Adoptive Immunotherapy

- Greatest initial success was in the eradication of relapsed CML after allogeneic transplant.
- Also useful in treatment of post-transplant EBV-lymphoproliferative disease
- Initial use of unselected leukocytes
- Dosed according to content of CD3+ T cells
- Other component leukocytes, e.g., NK cells, very likely play a role.

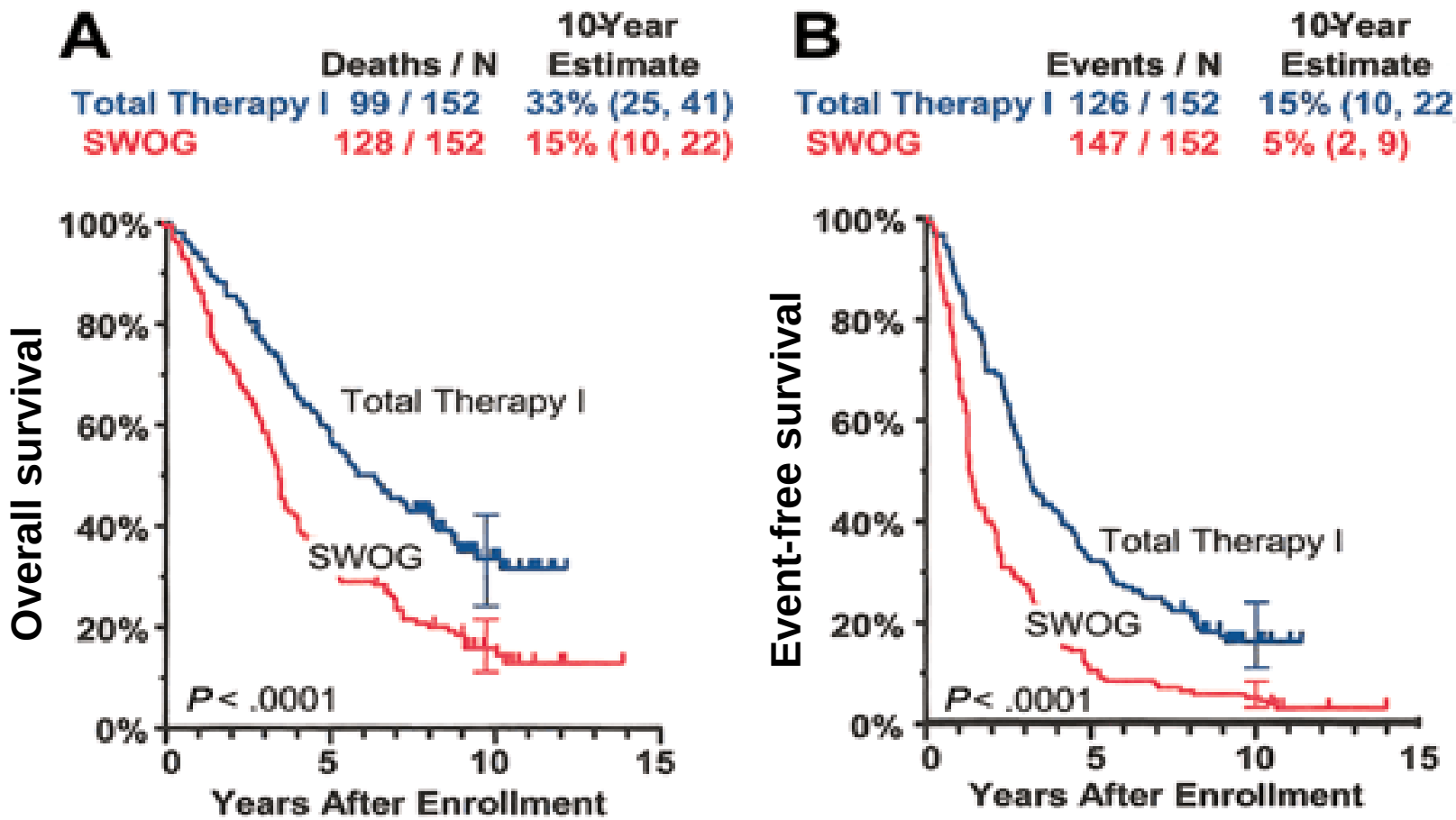
Adoptive Immunotherapy

- Success of donor leukocyte infusions has led to the incorporation of immunotherapy as an integral feature of preparative regimens.
- Nonmyeloablative preparative regimens shift the burden of tumor eradication from high-dose conditioning regimens to the donor’s immune cells

Adoptive immunotherapy

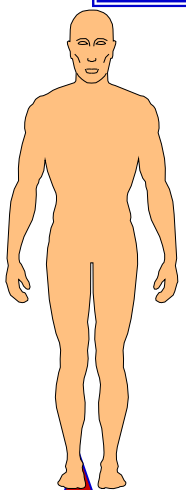
- Targeted therapy to enhance anti-tumor or anti-pathogen effect without exacerbating GvHD
  - tumor or virus specific Ag
  - minor histocompatibility Ags
  - specificity conferred by the APC, e.g., DCs
- Role of cytokines in expansion ex vivo or adjuvant administration in vitro.
- Route of administration

Comparison of standard chemoRx (SWOG) vs chemoRx→autograft→IFN maintenance (Total Therapy I), *median f/u 9yrs*



Barlogie et al., Blood, 103: 20-32, 2004

Clinical protocols using dendritic cells to generate Ag-specific T cells for adoptive immunotherapy



leukopheresis

CD34+ HPCs → Langerhans cells

versus

peripheral blood mononuclear cells → monocyte-derived dendritic cells

T

T blasts

T blasts

T blasts

T T T

Ag loading

- peptide
- dying cells
- gene transfer

Table 1. Different Sources of Antigens and Antigen-Presenting Cells in Preclinical and Clinical Studies Generating CMV-Specific CTLs

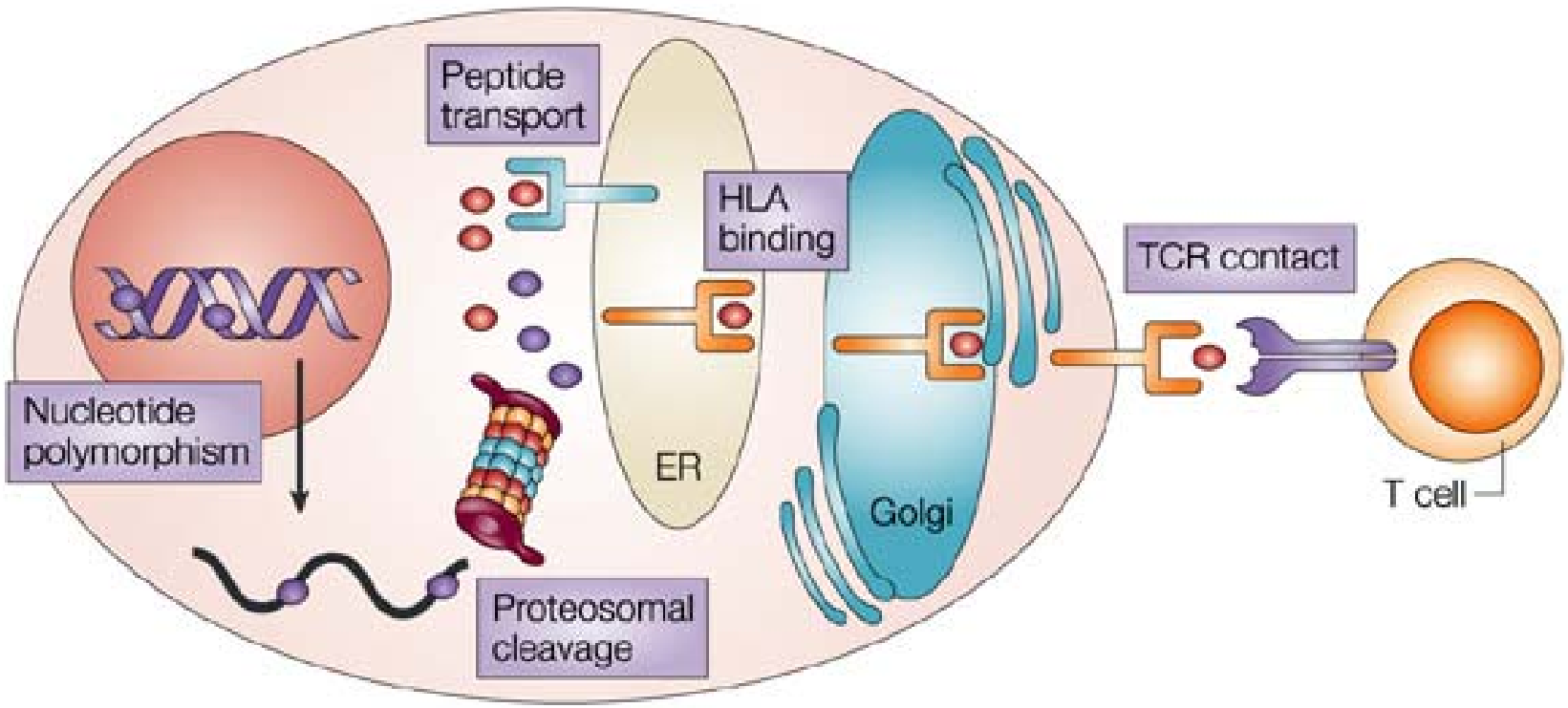
Antigen	Antigen-Presenting Cell	Reference
Virions	Skin fibroblast	Walter et al. [51]
Retroviral vector encoding pp65	B lymphoblastoid cell line	Sun et al. [36]
Adenoviral vector encoding pp65	Dendritic cells	Keever-Taylor et al. [56]
		Hamel et al. [72]
Adenoviral vector encoding pp65	Dendritic cells and B lymphoblastoid cell line	Sifi et al. [58]
CMV antigen derived from CMV-infected lung fibroblasts	Dendritic cells	Peggs et al. [54]
CMV lysate and antigen	Peripheral blood mononuclear cells	Einsele et al. [55]
HLA-A*0201-restricted CMV peptide pp65(495–503)	Dendritic cells and B lymphoblastoid cell line	Szmania et al. [92]
HLA-A*0201-restricted CMV peptide pp65(495–503)	Dendritic cells	Foster et al. [93]

Table 2. Published Reports on Use of EBV-Cytotoxic T Cells as Prophylaxis or Treatment for PTLD after BMT

Study	No. Pts. (Age)	Type of Transplant	Path. Evidence of PTLD	Cytotoxic T-Cell (CTL) Lines and Dose	Results
Rooney et al. [32]	39 (9 mo to 20 y)	T cell-depleted HSCT (mismatch related donor or matched unrelated donor)	No—prophylaxis study	Allogeneic (donor-derived) EBV CTL: minimum dose of 4 × $10^7/m^2$ and maximum dose of 12 × $10^7/m^2$	No patients developed PTLD compared with 11.5% of controls: no toxicity
Rooney et al. [32] and Gottschalk et al. [33]	3 (12–17 y)	T cell-depleted HSCT	Yes—lymphoblastic lymphoma	Allogeneic (donor-derived) EBV CTL 2–4 × $10^7/m^2$	2 compete remissions, 1 died (no response to CTL secondary to tumor mutation resistant to CTL)
Gustafsson et al. [13]	6 (1–39 y)	T cell-depleted HSCT or unmanipulated HSCT with ATG/OKT3 conditioning (mismatched or matched unrelated donor or matched related donor)	No—treatment based on increased EBV DNA levels	Allogeneic (donor-derived) EBV CTL 4 × $10^7/m^2$	5 patients had decreased EBV DNA levels. 1 patient subsequently died of PTLD (CTL showed poor specificity for EBV targets on cytotoxicity assay)

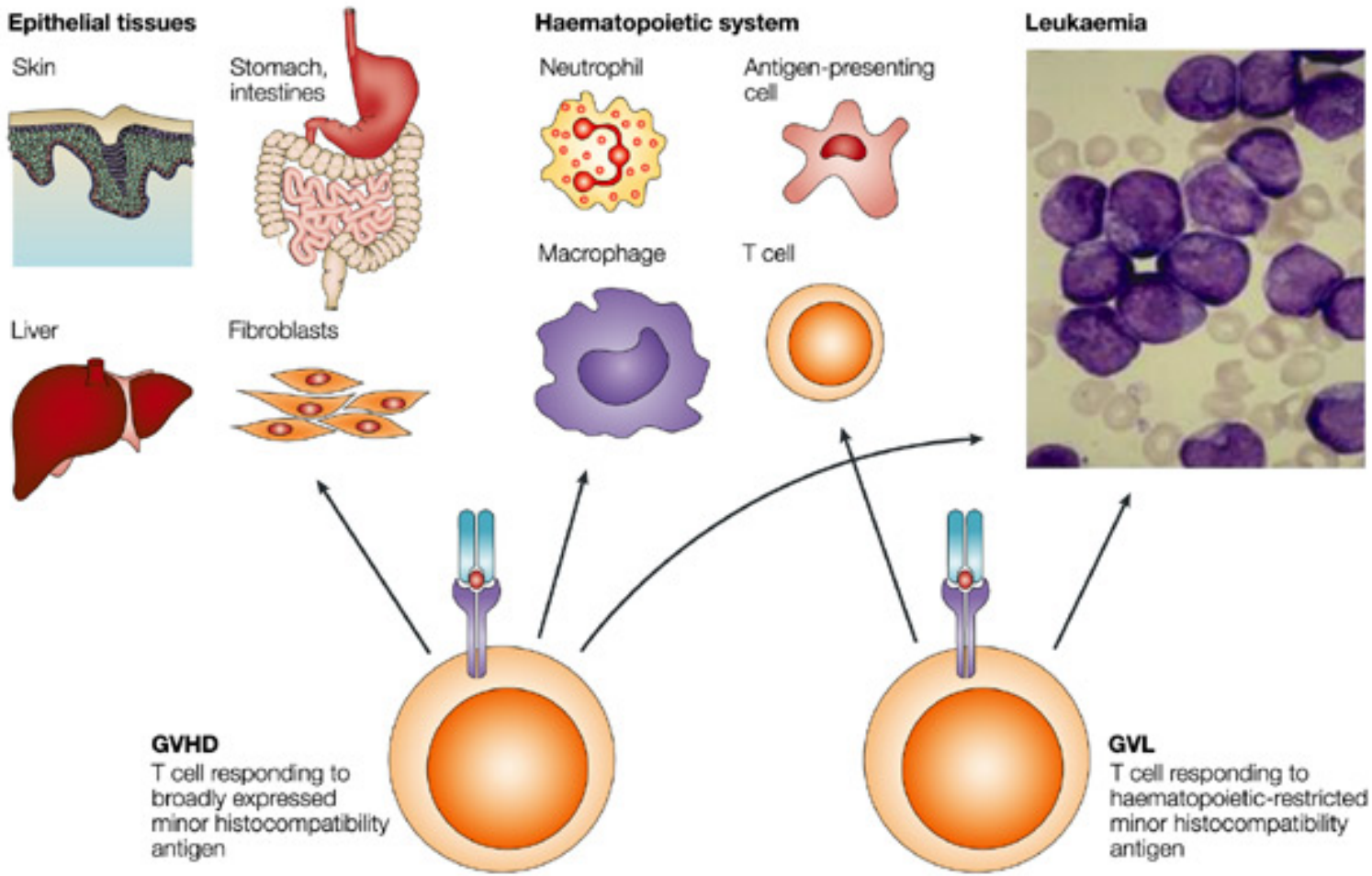
PTLD indicates posttransplantation lymphoproliferative disorder.

Generation of minor histocompatibility antigens



Bleakley and Riddell, Nature Rev Cancer, 2004

Distinguishing GvL from GvHD



Bleakley and Riddell, Nature Rev Cancer, 2004

Nature Reviews | Cancer

Minor histocompatibility antigens

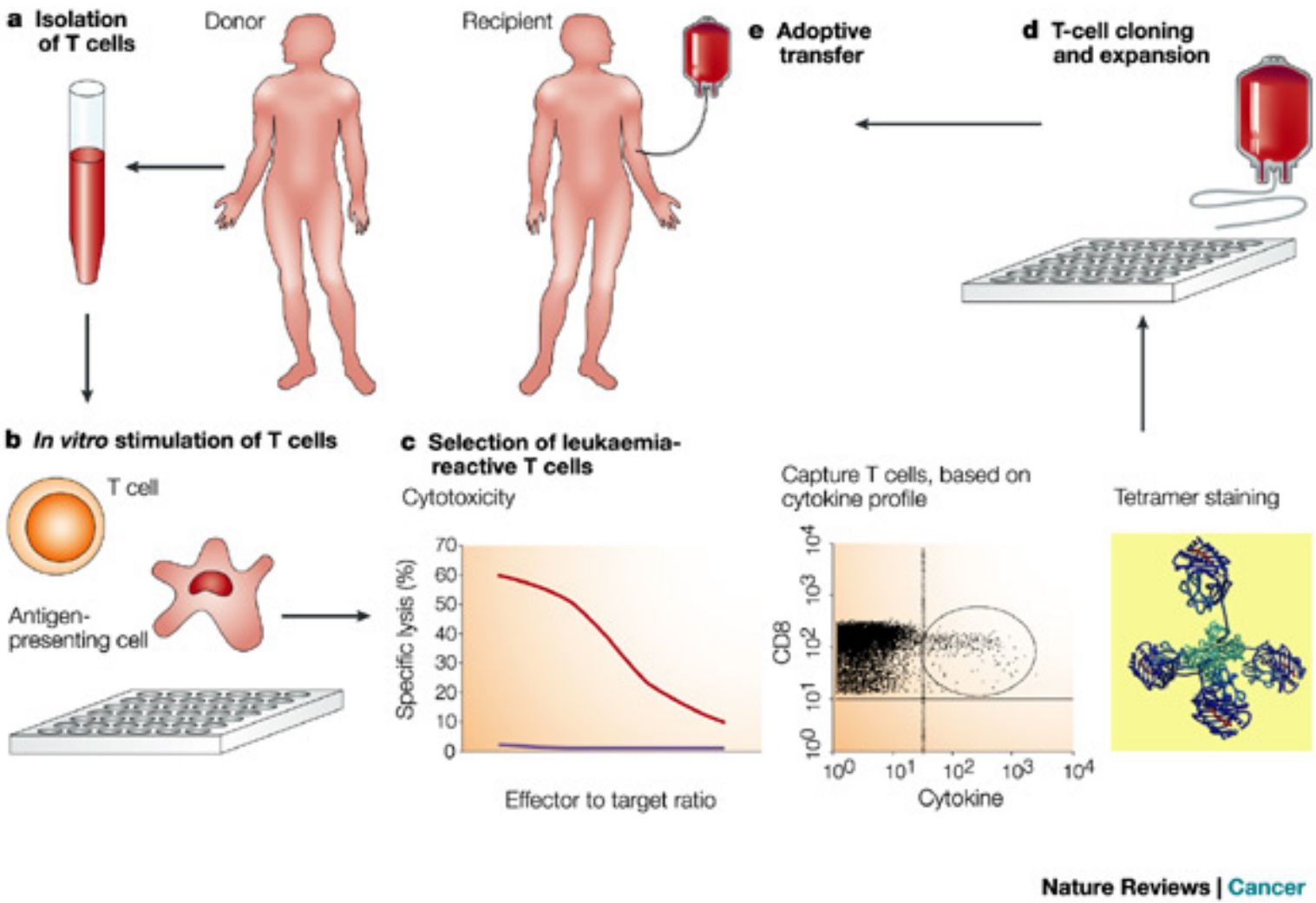
Table 2 | **Advantages and disadvantages of candidate antigens**

Class of target	Advantages	Disadvantages
Minor histocompatibility antigens	T cells have high avidity for antigen; both $CD8^+$ and $CD4^+$ T cells recognize antigen; potentially multivalent response	Limited to allogeneic transplantation; limited number of defined antigens; potential for GVHD
Overexpressed normal proteins	Broad applicability for different types of cancer	T cells have low avidity for antigen; potential for toxicity to normal tissues

GVHD, graft-versus-host disease.

Bleakley and Riddell, Nature Rev Cancer, 2004

Adoptive immunotherapy with donor T cells to augment GvL



Bleakley and Riddell, Nature Rev Cancer, 2004