Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Hematologic Malignancies

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Advances in Cancer Immunotherapy™ - Texas
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Society for Immunotherapy of Cancer

Objectives

- Understand the basics of immunotherapy for hematologic malignancies
- Identify tumor antigens that mediate the graft versus leukemia/lymphoma effects
- Understand the mechanisms of T cell receptor (TCR) recognition of leukemia/lymphoma antigens
- Highlight the role of serine proteases as targets for immunotherapy in hematologic malignancies

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Outline

- Stem Cell Transplantation
- Recognition of hematologic tumor antigens by immune cells
- Types of immunotherapies that have been used in hematologic malignancies
- Serine proteases as targets for immunotherapy in hematologic malignancies

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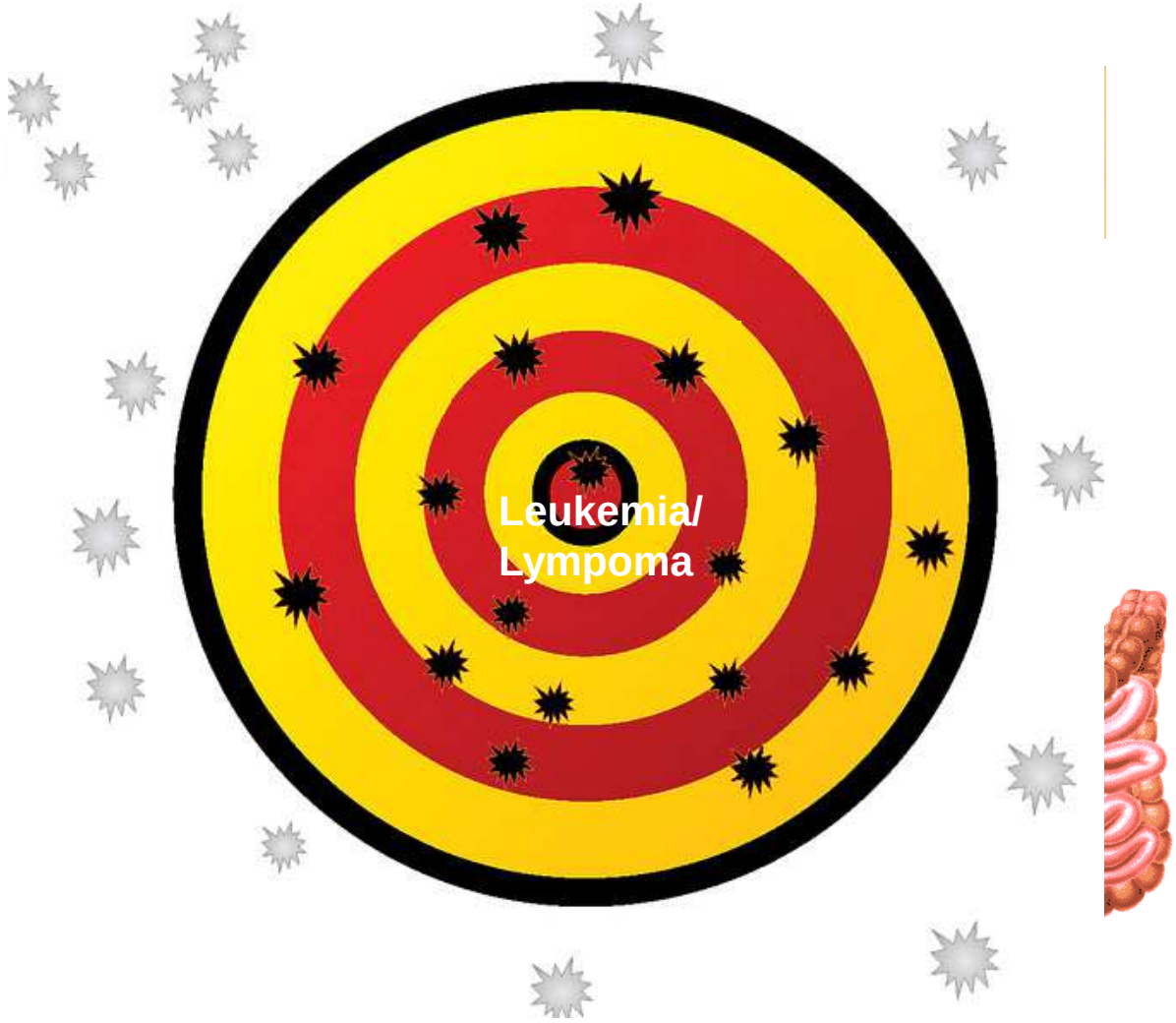
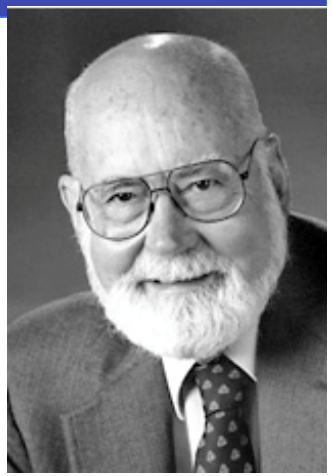


The Shotgun Approach to Immunotherapy

Stem Cell Transplantation (SCT)



- E. Donnall Thomas
- Nobel in 1990
- 1956: First SCT was performed between twins by Dr. Thomas
- 1958: Jean Dausset discovered MHC
- 1968: First MRD (siblings) SCT
- 1973: First MUD SCT

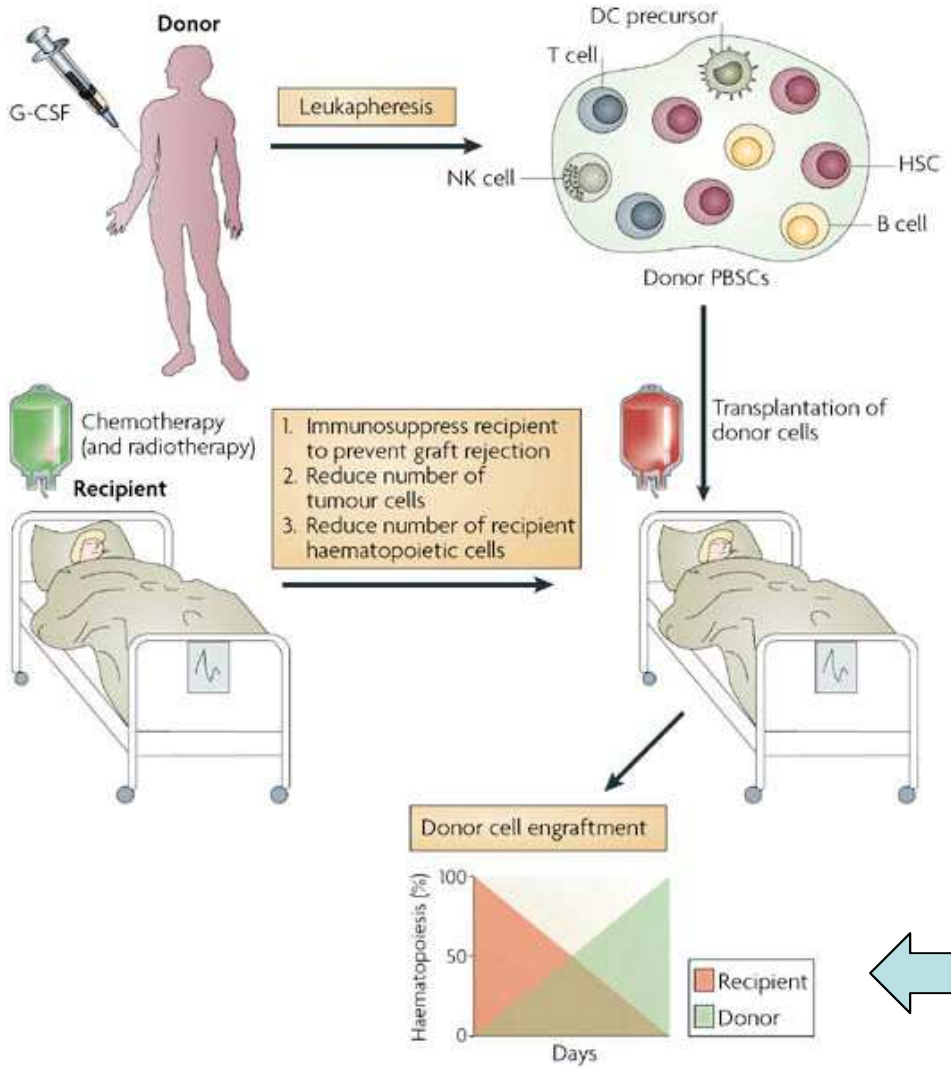
Stem Cell Transplantation (SCT)

- Autologous (Auto-SCT)
- Allogeneic (Allo-SCT)
  - MRD (Matched Related Donor)
  - MUD (Matched Unrelated Donor)
  - 1-2 Ag Mismatched
  - Haploidentical SCT
  - Cord

Stem Cell Transplantation (SCT)

- Purpose:
  - Reconstitution of Hematopoiesis
  - **Immunotherapy**

Allogeneic peripheral-blood stem-cell transplantation



Note product composition

Note time for reconstitution

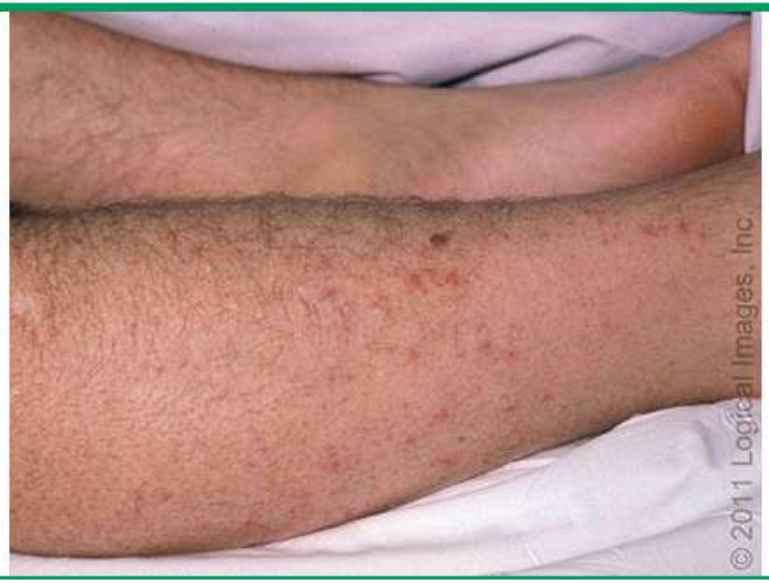
Shlomchik WD. Nature Reviews Immunology (2007).

SCT: a blessing or a curse?

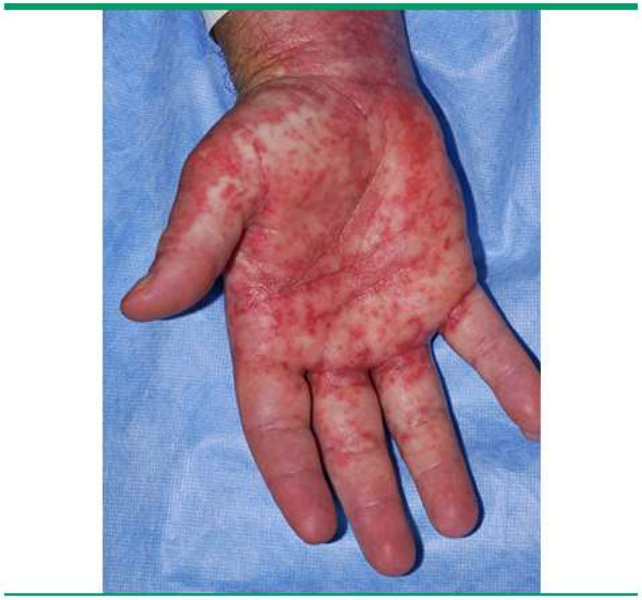
- Most crude form of immunotherapy (shotgun approach)
- Provides long lasting cures for some of the most aggressive hematologic malignancies (immune memory)
- Can cause major morbidity and mortality
  - Unlike chemo/XRT, SCT has long lasting side effects (immune memory)

Skin GvHD

Acute graft-versus-host disease

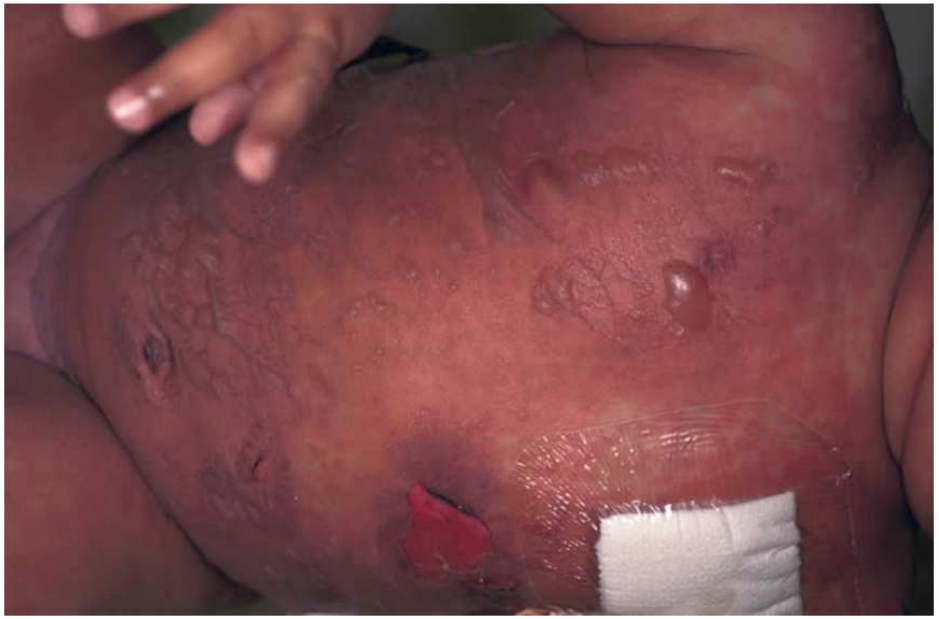


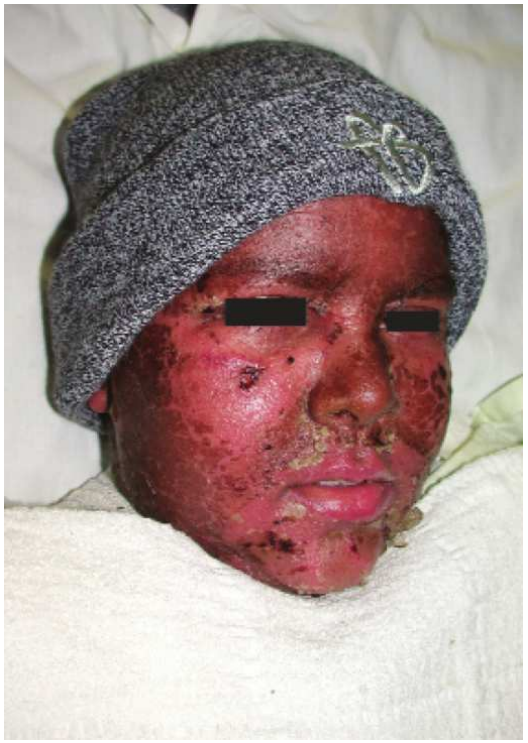
Palmar involvement in acute graft-versus-host disease



UpToDate.com

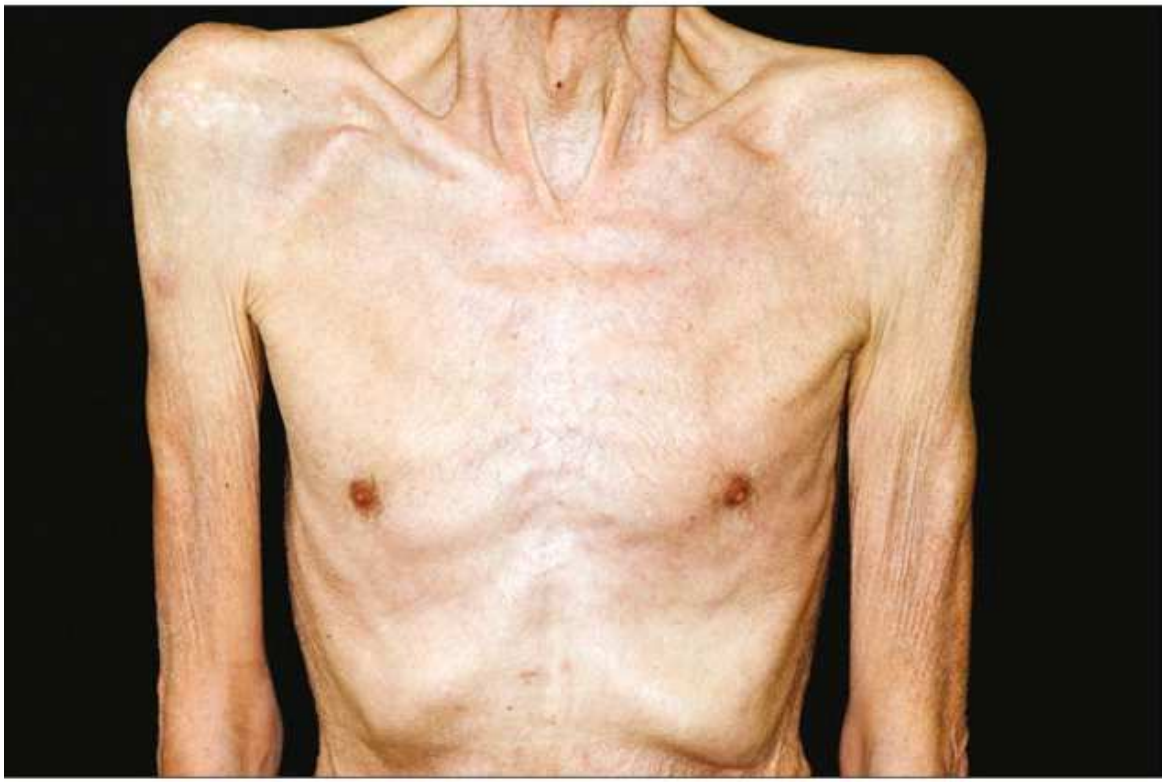
Skin GvHD





Silva et al., An Bras Dermatol. 2005;80(1):69-80
http://www.pedsoncologyeducation.com

GI GvHD



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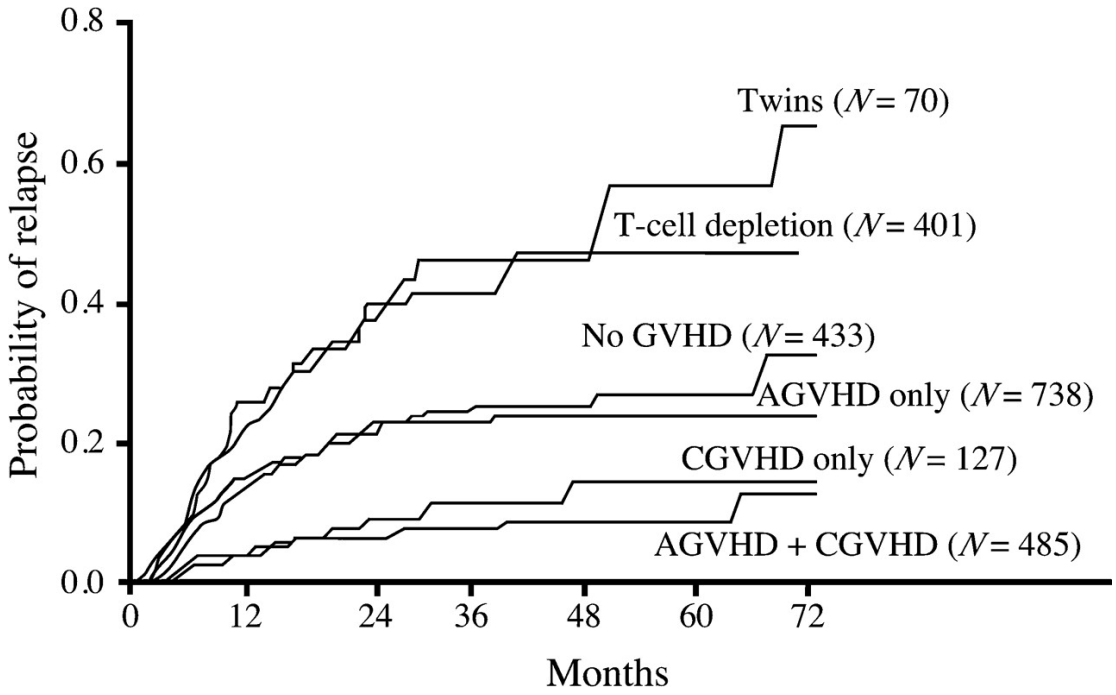
Clinical Outcomes Correlate with the Presence of Immunity in Allo-SCT



•GVL: graft-versus-leukemia effect

- leukemia or lymphoma (GVL), tumor (GVT)
- donor lymphocyte infusions (DLI)
- donor T cell manipulation
  effector / memory T cells
- generate tumor-specific T cells

Appelbaum FR. Annu. Rev. Med. (2003).

Why do patients get GvHD? Why are some patients cured?

- Don’t know what the tumor antigens are
- Don’t know what the GvHD antigens are
- We do know:
  - Many hematologic malignancies are sensitive to immunotherapy (SCT)
  - SCT offers cures!!

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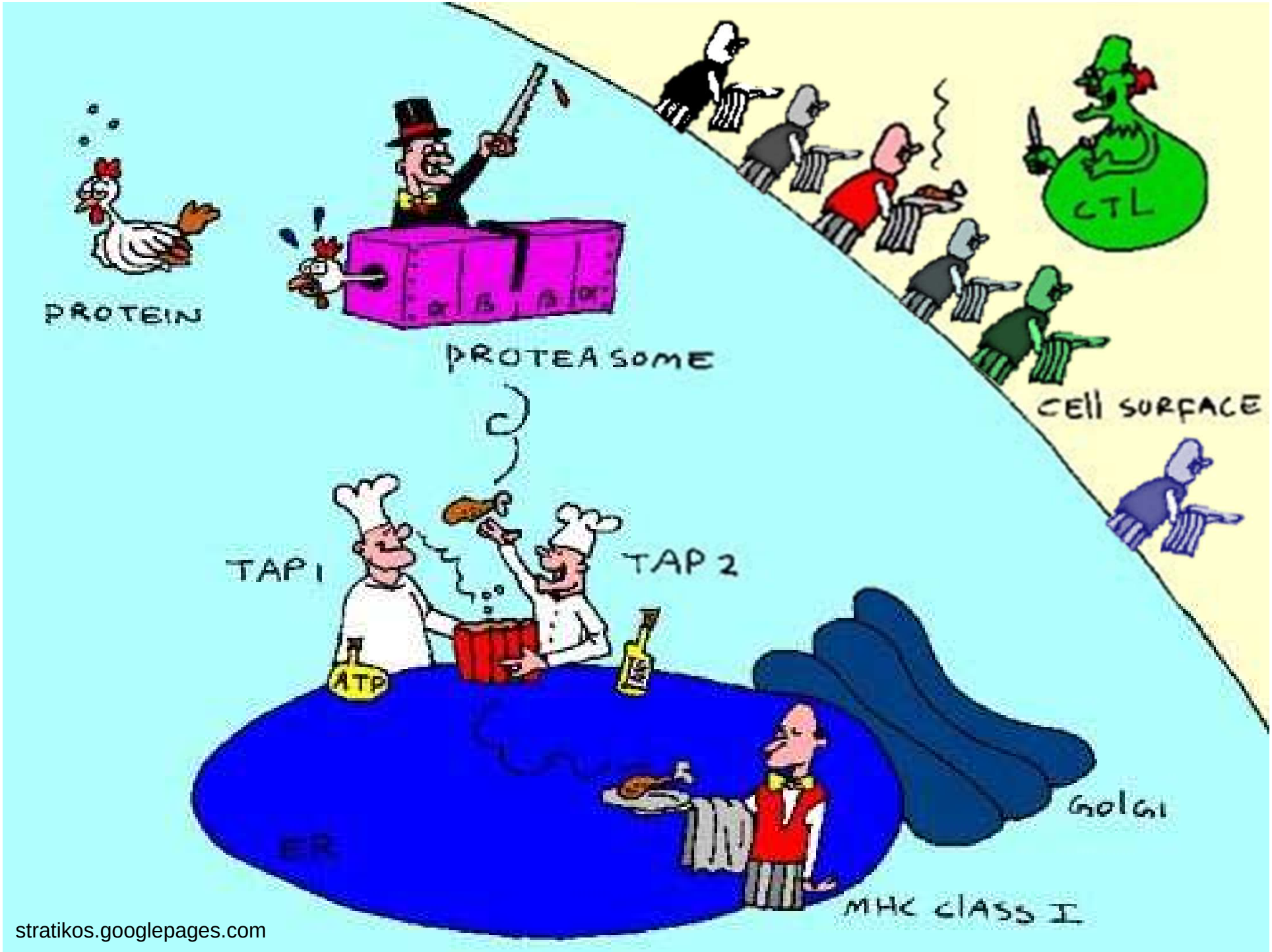


TCR-Peptide MHC Recognition

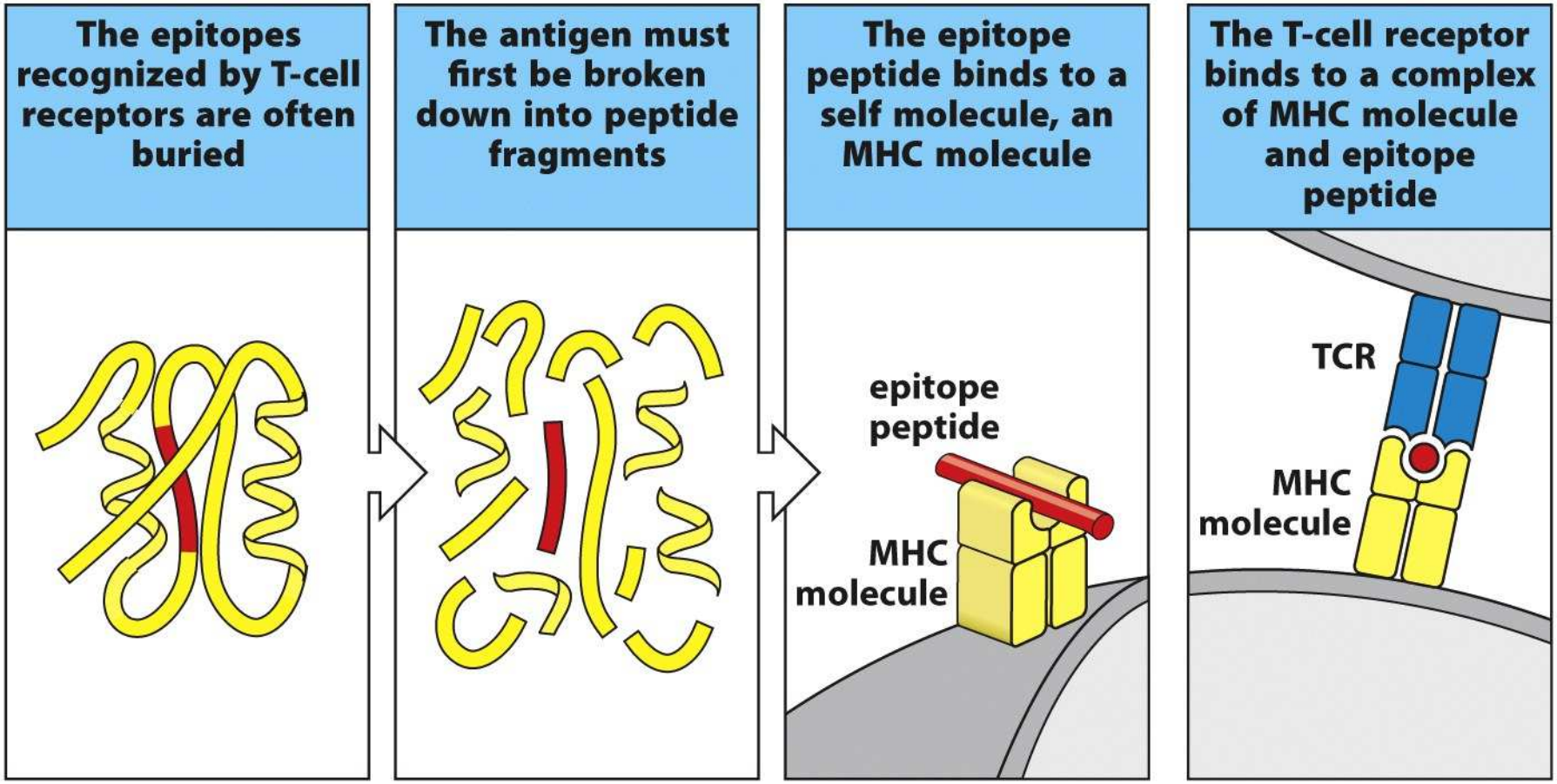


Figure 1.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

MHC/peptide is a complex 3D structure

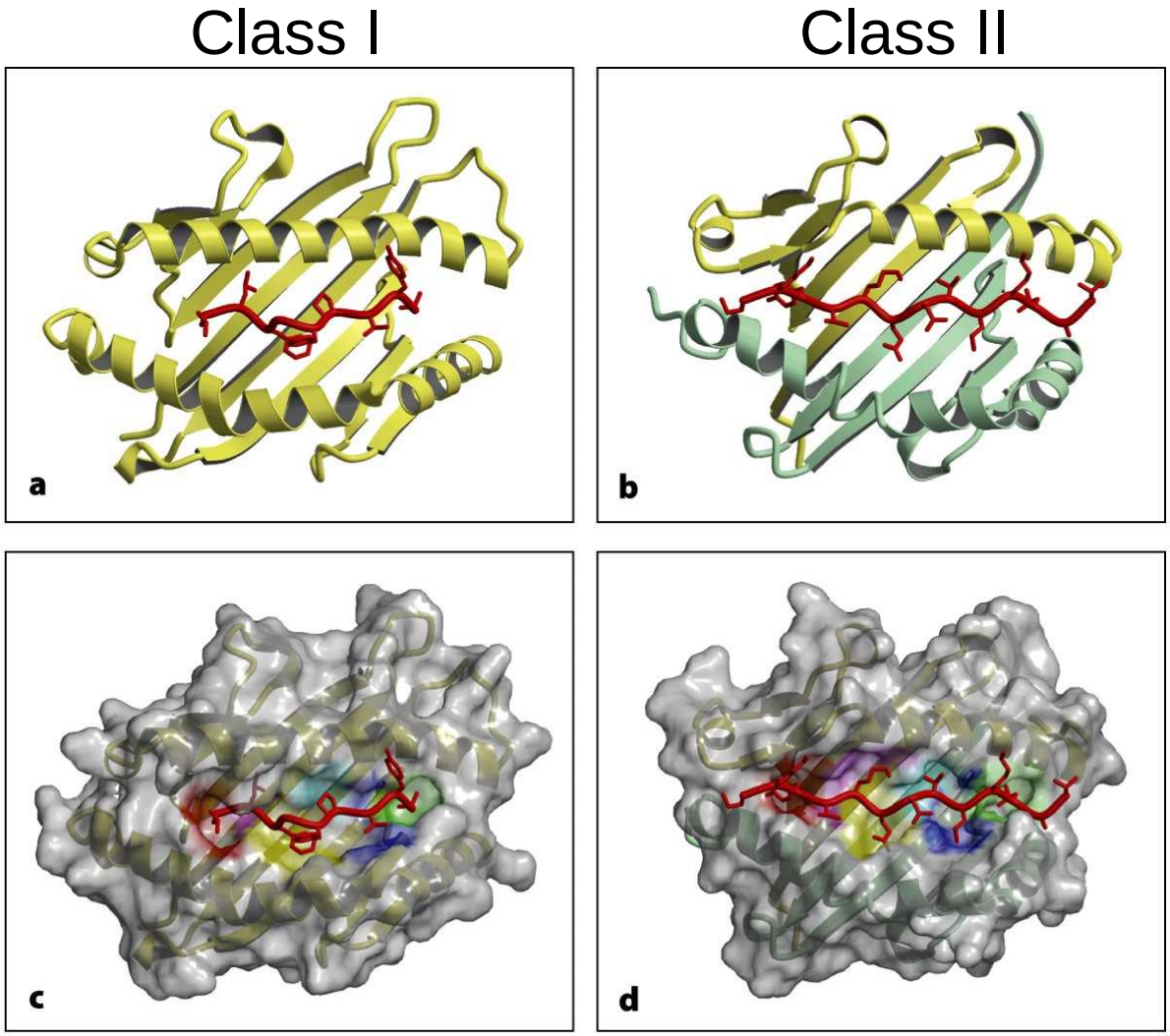


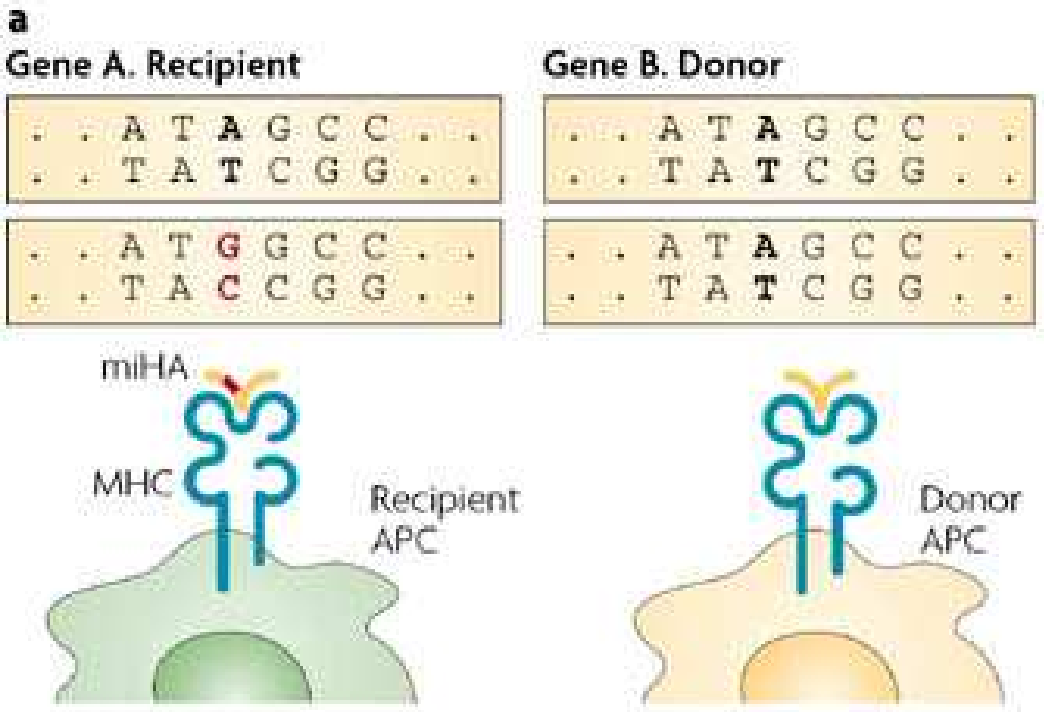
Figure 4.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Hematologic Tumor Antigens

LAA	Frequency in AML	Solid Tumors	Normal Tissue
BAGE	27%	Yes	No
BCL-2	84%	Yes	Yes
HAGE	23%	Yes	Unknown
hTERT	28%	Yes	Unknown
MPP11	86%	Yes	Yes
PRAME	64%	Yes	No
PR3/ELA2	67%	No	Yes
RHAMM	70%	Yes	No
Survivin	100%	Yes	Yes
WT-1	77%	Yes	Yes

Greiner et al, Haematologica. 2006 Dec;91(12):1653-61

Minor Antigens



Shlomchik, Nature Reviews Immunology **7**, 340-352

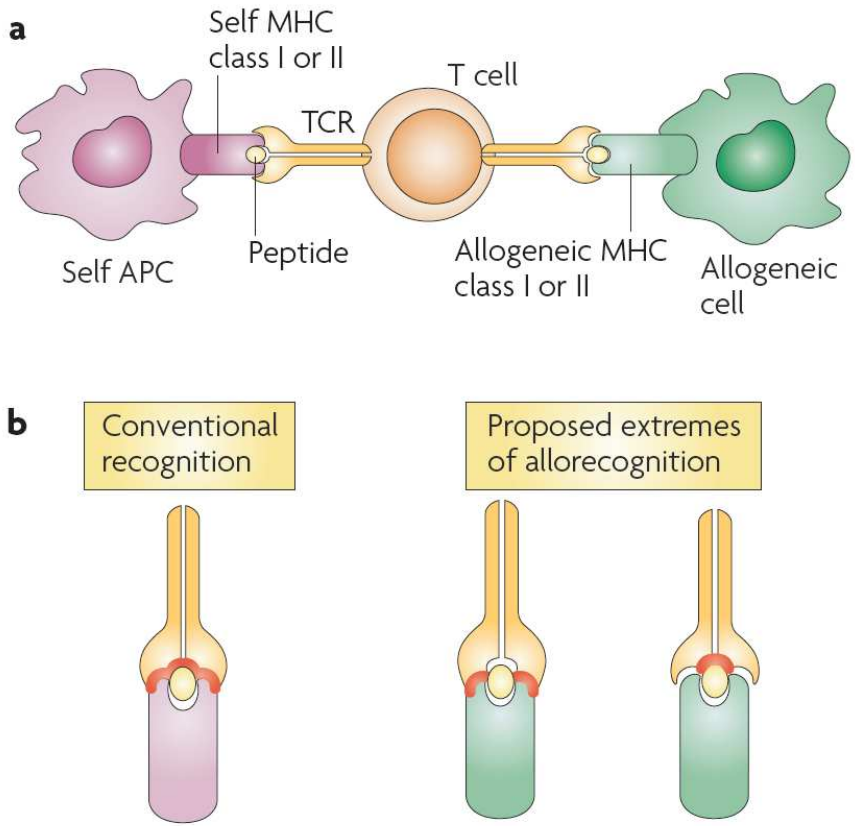
Table 1 | **Human minor histocompatibility antigens**

Minor histocompatibility antigen	HLA restriction	Gene/chromosome	Peptide sequence	Tissue distribution	Identification technique
HA-1	HLA A201	*KIAA0223*/19p13	VLHDDLLEA	Haematopoietic	HPLC with mass spectometry
HA-1	HLA B60	*KIAA0223*/19p13	KECVLHDDL	Haematopoietic	Polymorphic-peptide screening
HA-2	HLA A201	*MYOG1*/7	YIGEVLSV	Haematopoietic	HPLC with mass spectometry
HA-3	HLA A1	*LBC*/15q24-25	VTEPGTAQY	Ubiquitous	HPLC with mass spectometry
HA-8	HLA A201	*KIAA0020*/9	RTLDKVLEV	Ubiquitous	HPLC with mass spectometry
HB-1	HLA B44	5q32	EEKRGSLHVW	Haematopoietic, especially B-cell leukaemias	cDNA-expression cloning
UGT2B17	HLA 2902	*UGT2B17*/4q13	AELLNIPFLY	Ubiquitous	cDNA expression cloning
BCL2A1	HLA A24	*BCL2A1*/15q24.3	DYLQYVKQI	Haematopoietic	Genetic-linkage analysis
BCL2A1	HLA B4403	*BCL2A1*/15q24.3	KEFEDDIINW	Haematopoietic	Genetic-linkage analysis
HY B7	HLA B702	*SMCY*	SPSVDKARAEL	Ubiquitous	HPLC with mass spectometry
HY A2	HLA A201	*SMCY*	FIDSYICQV	Ubiquitous	HPLC with mass spectometry
HY A1	HLA A101	*DFFRY*	IVDCLTEMY	Ubiquitous	HPLC with mass spectometry
HY B60	HLA B60	*UTY*	RESEESVSL	Ubiquitous	cDNA-expression cloning
HY B8	HLA B8	*UTY*	LPHNHTDL	Ubiquitous	cDNA-expression cloning
HY DQ5	HLA DQ5	*DBY*	HIENFSDIDMGE	Ubiquitous	cDNA-expression cloning
HY DRB3	HLA DRB3	*RPS4Y*	VIKVNDTVQI	Not reported	cDNA-expression cloning

HLA, human leukocyte antigen; HPLC, high-performance liquid chromatography.

Bleakley, 2004,Pps: 371-380

TCR Can React with Allo-MHC



Felix and Allen, Nat. Rev. Immunol, 2007 Pgs 942-53

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Types of immunotherapies that have been used in hematologic malignancies

- SCT
- Chimeric Antigen Receptor (CAR) T cells (ALL, CLL, Lympoma)
- Immune Checkpoint Blockade (Lymphoma)
- Vaccines
- Antibodies

Ansell et al., NEJM, 2015
Westin, Lancet Oncology, 2015
Kochenderfer, JCO, 2015
Maude, NEJM, 2014
Armand et al., JCO, 2013
Grupp, NEJM, 2013
Porter, NEJM, 2011

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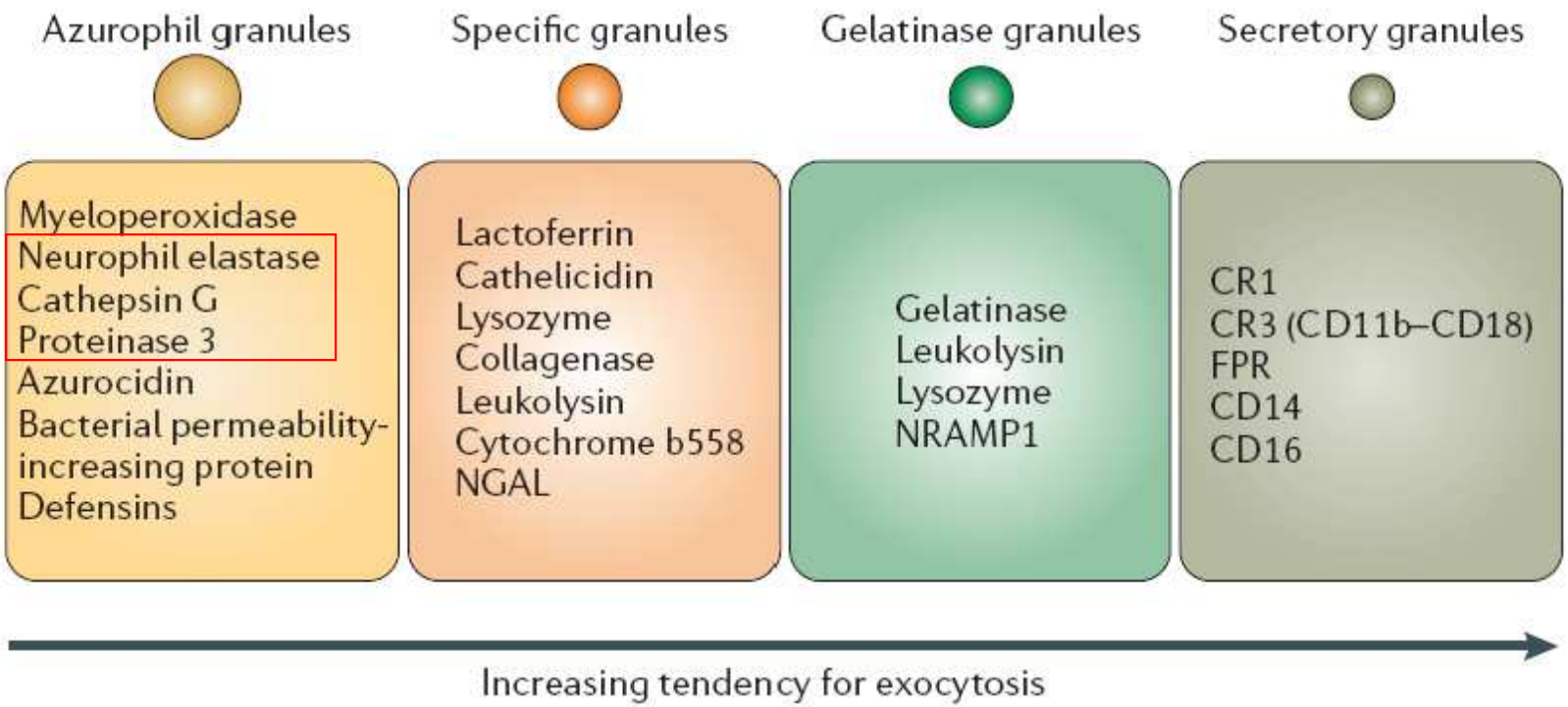
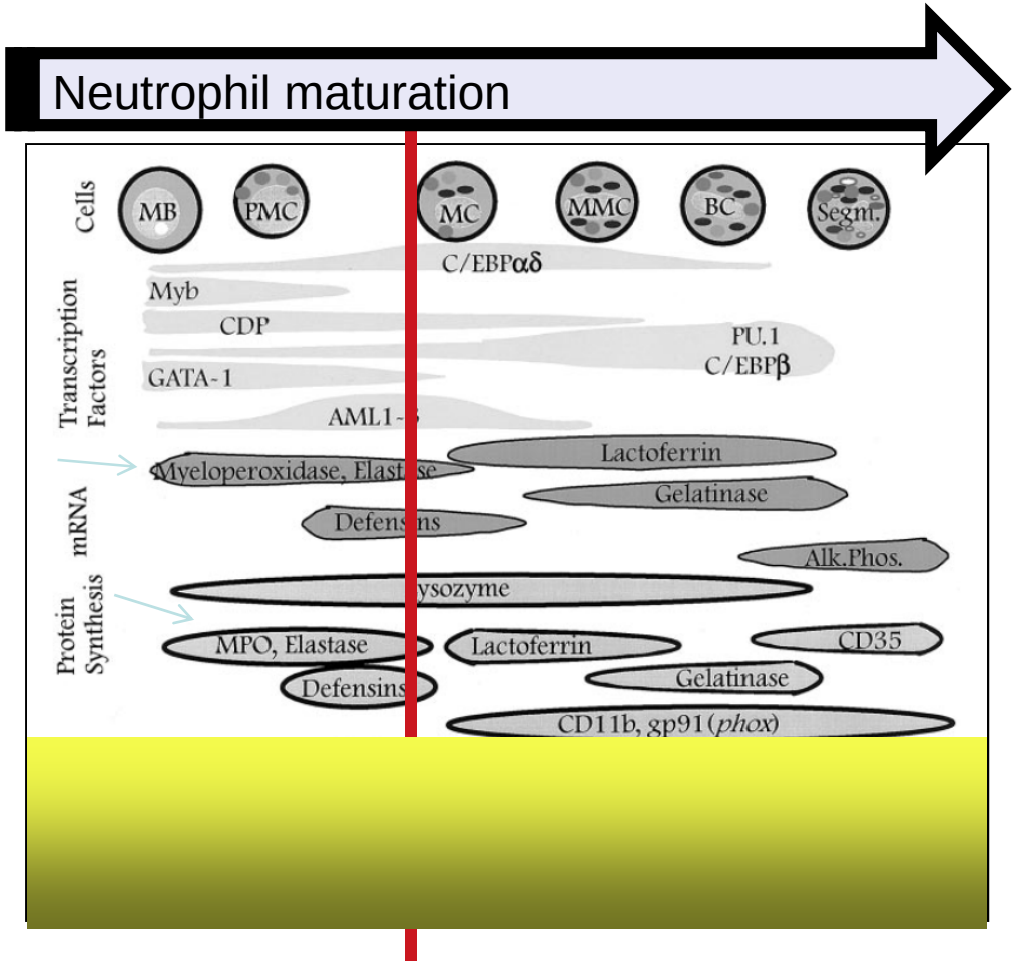
Granule Proteins as Tumor Antigens



CR: complement receptor
FPR: formyl peptide receptor
NGAL: neutrophil gelatinase-associated lipocalin
NRAMP1: natural-resistance-associated macrophage protein 1

C. Pham, Nat Rev Immunol, 2006

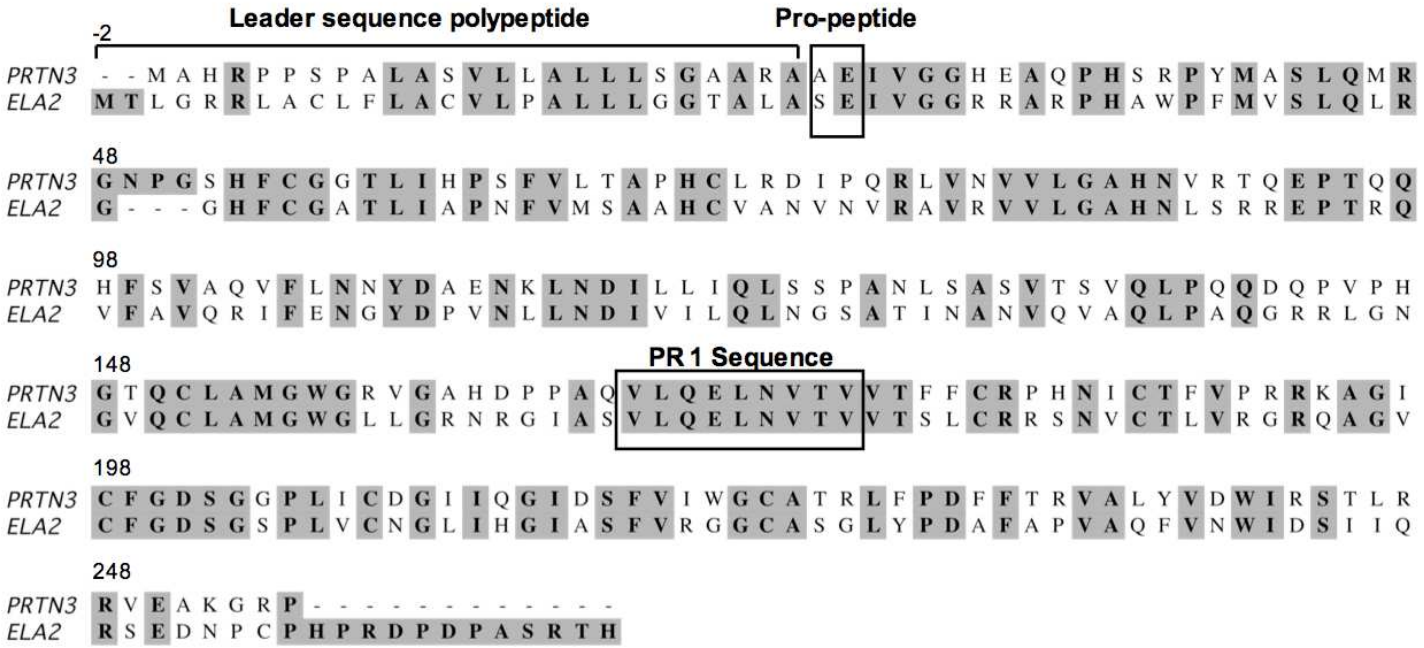
Neutrophil Granules During Myeloid Development



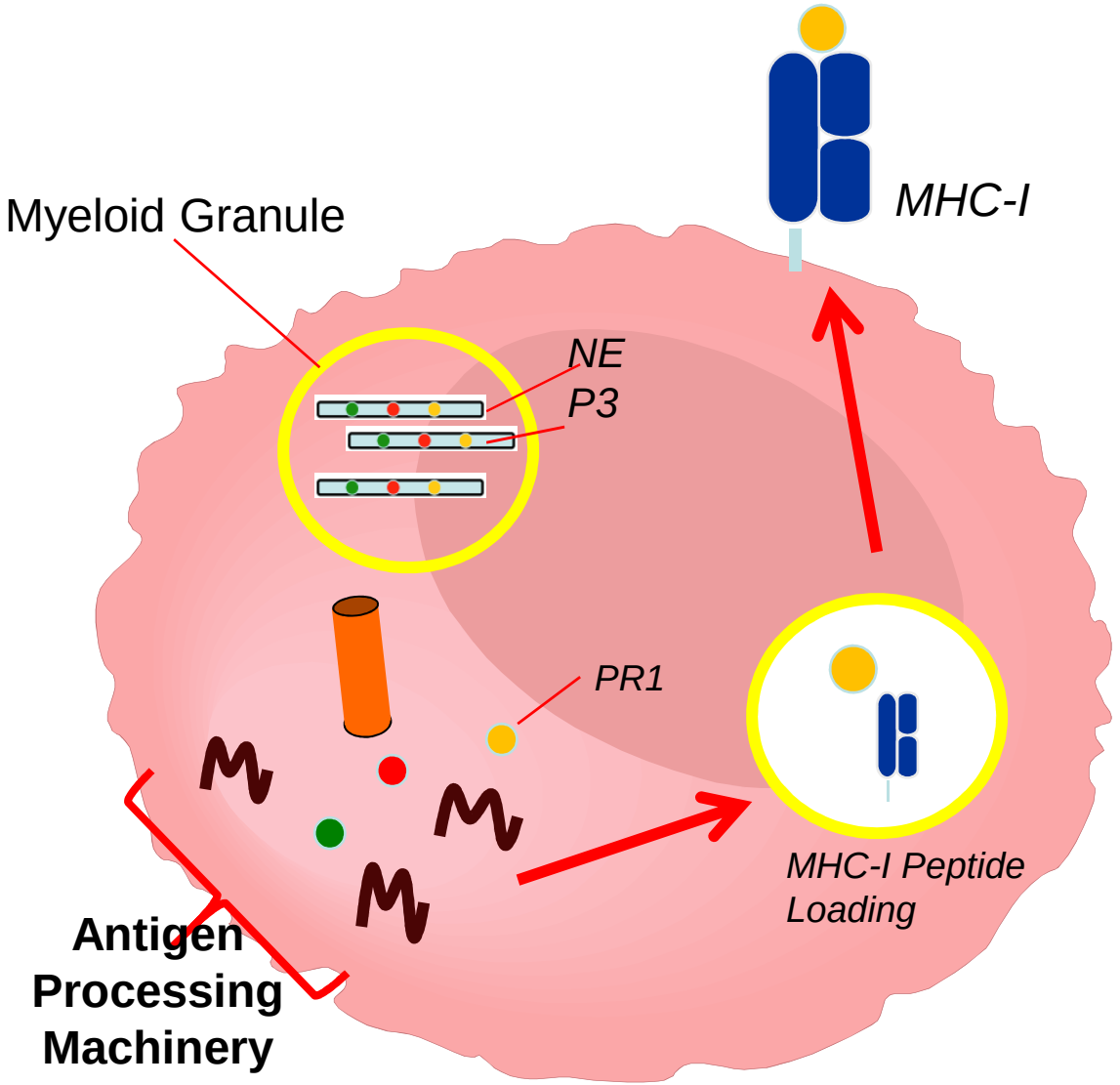
Borregaard et al. Blood, Vol 89, No 10 (May 15), 1997: pp 3503-3521

PR1

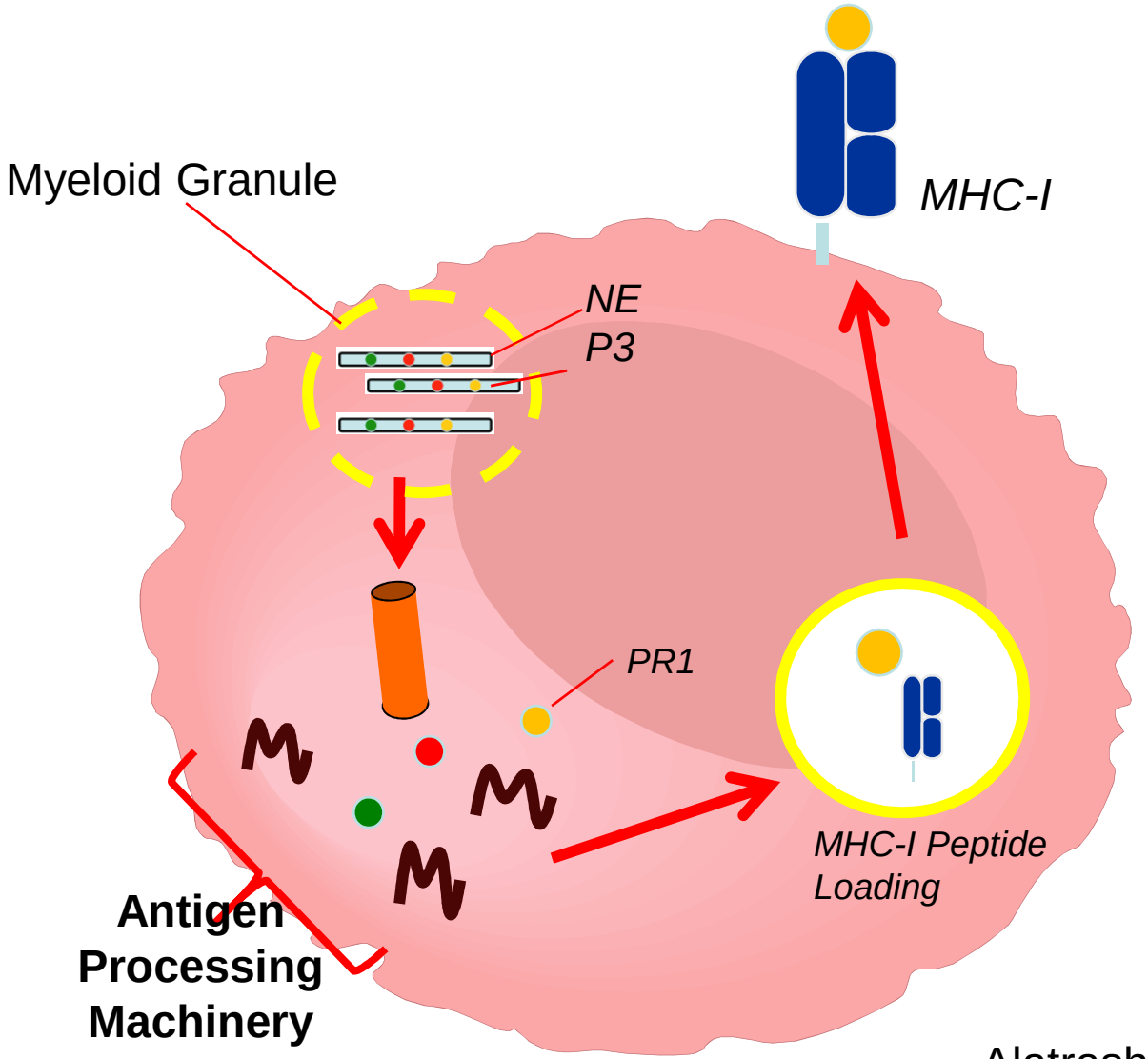
- HLA-A2 restricted epitope
- Sequence is conserved in NE and P3



Serine Proteases are Located Within Granules in Normal Myeloid Cells

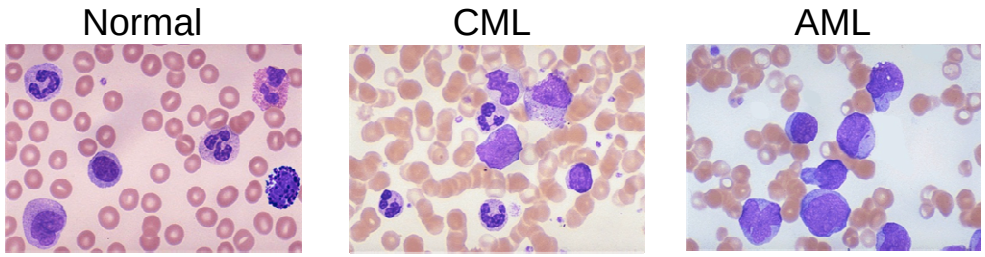


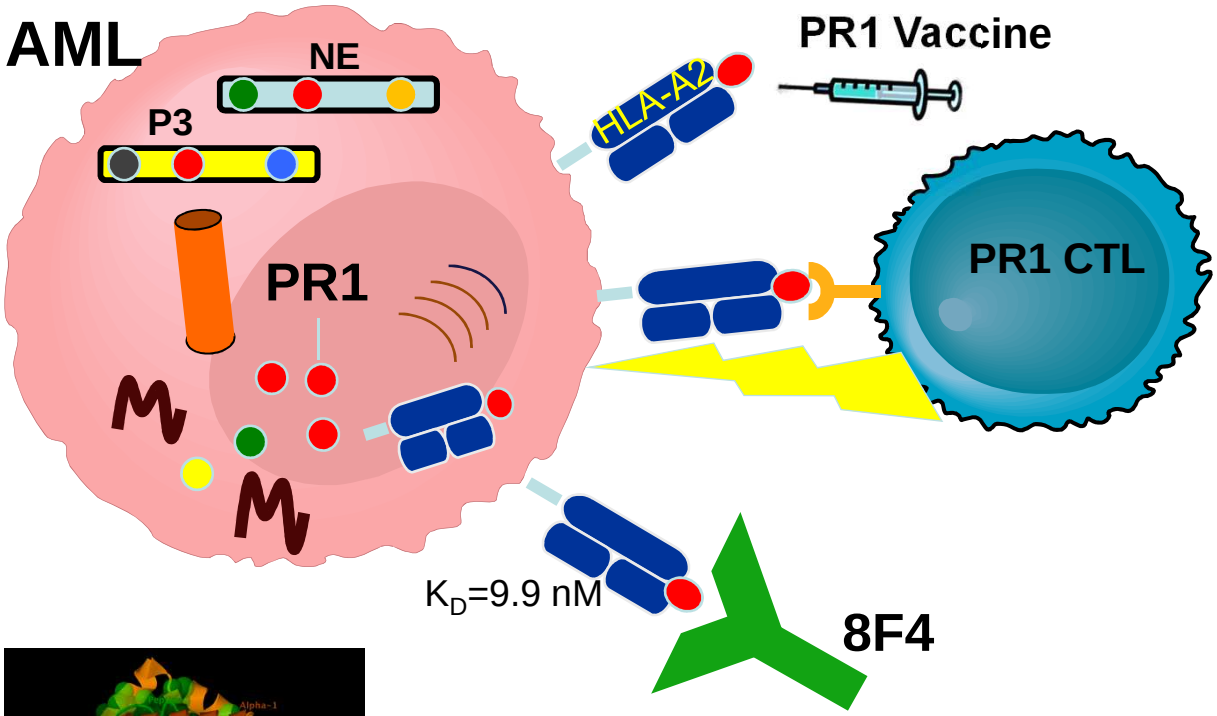
Serine Proteases are Located Outside Granules in AML

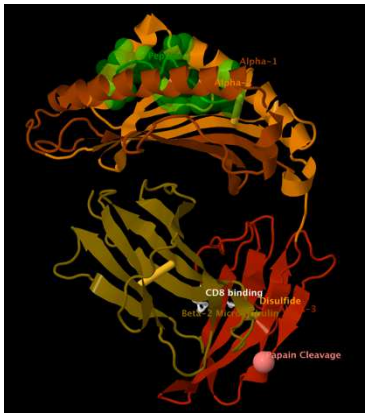


Alatrash et al., JIT, 2012

Immunity to the PR1/HLA-A2 leukemia-associated antigen







P3 and NE overexpression in myeloid leukemia increases susceptibility to lysis by PR1-CTL

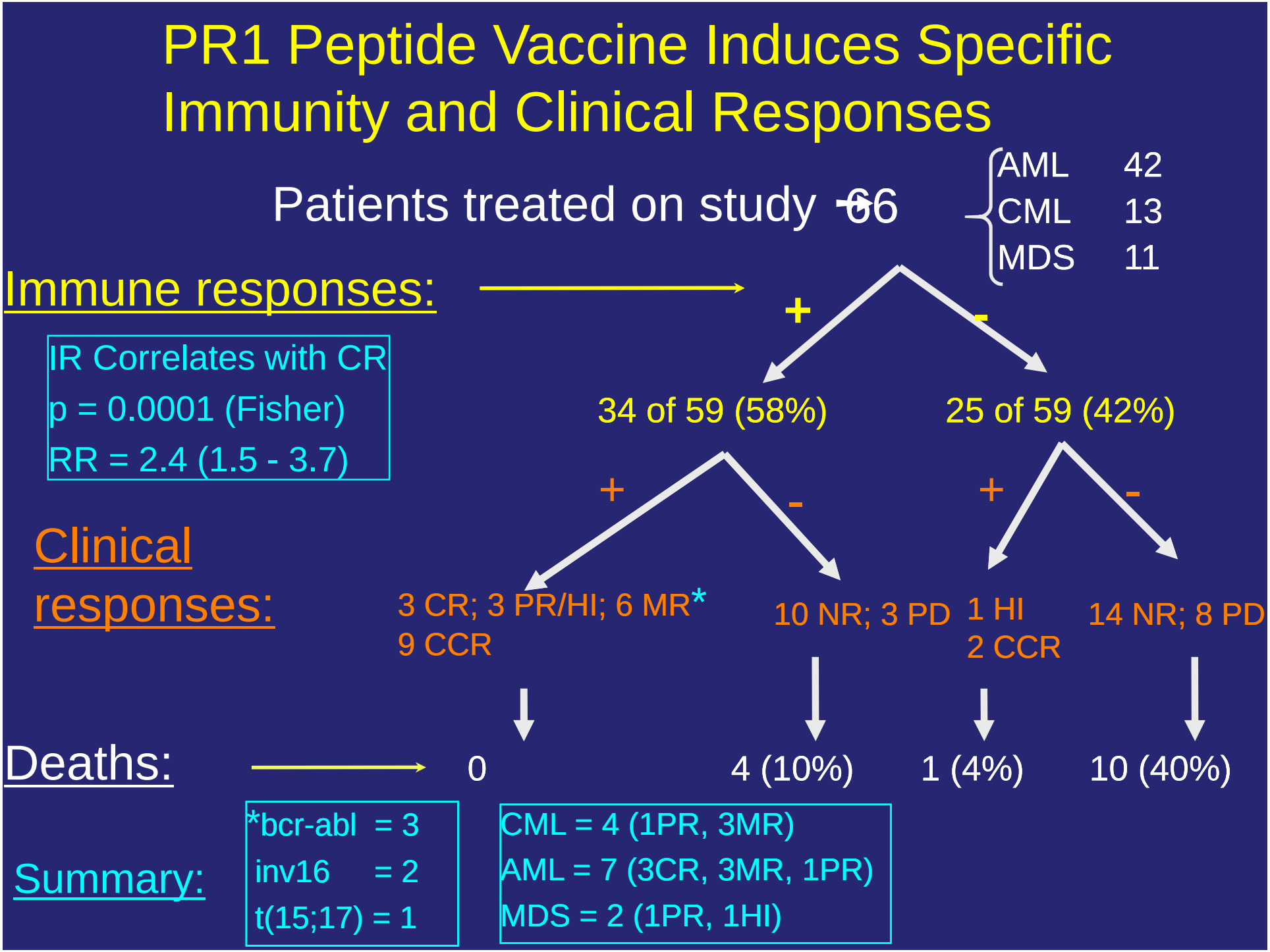
PR1 vaccination induces immune response in 58% of AML, CML, and MDS patients, and clinical response in 18%

An anti-PR1/HLA-A2 T cell receptor-like mAb (8F4) mediates CDC lysis of PR1-expressing AML and inhibits leukemia progenitors but not normal hematopoietic progenitors

Molldrem et al. Nat Med 2000

Sergeeva et al. Blood 2011

PR1 Peptide Vaccine Induces Specific Immunity and Clinical Responses



PR1 vaccine

Table 1. Patient characteristics

Patient	Sex/age, y	Diagnosis	Status at vaccination	Previous treatment	Prevaccination $PR1^+CD8^+$ T cells, % (absolute $PR1^+CD8^+$ T cells/mL)	Prevaccination $WT1^+CD8^+$ T cells, % (absolute $WT1^+CD8^+$ T cells/mL)	Max postvaccination $PR1^+CD8^+$ T cells, % (absolute $PR1^+CD8^+$ T cells/mL)	Onset of $PR1^+CD8^+$ T cells, wk after V	Max postvaccination $WT1^+CD8^+$ T cells, % (absolute $PR1^+CD8^+$ T cells/mL)	Onset of $WT1^+CD8^+$ T cells, wk after V	Sideeffects (grade)	Current status (d after V)
1	M/42	MDS	RARS	Epo/G-CSF	0.04 (70)	0.06 (105)	0.04 (111)	1	0.19 (471)	1	Local (1)	SD (523)
2	M/41	MDS	RA	Epo	0.00 (0)	0.16 (423)	0.34 (878)	2	0.42 (1085)	2	Local (1)	SD (446)
3	M/76	AML	CR1	Standard chemo	0.04 (199)	0.01 (49)	0.48 (3981)	2	0.16 (944)	1	Local (1)	CR (158)
4	F/48	AML	CR2	MUD (×2)	0.21 (1580)	0.03 (301)	0.42 (3820)	1	0.41 (4570)	2	Local (1)	CR (278)
5	M/71	Ph^+ AML	CR1	Standard chemo	0.04 (53)	0.02 (107)	0.34 (644)	1	0.02 (113)		Local (1), systemic (2)	Rel (198)
6	M/55	AML	CR1	Standard chemo	0.11 (276)	0.03 (75)	0.25 (606)	1	0.05 (218)	1	Local (1)	Rel (145)
7	M/54	CML	CP	Imatinib	0.04 (144)	0.03 (86)	0.11 (279)	3	0.01 (98)		Local (1)	Mol R (164)
8	M/55	AML	CR1	Standard chemo	0.00 (0)	0.01 (20)	0.36 (264)	2	0.38 (325)	1	Local (1)	CR (105)

Significant PR1- and WT1-specific $CD8^+$ T-cell responses are highlighted. The percentages of PR1- and WT1-specific $CD8^+$ T cells as a fraction of $CD8^+$ T cells and the absolute numbers of PR1- and WT1-specific $CD8^+$ T cells/mL before and after vaccination are presented for each patient.

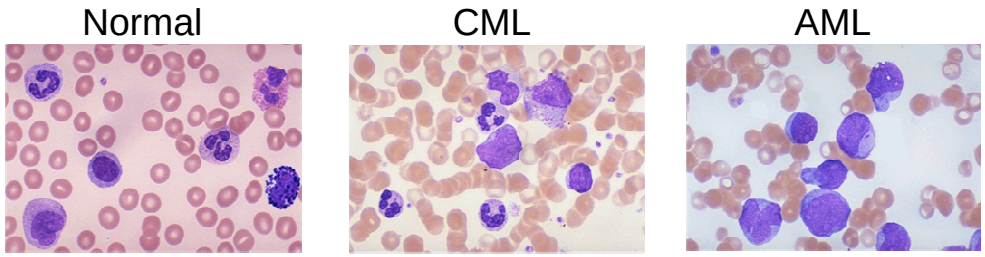
V indicates vaccination; Max, maximum; RARS, refractory anemia with ringed sideroblasts; G-CSF, granulocyte colony stimulating factor; SD, stable disease; CR, complete remission; chemo, chemotherapy; MUD, matched unrelated donor transplantation; Ph: Philadelphia; Rel, relapse; CP, chronic phase; and Mol R, molecular response.

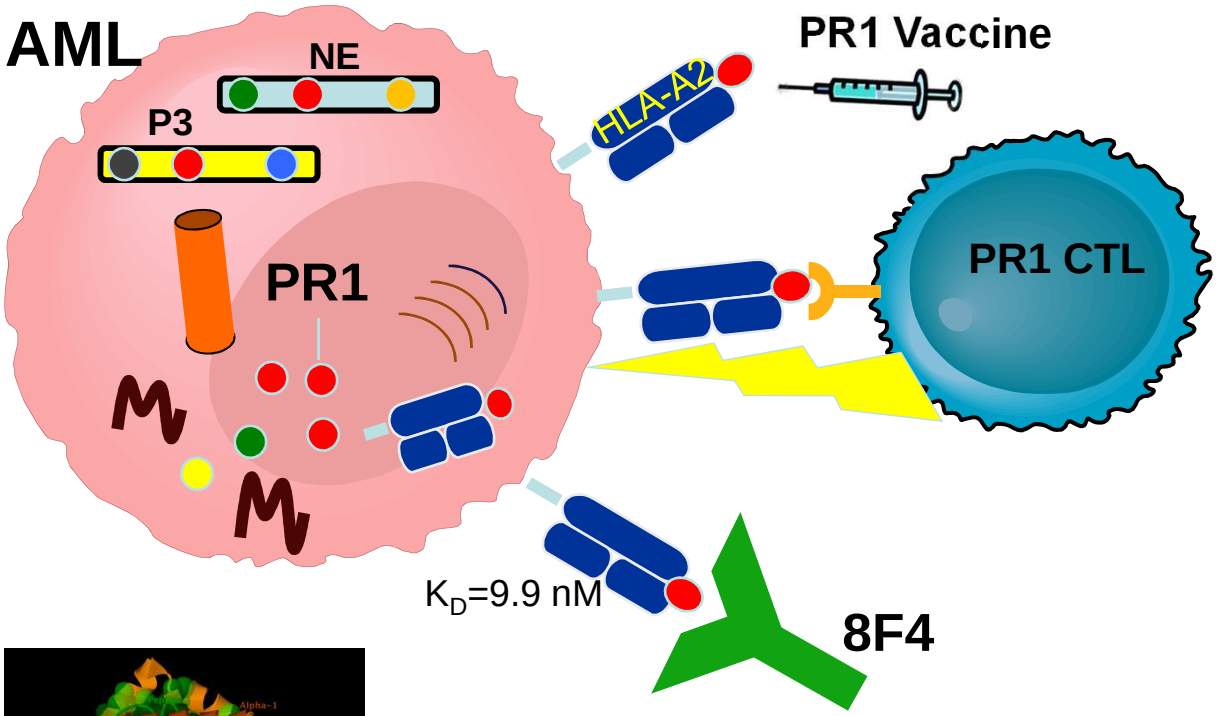
Rezvani et al., Blood, 2008

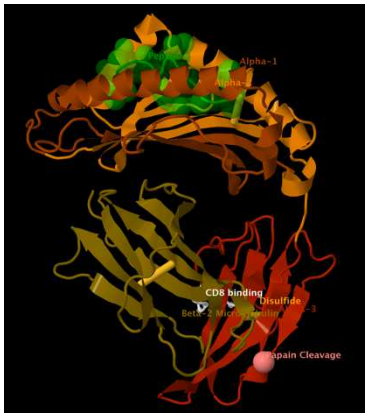
Limitations to Vaccine in Hematologic Malignancies

- Oftentimes the malignancy affects the immune system
- Large disease burden
- Aggressiveness of some of the hematologic malignancies (AML, ALL, accelerated/blast phase CML)

Immunity to the PR1/HLA-A2 leukemia-associated antigen







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Molldrem et al. Nat Med 2000

Sergeeva et al. Blood 2011

MHC/peptide is a complex 3D structure

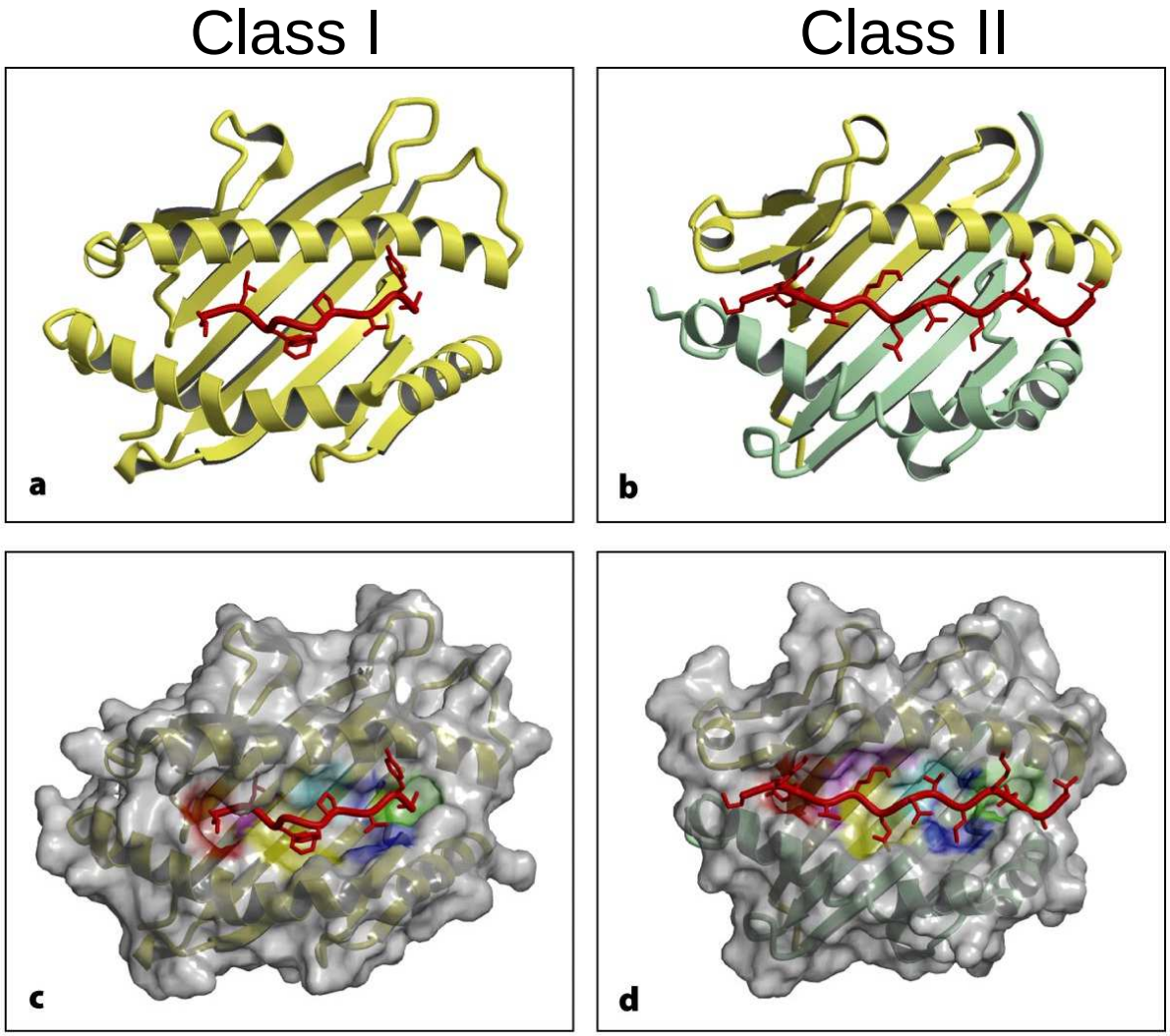
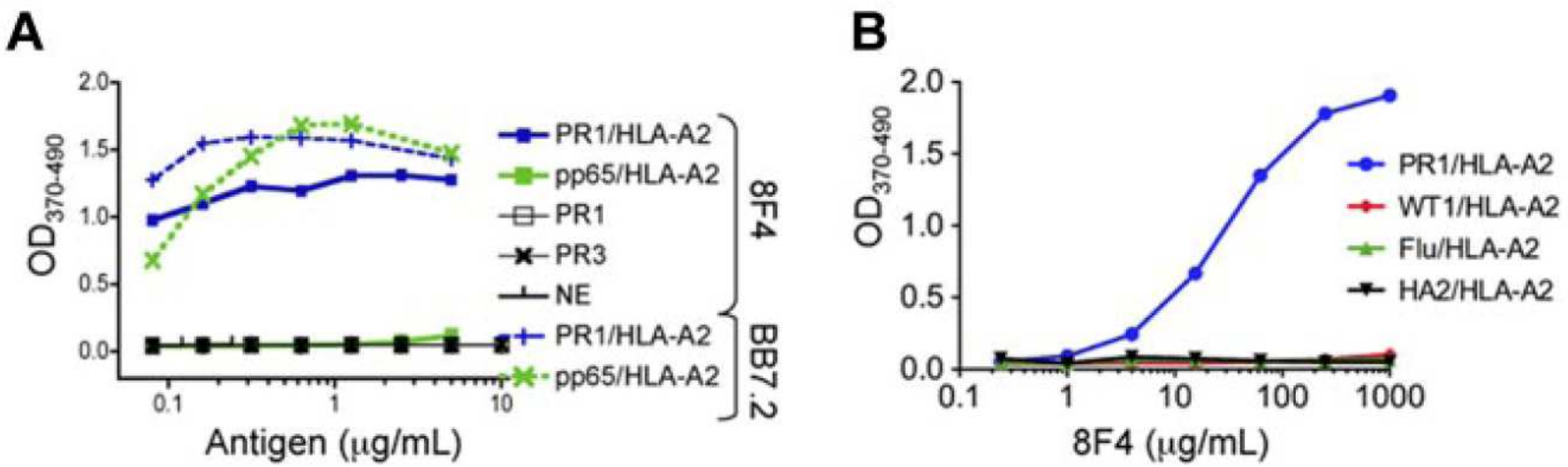
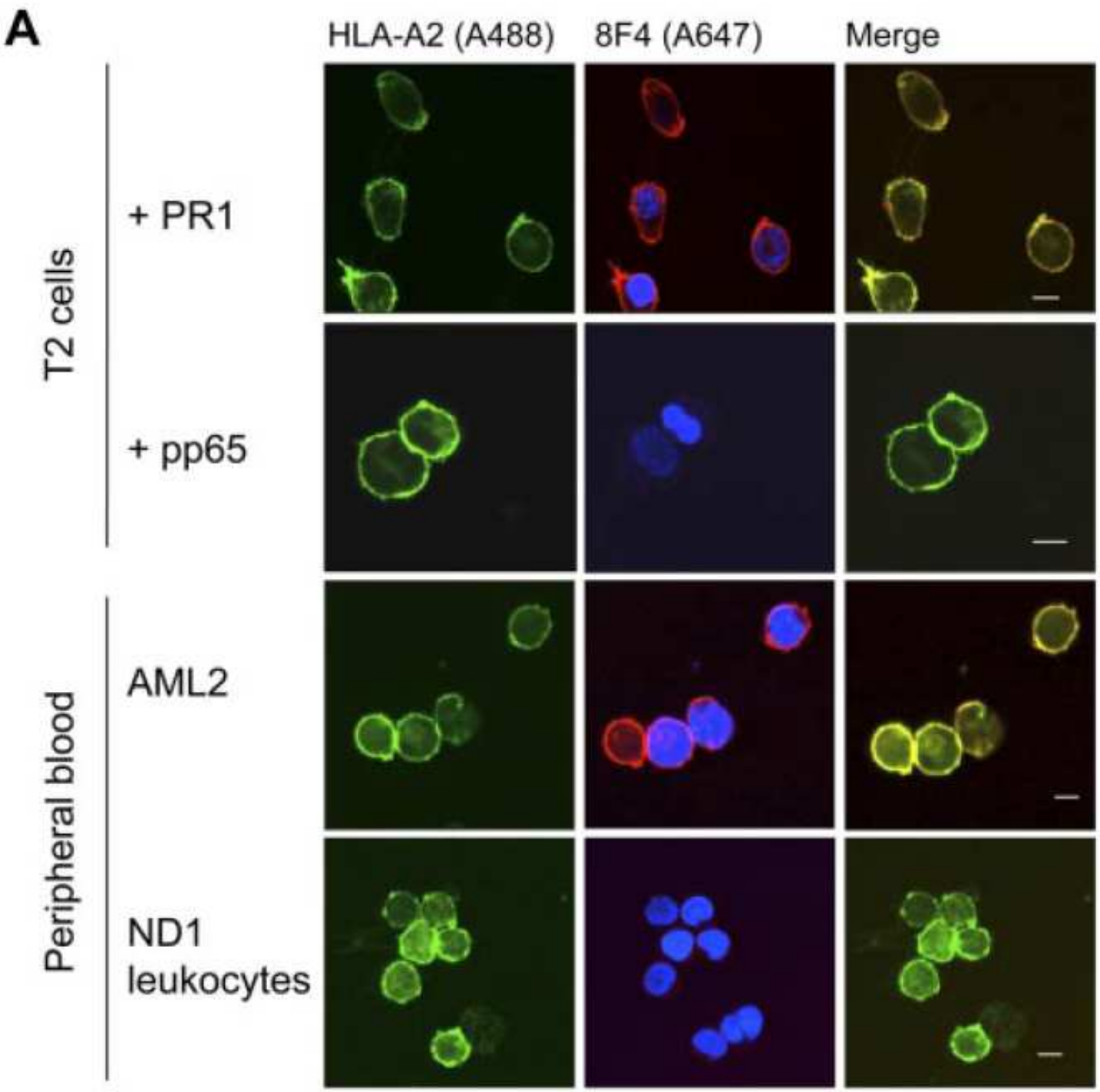


Figure 4.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

TCR-mimic antibody 8F4 is specific for PR1/HLA-A2



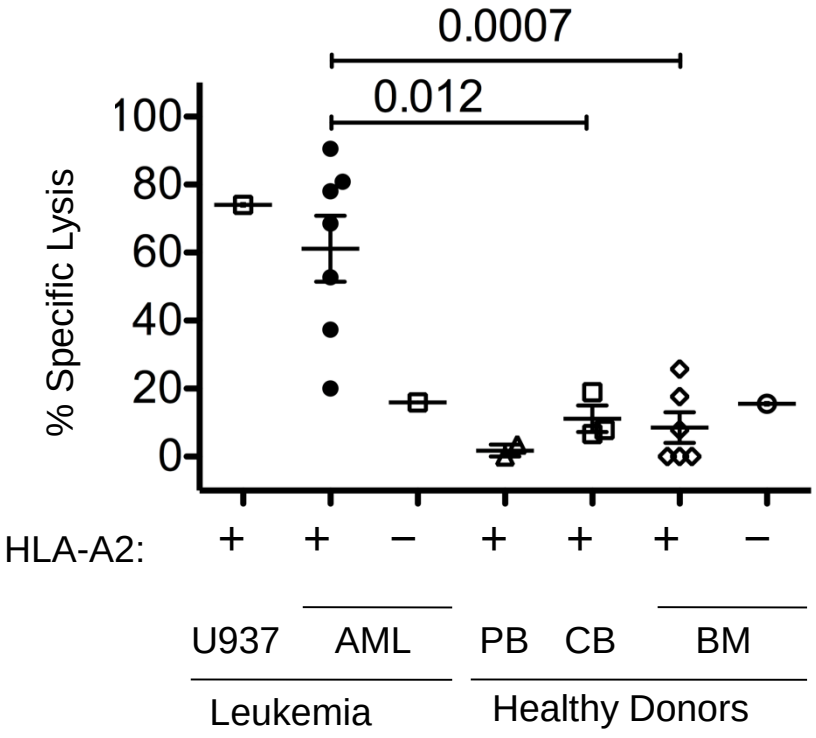
Sergeeva et al. Blood 2011



Sergeeva et al. Blood 2011

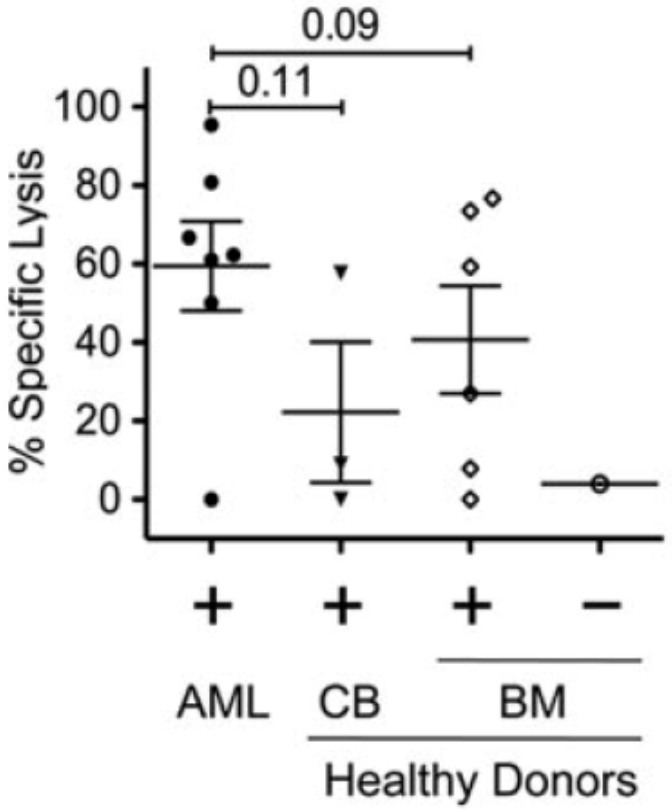
8F4 mediates CDC of AML blasts and stem cells

CDC killing of AML



AML from treatment-refractory patients

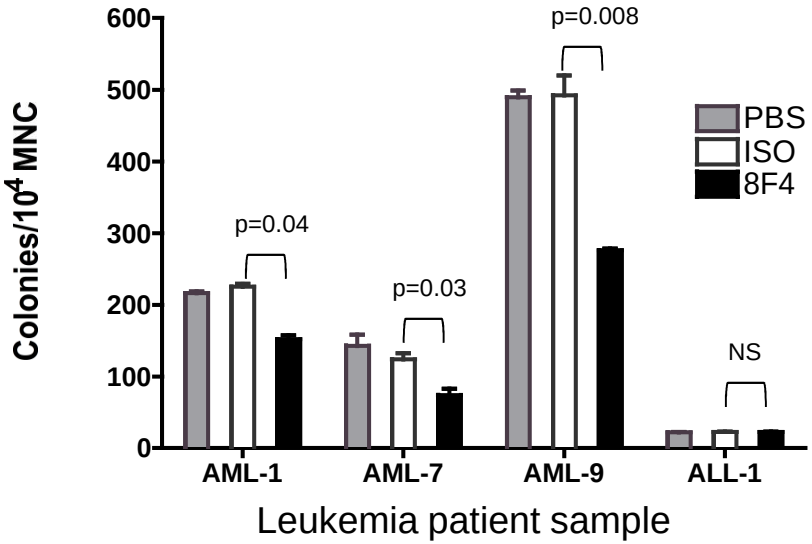
CDC killing of Lin$^-$ CD34$^+$ CD38$^-$ stem cells



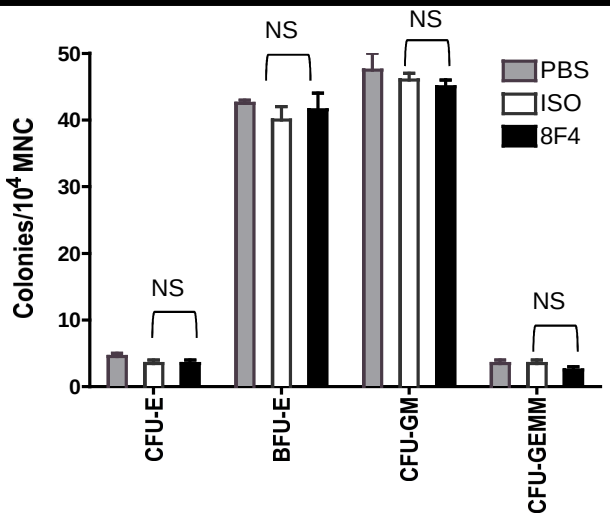
Sergeeva et al. Blood 2011

8F4 inhibits the growth of AML but not normal progenitor cells

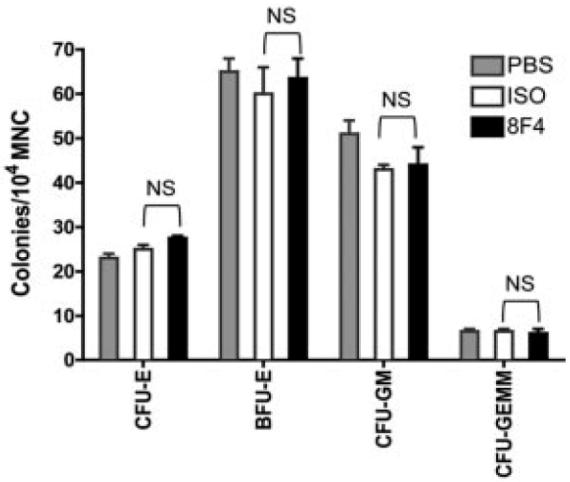
8F4 inhibits AML progenitor cells



Minimal inhibition of normal BM progenitor cells

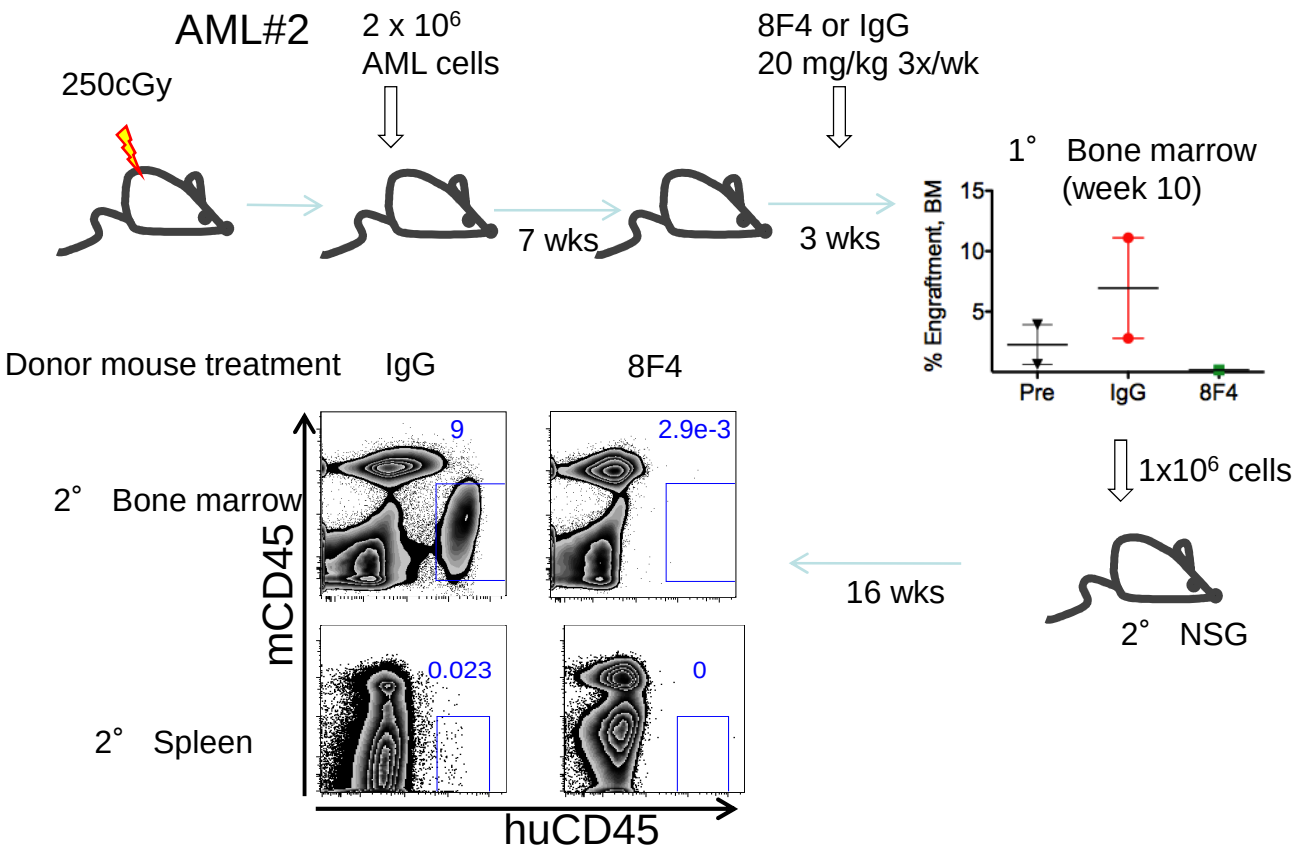


Minimal inhibition of normal cord progenitor cells



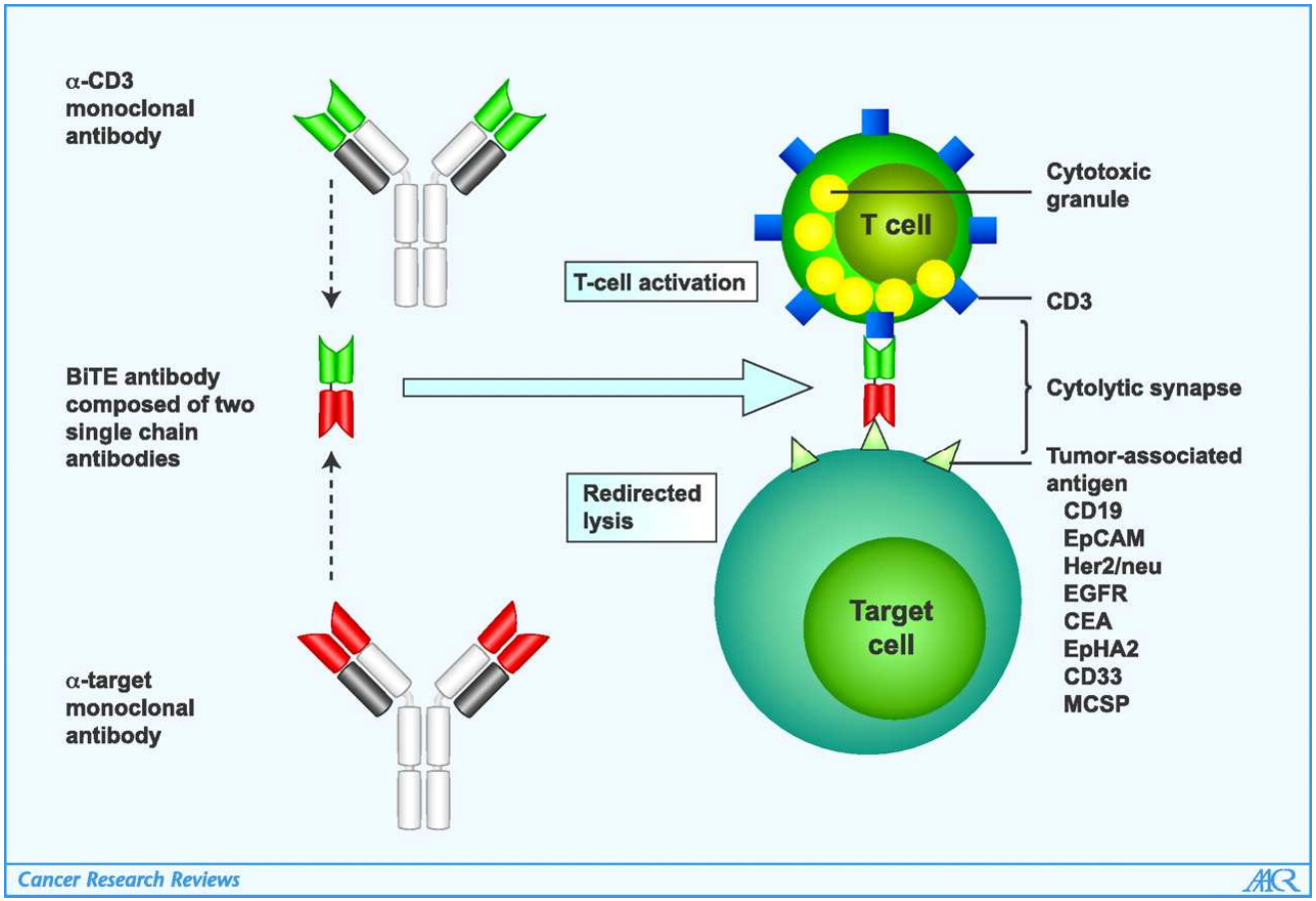
Sergeeva et al. Blood 2011

8F4 eliminates AML initiating cells with stem cell potential (2nd transplant)



Sergeeva et al., ASH Annual Meeting, 2011

Bispecific T cell Engager (BiTE) antibodies



Baeuerle et al., C Cancer Res, 2009

Blinatumomab (anti-CD19/anti-CD3)

	N (%)	
Parameter	Pivotal Study, n=36	Confirmatory Study, n=189
Response		
CR	15 (42)	62 (33)
CR with incomplete count recovery	10 (28)	19 (10)
All responders	25 (69)	81 (43)
Salvage Status		
Salvage 1	11 (31)	38 (20)
Salvage 2+	10 (28)	151 (80)
Median survival (months)	9.8	6.1

Jabbour, Blood, 2015
Topp, JCO, 2014
Topp, Lancet Onc, 2015

Lessons and Take Home Messages

- Hematologic malignancies can be very sensitive to immunotherapy
- Antigen specific approaches to immunotherapy have and will continue to improve the outcomes for patients with leukemia, myeloma and lymphoma
- Novel promising therapies in hematologic malignancies include immune checkpoint blockade antibodies, TCR-mimic and bispecific T cell engager (BiTE) antibodies
- SCT for hematologic malignancies will likely look much different in the years to come

Thank You