Bio 5487: Immunotherapy

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Can the immune system identify inherited genetic differences (i.e. allelic or DNA polymorphisms) or acquired differences (i.e. somatic mutations) to eliminate malignant cells?
Established Cancer Immunotherapies

• **Cytokines**
  – Interferon α2b
  – IL-2
  – GM-CSF

• **Monoclonal antibodies**
  – Targets include: her2/neu, EGFR, VEGF, CD20, CD52, CD33

• **Cell therapy**
  – Bone marrow transplants
  – Donor lymphocyte infusions (DLI)
  – sipuleucel-T (Provenge)

• **Vaccines**
  – HPV
  – HBV
Established Cancer Immunotherapies do not discriminate between self and non-self

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* Maybe the one exception
Two topics for today

• Allelic differences between 2 individuals.

• Somatic cancer mutations within 1 individual.
ANTILEUKEMIC EFFECT OF GRAFT-VERSUS-HOST DISEASE IN HUMAN RECIPIENTS OF ALLOGENEIC-MARROW GRAFTS

PAUL L. WEIDEN, M.D., NANCY FLOURNOY, M.S., E. DONNALL THOMAS, M.D., ROSS PRENTICE, PH.D., ALEXANDER FEFER, M.D., C. DEAN BUCKNER, M.D., AND RAINER STORB, M.D.

Figure 1. Kaplan-Meier Product Limit Estimate of the Probability (Expressed as per Cent) of Remaining in Remission from Acute Lymphoblastic or Nonlymphoblastic Leukemia as a Function of Time after Transplantation.

Data are shown for 46 syngeneic-marrow recipients, 117 allogeneic-marrow recipients with no or Grade I GVHD and 79 allogeneic-marrow recipients with Grades II to IV or chronic GVHD. Each open symbol represents one patient who is now alive in remission.
Allogeneic bone marrow (stem cell) transplant

Donor hematopoietic stem cells repopulate the patients bone marrow after high dose chemotherapy and total body radiation are administered.

Patients are hospitalized for 2-3 weeks.
Types of Transplants

Allogeneic: Family/Unrelated Donor

Autologous: Self-Donation

Syngeneic: Identical Twin
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LETHAL GRAFT-VERSUS-HOST DISEASE AFTER BONE MARROW TRANSPLANTATION ACROSS MINOR HISTOCOMPATIBILITY BARRIERS IN MICE
Prevention by Removing Mature T Cells from Marrow*

BY R. KORNGOLD AND J. SPRENT

From Immunobiology Unit, Department of Pathology, University of Pennsylvania School of Medicine and the Wistar Institute, Philadelphia, Pennsylvania 19104

Fig. 4. Lethal GVHD in irradiated (750 rads) B10.BR mice given unfractionated CBA/J marrow cells. The data show cumulative mortality after injection of untreated syngeneic marrow cells (B10.BR BM), anti-Thy 1.2-serum-treated CBA/J marrow cells (CBA αα BM), untreated CBA/J marrow cells (CBA BM) or CBA/J marrow cells supplemented with $10^6$ or $10^7$ peripheral lymphocytes (PL) from pooled spleen and LN cells of normal CBA/J mice. Data from a single experiment involving six mice per group.
Relapse after marrow transplantation is a function of the graft type and the occurrence of graft-vs-host disease

Blood 75:555, 1990
RAPID COMMUNICATION

Donor Leukocyte Transfusions for Treatment of Recurrent Chronic Myelogenous Leukemia in Marrow Transplant Patients

By H.J. Kolb, J. Mittermüller, Ch. Clemm, E. Holler, G. Ledderose, G. Brehm, M. Heim, and W. Wilmanns

Three patients with hematologic relapse after bone marrow transplantation for chronic myelogenous leukemia were treated with interferon α and transfusion of viable donor buffy coat. All had complete hematologic and cytogenetic remission, which persisted 32 to 91 weeks after treatment. In two patients graft-versus-host disease developed and was treated by immunosuppression. These results are an example of adoptive immunotherapy without cytoreductive chemotherapy or radiotherapy in human chimeras.

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<table>
<thead>
<tr>
<th>Table 3. Percentage of Ph1-Positive Metaphases Before and After Treatment With IFN and Buffy Coat Transfusions</th>
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<tbody>
<tr>
<td><strong>UPN 105</strong></td>
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<tr>
<td>Weeks Posttransplant</td>
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<td>Relapse</td>
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Abbreviation: NE, not evaluable.
DLI provides durable remission in CML patients

Dazzi et al. Blood 2000
Two central questions emerge from the initial clinical observation with donor lymphocyte infusions:

- What are the **effector cells** that mediate the anti-leukemia effect?

- What are the **antigens** present on the leukemia cells?
What are the antigens present on the leukemia cells?

Peptide-MHC complexes

Cell surface proteins
Patients that received allogeneic marrow transplantation from a HLA-matched sibling and exhibit severe GVHD were observed to have strong cytotoxic T cell reactivity to their own tissues.

**HLA-identical (a/d) marrow from sibling**

Patient (a/d)

a: A2, B62, DR4
d: A2, B27, DR1

Severe aGVHD

↓

Culture post-Tx PBL (DONOR) with irradiated PBL obtained pre-Tx (PATIENT) (karyotype analysis confirmed that post-Tx PBL are donor origin)

↓

Test reactivity (D anti-P) against a panel of HLA-typed target cells from related and unrelated donors.
Analysis of T cell reactivity (D anti-P) in HA family (% killing)

Haplotypes:
- a: 2, 62, Cw3, DR4
- b: 24, 35, Cw4, DR7
- c: 3, 35, Cw4, DR1
- d: 2, 27, Cw1, DR1

Why isn’t #3 killed?
Biochemical identification of HA-1
Science 279:1054, 1998

HLA-A2 bound peptides were eluted from HA-1+ cells, separated on HPLC, and fractions tested on target cells in a lysis assay using CTL clone.

\[\text{VLHDDLLEA}\] synthetic peptide was recognized by CTL and shared identity to KIAA0223 cDNA.
HA-1 is diallelic

Transfection of HA-1 H allele confers susceptibility to CTL recognition

allele frequency (population)

HA-1 H allele 0.441
HeLa cells (HA-1 negative)

HA-1 R allele 0.559

VLH/RDDLLEA
HA-1 mHag

• Diallelic gene with a single amino acid polymorphism encoded by *KIAA0223 locus*. (Science 279:1054, 1998)

• Clear evidence (using HLA class I tetramers) showing a correlation between GVHD and increased frequency of circulating HA-1 specific CTL. (Nature Med 5:839, 1999)

• A mismatch of HA-1 can cause GVHD in BMT patients receiving HLA-matched marrow from sibling donors. (NEJM 334:281, 1996)

• HA-1 specific CTL can inhibit the clonal growth in vitro of HA-1 antigen positive leukemia cell lines. (J Exp Med 174:27, 1991)

• HA-1 expression is limited to hematopoietic tissues. (J Immunol 149:1788, 1992)
Human minor histocompatibility antigens
Current Opinion in Immunology 8:75, 1996

- Both MHC class I (CD8+ T cell) and MHC class II (CD4+ T cell) mHag have been described.
- Variable phenotype frequency.
- Mendelian segregation (except H-Y).
- Tissue distribution can be either limited or ubiquitous.
- H-Y antigen (1976) was discovered in a female aplastic anemia patient transplanted with marrow from a HLA identical brother. Despite a transient chimerism, the patient’s T cells recovered and rejected the allo-graft.
Separating GVL and GVHD: mHag-specific CTL are the key

Transplant patient (recipient)
HLA-A2+, (HA-1^H)

Transplant donor
HLA-A2+, (HA-1^R)

GVL: Yes
GVHD: No
Aplasia: No

Patient leukemia cell (HA-1^H)
Patient non-hematopoietic tissues (HA-1^neg)
Donor derived hematopoietic cells (HA-1^R)

HA-1 specific CTL

How can we isolate these effector T cells?

Blood 93:2336, 1999 for discussion
Checkpoint Inhibition
CTLA-4 is a negative regulator of T cell activation

CD28 - B7 interaction provides co-stimulation ("the accelerator") and controls T cell growth

CTLA-4 – B7 interaction provides a negative signal ("the brake") and controls T cell survival

Immunity 1:405, 1994
Ipilimumab prolongs survival

Ipi alone 10.1 mo
Ipi+gp100 10.0 mo*
Gp100 vaccine 6.4 mo

*HR 0.68, p<0.001
Ipi/gp100 vs gp100

NEJM 363: 711, 2010
Anti-CTLA-4 treatment

Nature 480: 480, 2011
PD-L1 is expressed by the cancer cell
Anti-PD-1 treated melanoma patients

Pembrolizumab (Merck)
Activating receptors:
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors:
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic antibodies

Blocking antibodies

T-cell stimulation