Challenges of Hematopoietic Stem Cell Transplantation

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Hematopoietic Stem Cell Transplantation

Objectives

- Deliver sufficient chemo-radio therapy to destroy tumor cells (old paradigm)
- Provide a source of hematopoietic stem cells to replace ablated marrow of patient
- Establish organ graft tolerance to prevent rejection of donor cells
- Provide immune effector cells to mediate graft-vs-tumor activity

Indications for Stem Cell Transplantation

- **Benefit documented by randomized trials**
  - intermediate grade NHL, sensitive relapse
  - multiple myeloma
  - High risk first remission acute leukemia
- **Curative potential, benefit inferred**
  - AML/ALL beyond CR1
  - CML
  - MDS
  - Aplastic anemia, congenital immune deficiencies
  - low grade lymphoma/CLL
  - hemoglobinpathies
- **Benefit not yet established**
  - Solid tumors, autoimmune disease, regenerative medicine

Obstacles to Success

- Finding a compatible donor
- Limiting transplant related complications
- Preventing disease relapse

Hematopoietic Stem Cells

- **Source**

  Autologous vs Allogeneic

  Bone Marrow vs Peripheral Blood vs Cord Blood

  Related vs Unrelated

  HLA matched vs mismatched

Sources of Stem Cells for Transplantation

Autologous	Allogeneic
• Donor available	Undamaged stem cells
• No GVHD	No tumor contamination
• No immunosuppression	Graft-vs-tumor effect
Less toxicity	*More toxicity*
Higher relapse rates	*Lower relapse rates*

Allogeneic PBSCT vs BMT

- Engraftment of PBSCs faster than BM
- Acute GVHD ?minimally higher after PBSCT despite much greater T cell number than BM
- Chronic GVHD higher with PBSC
- Immune reconstitution faster with PBSC

Chronic GVHD

- Clinically and pathologically distinct from acute GVHD
- Presentation:
  - lichenoid or scleradermatous skin involvement
  - cholestasis
  - sicca syndrome
  - GI tract strictures
  - bronchiolitis obliterans
- Poorly responsive to treatment
- Extensive chronic GVHD - high mortality

Histocompatibility Issues

- **Major HLA antigens**
  - **located on chromosome 6**
  - **1 in 4 likelihood of match with sibling**
  - **direct sequencing for Class 1 (A, B, C)**
  - **site specific oligonucleotide probes for Class 2 (DR)**
- **Minor HLA antigens**
  - **only a handful identified (HA-1, H-Y)**
  - **routine testing not yet available**
  - **probably play critical role in GVHD and ? GVL**

Unrelated Donor HSCT

- 4 million potential registered donors
- 60-80% of patients can find match
- Likelihood of finding a donor dependent upon racial and ethnic background
- Higher risk of GVHD and graft failure, but lower risk of relapse
- Overall outcome almost equal to MRD

Effect of Single Antigen/Allele HLA Mismatch on Outcome after Unrelated BMT (NMDP)

- **HLA -A, - B, - C, and – DR *antigen and allele* mismatches are all associated with increased GVHD and mortality**
- **It remains unclear if a mismatch at one particular locus is superior a mismatch at another.**

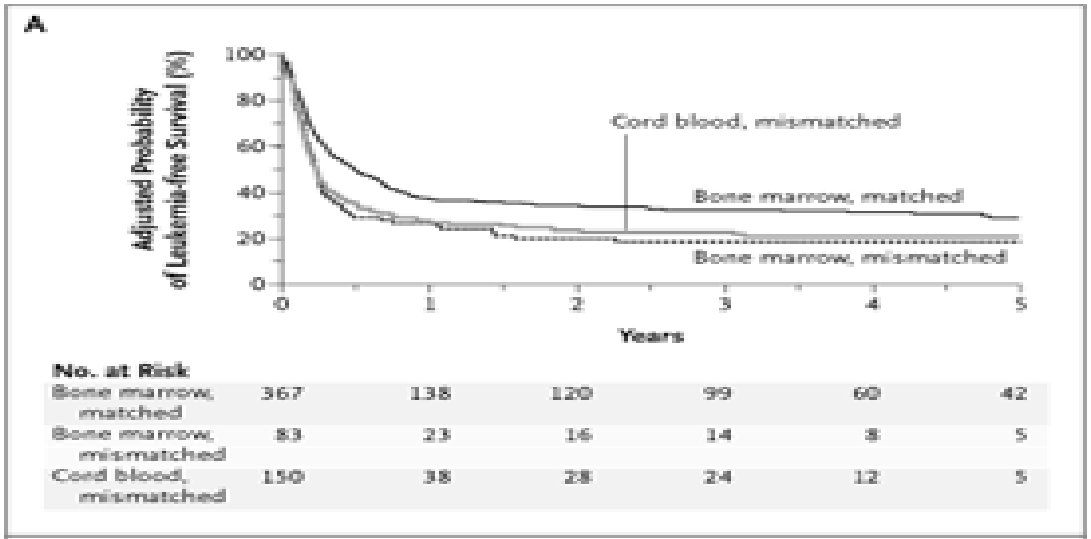
Umbilical Cord Blood Transplantation

- Stem cells present in cord blood
- Number of mature T cells low
- UCB transplantation can be performed between 2-3 antigen mismatched donor/patient pairs with low GVHD
- Engraftment and immune reconstitiution delayed compared with BM or PBSC

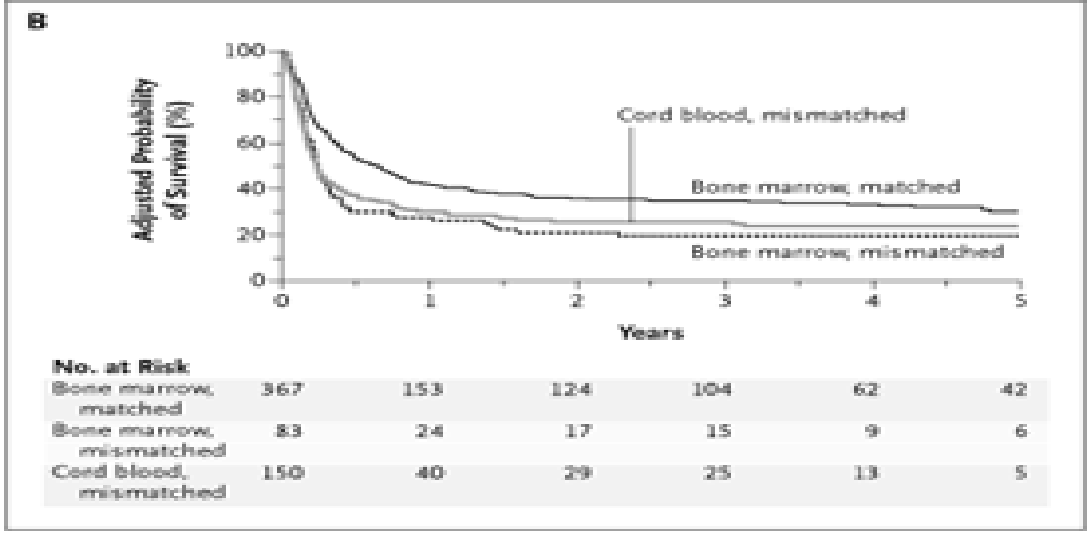
Selection of Cord Blood Unit

- Cell Dose most important factor
  - Cell dose >3x10(7) NC/kg optimal
- HLA typing second most important factor
  - 4/6 matched unit or better
- Unknown factors: age of unit, collection method, processing technique

Outcome after Unrelated Cord Blood and Marrow Transplant



No. at Risk						
Bone marrow, matched	367	138	120	99	60	42
Bone marrow, mismatched	83	23	16	14	8	5
Cord blood, mismatched	150	38	28	24	12	5



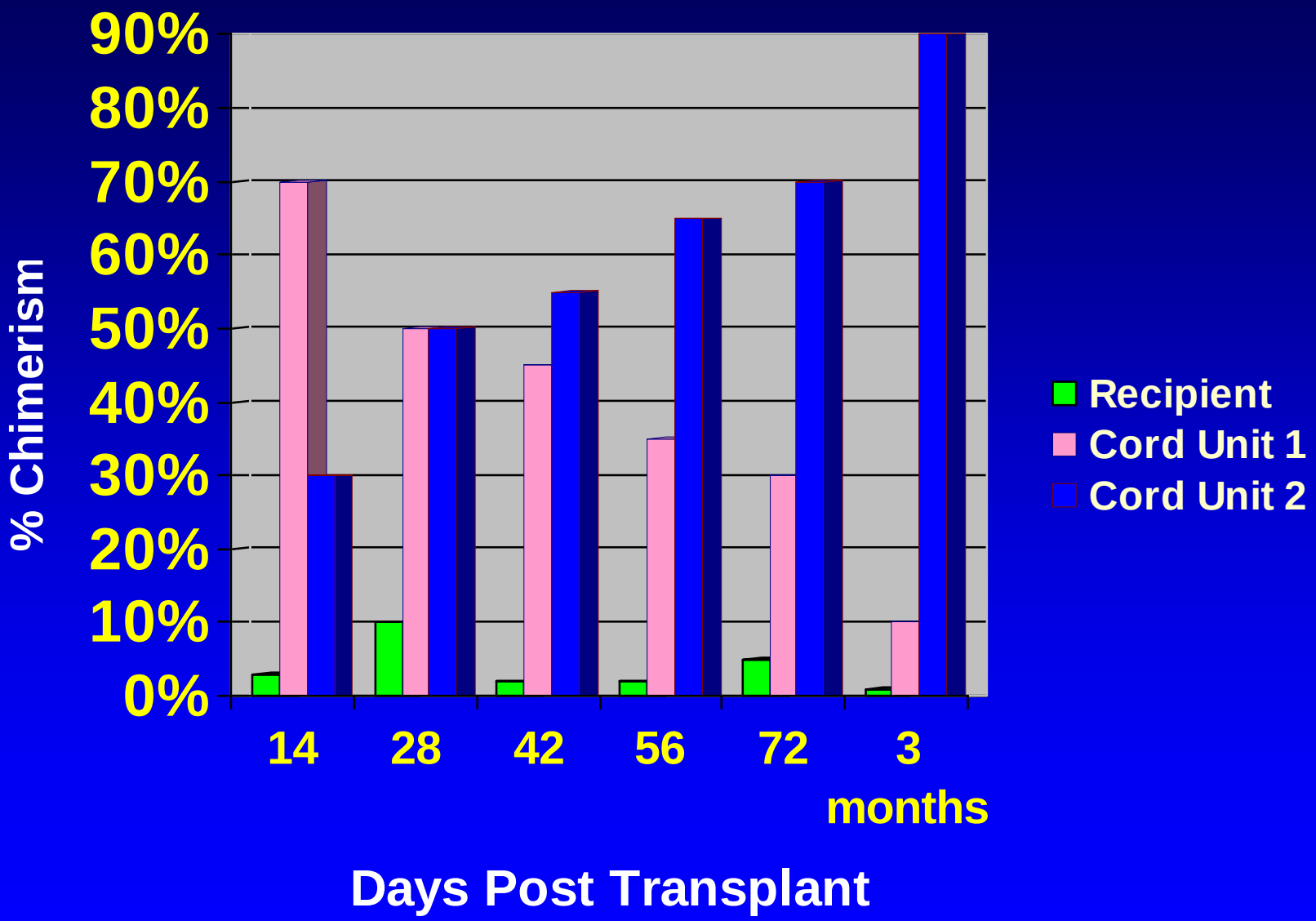
No. at Risk						
Bone marrow, matched	367	153	124	104	62	42
Bone marrow, mismatched	83	24	17	15	9	6
Cord blood, mismatched	150	40	29	25	13	5

Laughlin, et al, NEJM 2004

Double Cord Blood Transplants

- Cell dose is the most important factor to success of cord blood transplant
- Two cords can be infused sequentially which appears to speed engraftment
- Both contribute to early engraftment, but ultimately one cord predominates

Chimerism Patient One



Complications of HSCT

- Conditioning-related organ toxicity
- Infection
- Graft-versus-host disease

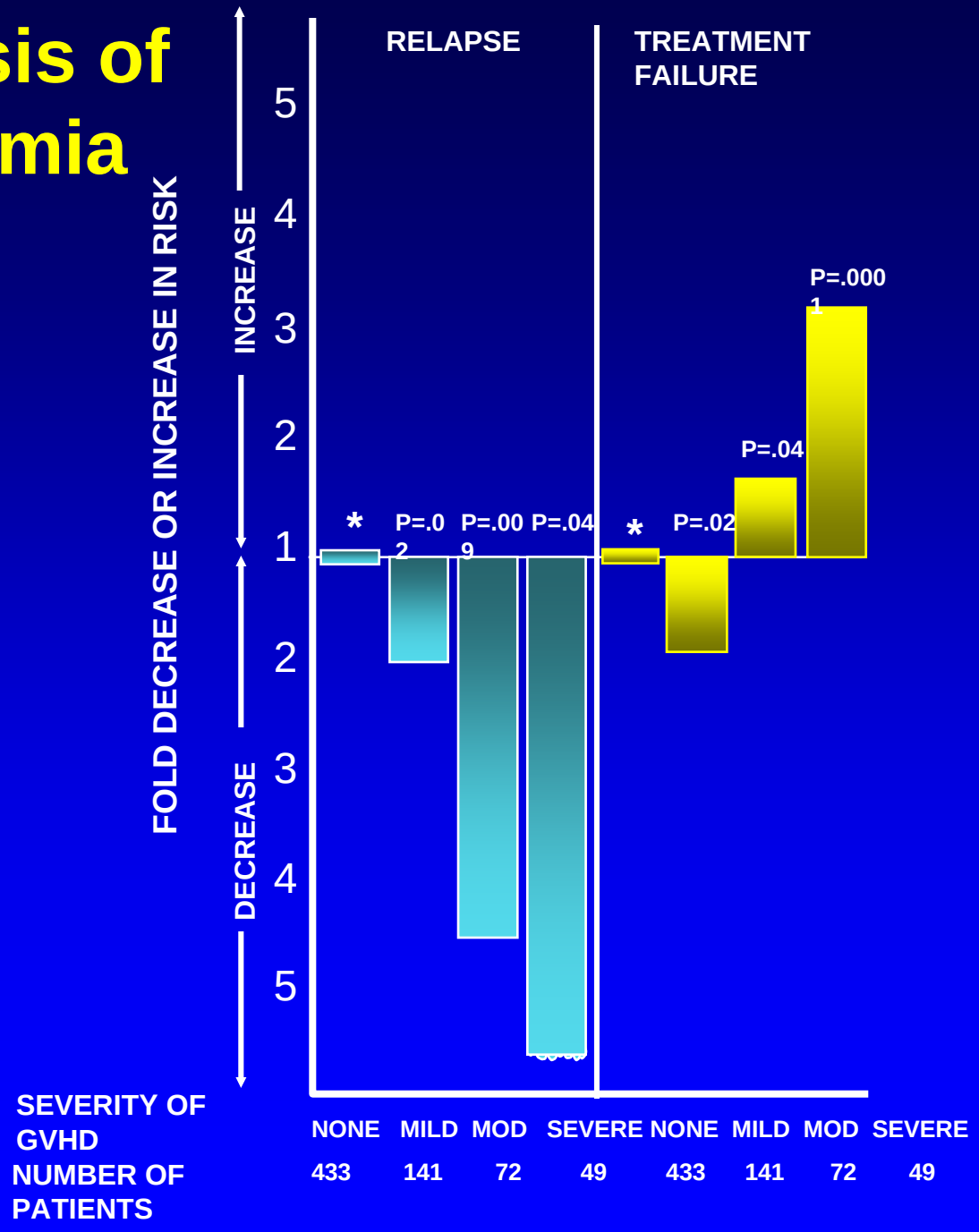
GVHD
Effect on Outcome

- **Moderate-to-severe GVHD increases morbidity and mortality of transplantation**

- **Development of GVHD may prevent disease relapse post-BMT. (CML>>CLL/MDS >AML/ALL).**

IBMTR Analysis of Graft-v-Leukemia

Horowitz, Blood 1990;75:555



Clinical Evidence for Graft vs. Leukemia Effect

- ↓ Relapse in patients with GVHD
- ↑ Relapse after identical twin transplants
- ↑ Relapse after T-cell depleted transplants
- Durable remissions after donor lymphocyte infusions, not always associated with GVH

Separating GVL from GVH

- **Elimination of leukemia in the absence of lethal GVHD after allogeneic BMT**
- **LPS antagonism reduces GVHD and preserves GVL activity after experimental BMT**
- **Il-11 separates GVL effects from GVHD after BMT**
- **Donor –derived interferon gamma separates GVL effects and GVHD induced by donor CD8+ T cells**

Separating GVL from GVH

- G-CSF-mobilized allogeneic SCT maintains GVL effects through a perforin-dependent pathway while preventing GVHD
- Keratinocyte growth factor separates GVL effects from GVHD
- Leucyl-leucine methyl ester-treated haploidentical donor lymphocyte infusions can mediate GVL activity with minimal GVHD risk

Separating GVL from GVH

- Crucial role of timing of donor lymphocyte infusion in generating dissociated GVH and GVL responses in mice receiving allogeneic BMT
- Mixed chimera converted into full donor chimera with powerful GVL effects but no GVHD after non T cell depleted HLA mismatched peripheral blood stem cell transplantation
- Definitive separation of GVL and GVH specific CD4+ T cells by virtue of their receptor beta loci sequences

Strategies to Prevent GVHD

- Interfere with T cell activation/function
  - cyclosporine
  - tacrolimus
  - rapamycin? (sirolimus)
- Interfere with T cell proliferation
  - methotrexate
  - mycophenolate
- Reduce T cell number (T cell depletion)

T Cell Depletion - Advantages

- Decreased incidence and severity of acute GVHD
- Decreased incidence of chronic GVHD
- May eliminate need for immune suppressive medication
- Decrease in organ toxicity

T Cell Depletion - Disadvantages

- Increased rate of graft rejection (early series)
- Increase rate of disease relapse
  - CML clearly
  - less certain with other malignancies
- Increase in EBV lymphoproliferative disease
- Delayed immune reconstitiution

Randomized TCD URD Trial

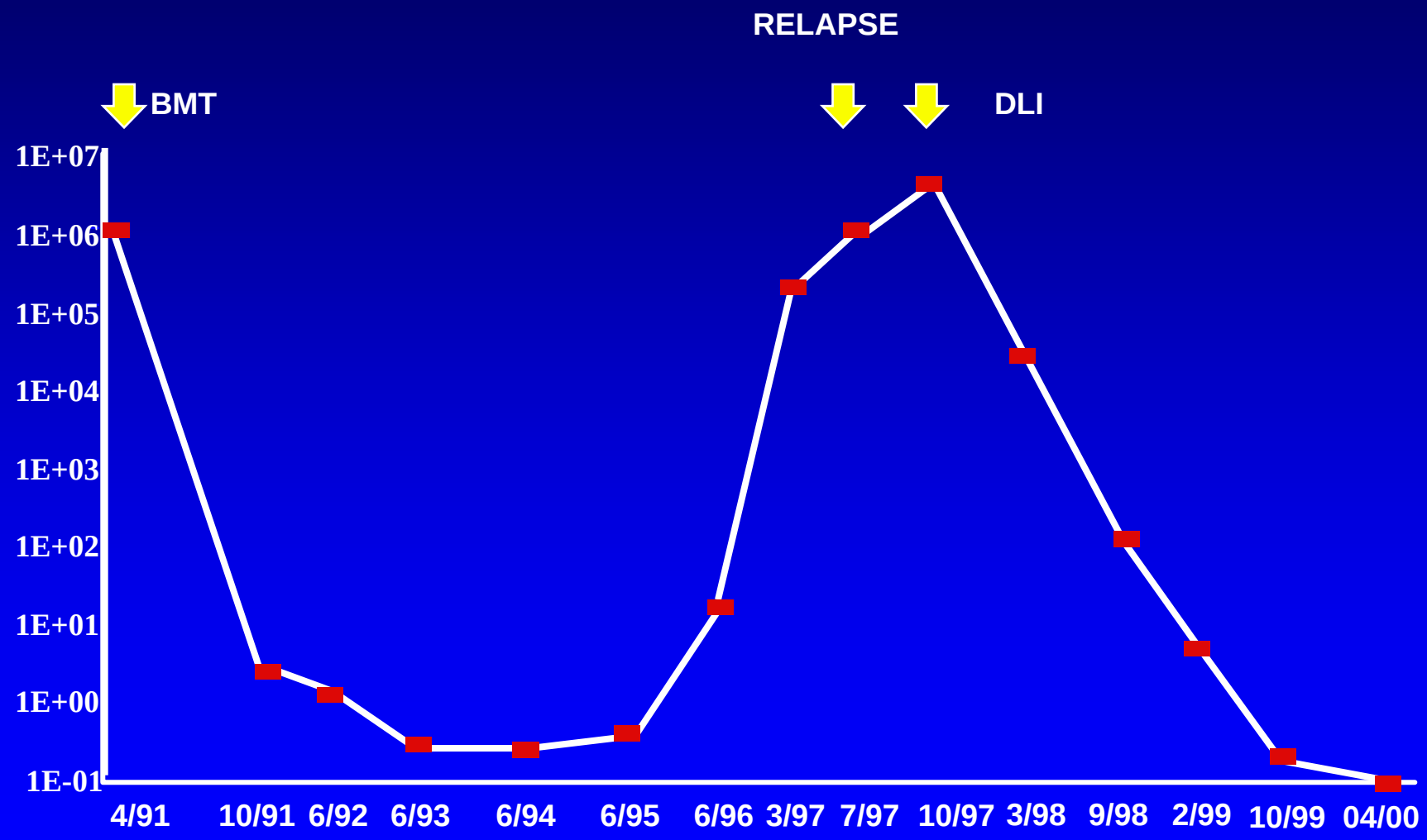
	TCD	CyA/Mtx	p
Engraftment	.94	.93	NS
Gr 3-4 GVHD	.15	.27	<0.01
cGVHD	.24	.29	0.10
Bearman tox.	Less	More	<0.01
Hosp days	32.0	37.5	0.03
Bact/Fung infx	Same	Same	NS
CMV infx	More	Less	0.008
Relapse -CML	0.16	0.06	0.01
Relapse – Ac. Leuk	0.26	0.24	NS
OS	.31	0.33	NS

Wagner, et al Lancet 2005

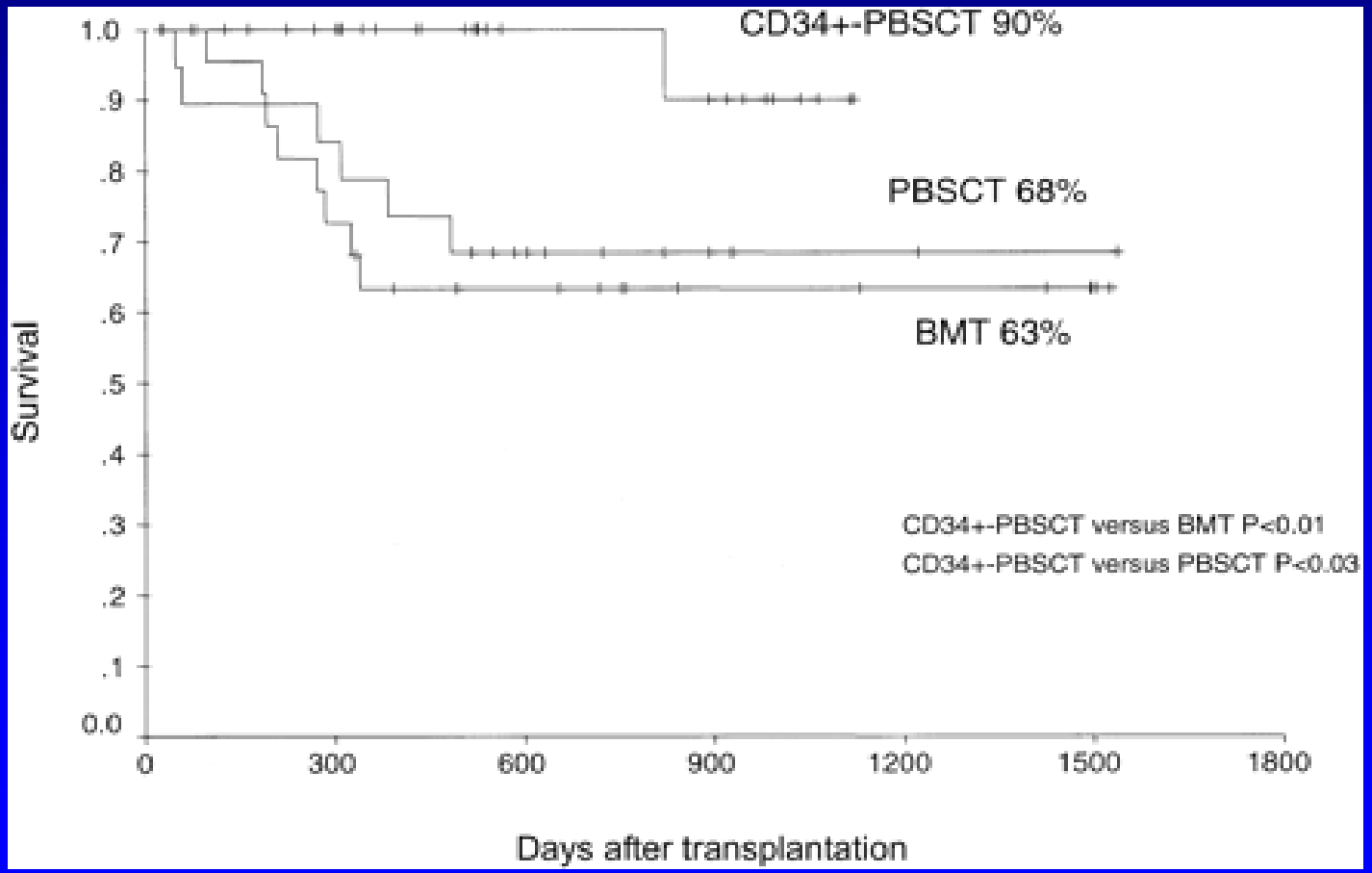
Donor Lymphocyte Infusions

- Can induce patients who have relapsed after BMT into complete remission without use of additional chemotherapy
- Most effective for CML (70-85%) with activity in myeloma, MDS, CLL also noted
- Can cause GVHD

Quantitative PCR Analysis After Allogeneic BMT and DLI for Low Grade Lymphoma



Survival after PBSCT, BMT, or CD34+ PBSCT (+DLI) for CML (Elmaagacli, et al Blood 2003)



Non-Myeloablative Transplantation

- Goal of conditioning is to facilitate engraftment, not eradicate tumor
- Engraftment can be achieved with reduced conditioning
- Early toxicity low and allows transplantation of older patients and those with medical contraindications to high dose therapy –though chronic GVHD a major problem
- Unclear whether superior or inferior to conventional transplantation

Graft Engineering Strategies: Beyond the Average T Cell

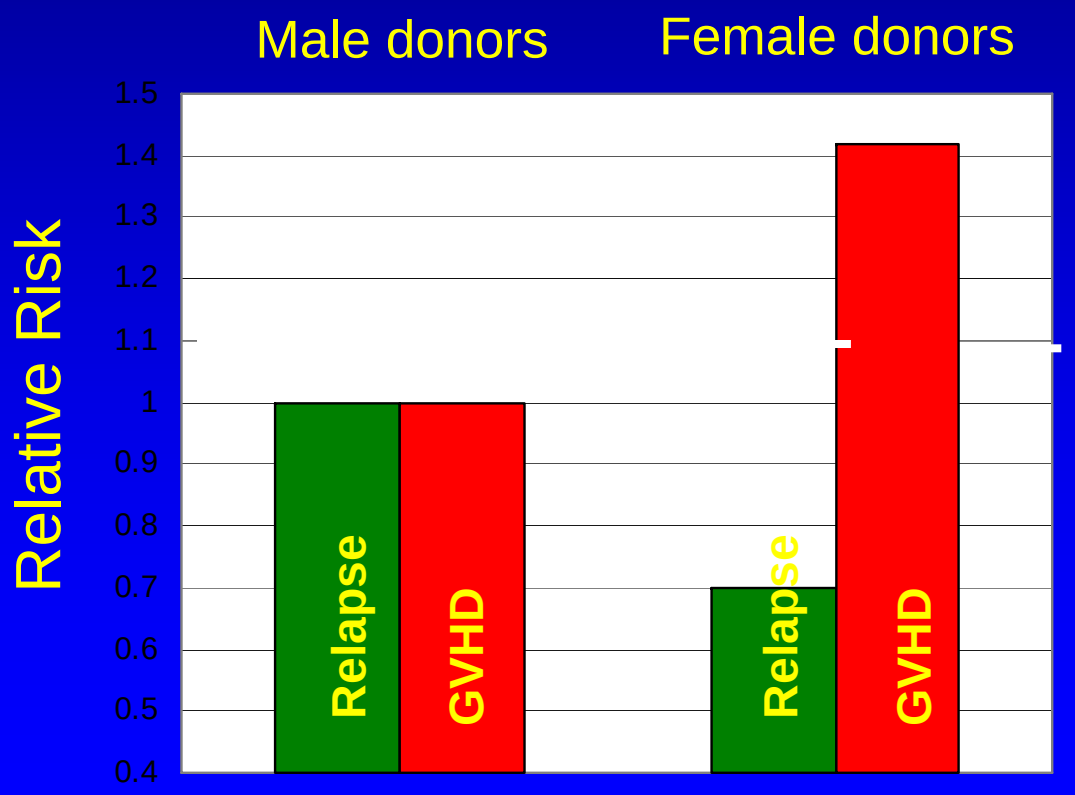
- Expansion and infusion of immune suppressive CD4+CD25+ Tregs
- Manipulation of B Cells to treat/prevent chronic GVHD
- Infusion of KIR-mismatched NK Cells to augment GVL and prevent GVH
- Modulation of recipient and host DCs to affect GVHD and GVL

Graft Engineering Strategies

- **Insertion of suicide genes (e.g., HSV-TK) which will make T cells susceptible to in vivo destruction during GVHD reaction**
- **Depletion of activated T cells after co-cultivation of marrow with allo-antigen presenters**
- **Anergization of T cells (e.g. CTLA4Ig) against alloantigens after co-cultivation with APCs**

Gender and GVHD
Male patients with female donors

-Relapse less often
-Suffer more GVHD



Randolph, Blood 2004

Clinical Relevance of H-Y Antibody?

- 75 F→M HSCT patients with plasma collected 6 months to 5 years after HSCT
- Analyze B cell immune responses against five H-Y antigens in relation to:
  1. Donor selection criteria
  2. Transplant and immunosuppressive treatment regimens
  3. Clinical outcome.

Antibody Response to H-Y Antigens correlates with Chronic GVHD

	odds ratio	95% CI	p-value
univariate analysis			
Chronic GVHD vs. none	**15.45**	**(4.8- 50)**	**<0.0001**
multivariable analysis			
Chronic GVHD vs. none	**55**	**(7.6-402)**	**<0.0001**

Variables:

Patient age

Donor age

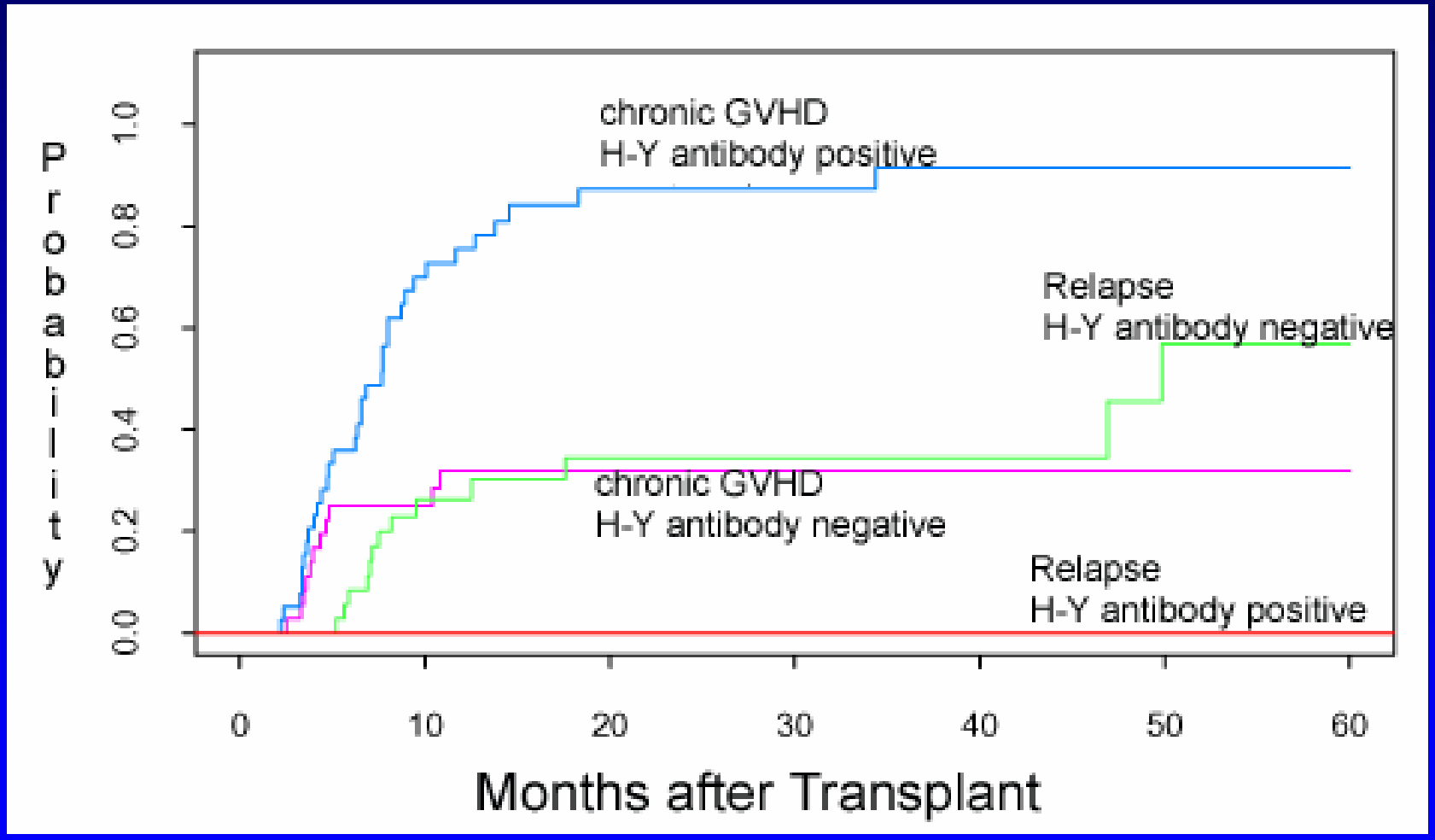
Conditioning:

- Ablative vs Nonmyeloablative

Stem Cell Source:

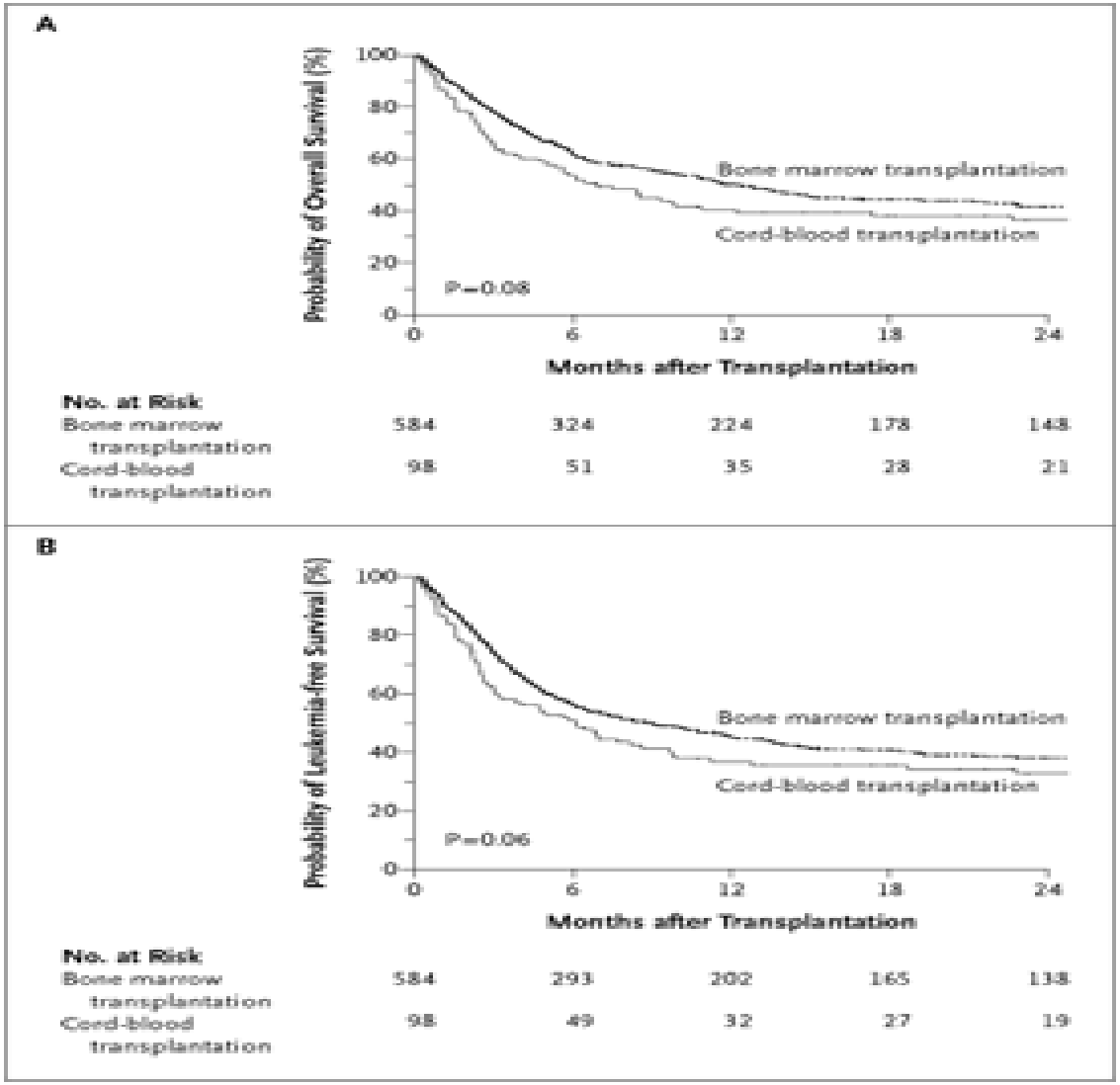
- Unrelated vs Related Donor
- Marrow vs PBSC
- T cell depletion

H-Y antibody: Chronic GVHD and Relapse



Miklos, et al 2004

Outcome after Unrelated Cord Blood and Marrow Transplant (EBMT)



Rocha, et al
NEJM 2004

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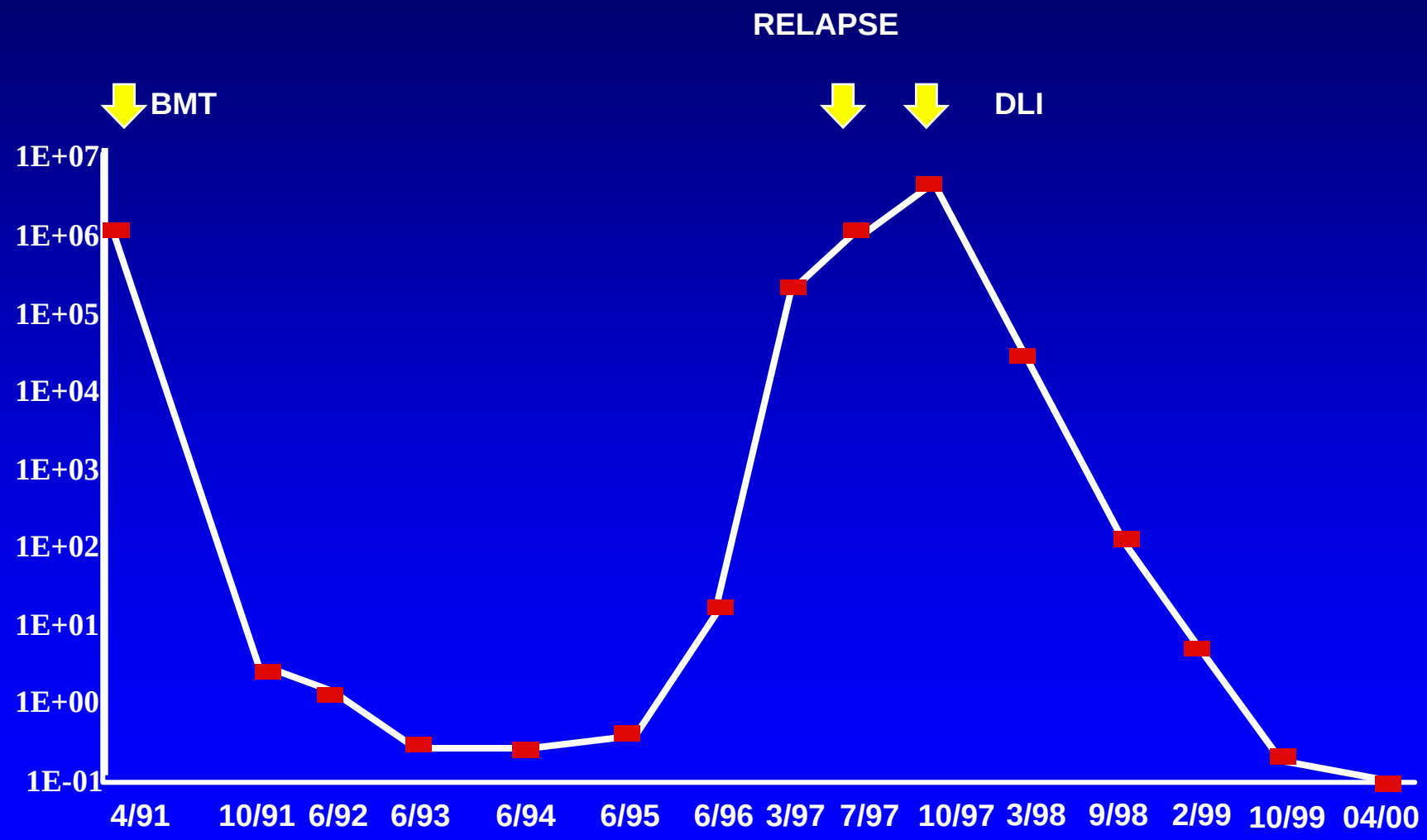

On the Horizon

- **Identification of DLI target antigens for future development as tumor vaccines**
- **Identification of minor histocompatibility antigens and their roles in GVH/GVL**
- **Development of new drugs which can eliminate transplantation altogether**