- B7RP1
- B7-H3
- B7-H4
- HVEM
- MHC class I or II

T cell:
- PD1
- CD28
- CTLA4
- ICOS
- ?
- ?
- BTLA
- KIR
- TCR
- LAG3
- CD137L
- OX40L
- CD70
- CD40
- GAL9
- Adenosine

Cytokines:
- (TGFβ, IL-1, IL-6, IL-10, IL-12, IL-18)

Nature Reviews | Cancer
T Cells can be Down-regulated in Lymph Nodes and/or in Tissues, by CTLA-4 and PDL1
Blockade of CTLA-4 can Shrink Tumors, but also Trigger Autoimmunity
Tumors can Up-regulate PDL1 (making matters worse), autonomously and in (unholy) collaboration with T cells
TCR activation of murine and human T cells in the presence of PD-L1 results in inhibition of T cell proliferation and cytokine production.

Freeman, Gordon et al. JEM 2000;192:1027-1034
### Clinical Trials of Inhibitory Receptor Blockade

<table>
<thead>
<tr>
<th>Target</th>
<th>Biological function</th>
<th>Antibody or Ig fusion protein</th>
<th>State of clinical development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA4</td>
<td>Inhibitory receptor</td>
<td>Ipilimumab</td>
<td>FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers</td>
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<tr>
<td></td>
<td></td>
<td>Tremelimumab</td>
<td>Previously tested in a Phase III trial of patients with melanoma; not currently active</td>
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<tr>
<td>PD1</td>
<td>Inhibitory receptor</td>
<td>MDX-1106 (also known as BMS-936558)</td>
<td>Phase I/II trials in patients with melanoma and renal and lung cancers</td>
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<td></td>
<td></td>
<td>MK3475</td>
<td>Phase I trial in multiple cancers</td>
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<td>CT-011†</td>
<td>Phase I trial in multiple cancers</td>
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<td>AMP-224§</td>
<td>Phase I trial in multiple cancers</td>
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<tr>
<td>PDL1</td>
<td>Ligand for PD1</td>
<td>MDX-1105</td>
<td>Phase I trial in multiple cancers</td>
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<td></td>
<td></td>
<td>Multiple mAbs</td>
<td>Phase I trials planned for 2012</td>
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<tr>
<td>LAG3</td>
<td>Inhibitory receptor</td>
<td>IMP321‖</td>
<td>Phase III trial in breast cancer</td>
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<td>Multiple mAbs</td>
<td>Preclinical development</td>
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<tr>
<td>B7-H3</td>
<td>Inhibitory ligand</td>
<td>MGA271</td>
<td>Phase I trial in multiple cancers</td>
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<td>B7-H4</td>
<td>Inhibitory ligand</td>
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<tr>
<td>TIM3</td>
<td>Inhibitory receptor</td>
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<td>Preclinical development</td>
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</tbody>
</table>

CTLA4, cytotoxic T-lymphocyte-associated antigen 4; FDA, US Food and Drug Administration; Ig, immunoglobulin; LAG3, lymphocyte activation gene 3; mAbs, monoclonal antibodies; PD1, programmed cell death protein 1; PDL, PD1 ligand; TIM3, T cell membrane protein 3. *As of January 2012. †PD1 specificity not validated in any published material. §PDL2–Ig fusion protein. ‖LAG3–Ig fusion protein.
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camachio, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

n engl j med 366;26; 2012
Reversing Immune Checkpoint Blockade in Melanoma by Targeting CTLA4 (IPI) and PD-1

**Week 12**

- Increase in tumor burden

**Week 72**

- Late, durable response

**IPI**

- Screening
- Week 12
- Week 72

**PD-1**

- Screening
- Week 12

**IPI + PD-1**

- “Spider Plot”

IPI + PD-1

Change in Target Lesions from Baseline (%)
Immune Checkpoint Inhibition in Melanoma

2 Year Overall Survival Rate: Advanced Melanoma, since 2009

%
Many Aggressive Large B Cell Lymphoma’s can’t present their Internal Antigens: No Cell Surface HLA

Innate & Adaptive Immune (Local) Suppression of T Cell Anti-Tumor Killing: Myeloid Suppressor Cells
Innate & Adaptive Immune (Local) Suppression of T Cell Anti-Tumor Killing: Regulatory T Cells (T regs)
The Future of Cancer Immunotherapy

- Understand How the Immune System Works!
  - How/Why did it Evolve?
  - What Problems has Evolution Selected our Immune Network to Solve?

- Understand Each Tumor, Class of Tumors

- Identify and Test Anti-Tumor Approaches Based on the Biology of Each Tumor
  - Test in Mice with Genetically Engineered Mouse Tumors
  - Test in Human Clinical Trials