阪神異科セミナー
2014. 4. 19

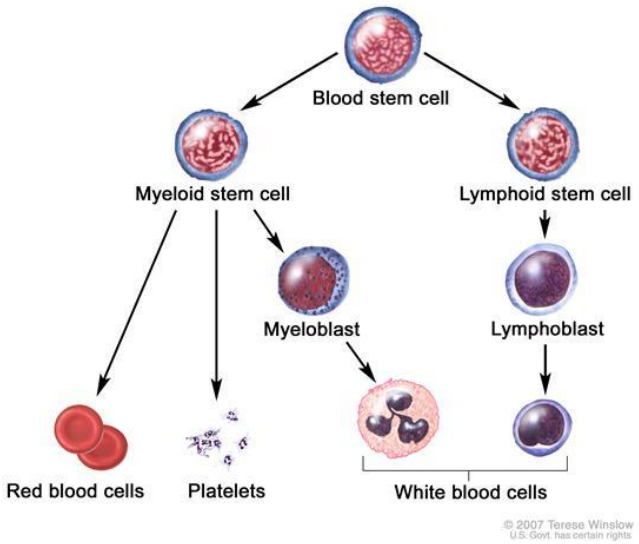
治癒を目指した移植治療
＝悪性血液疾患との戦い＝

明和病院　血液内科　　林　邦雄

プログラム

1. 急性骨髄性白血病AMLと移植
2. Thomas と移植の歴史
3. 移植と免疫
4. 21世紀の移植
5. 移植の課題
    - 5-1. GVHD
    - 5-2. 再発とHaplo-SCT
      （HLA barrierを超えて）
    - 5-3. 感染症

血液



急性骨髄性白血病AMLの分類

1976: FAB分類 M1-M6, L1-L3
1982: MDS (CMMoL)
1985: M7
1990: Mo
2001: WHO
2008: WHO (Blue Book)
　　PDGFRA, PDGFRBキメラ遺伝子
　　JAK2V617F
2010: Leukemia NET予後分類

急性白血病の疫学

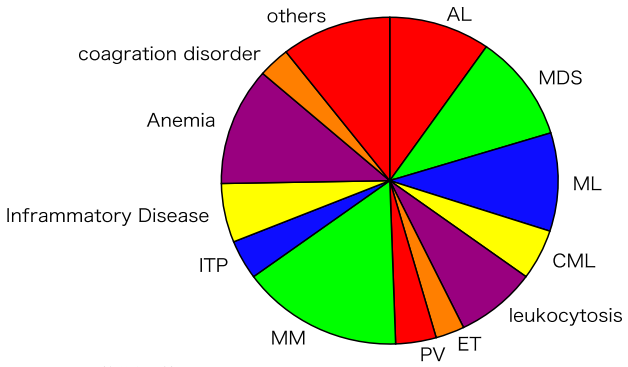
悪性腫瘍全体の3%以下、
白血病全体の約60～70%が急性白血病

。有病率は、人口10万人あたり約2～4人
男：女＝1.5：1

急性骨髄性白血病＝55～65%
年齢中央値は、65歳
年間約3,000～4,000人の発生

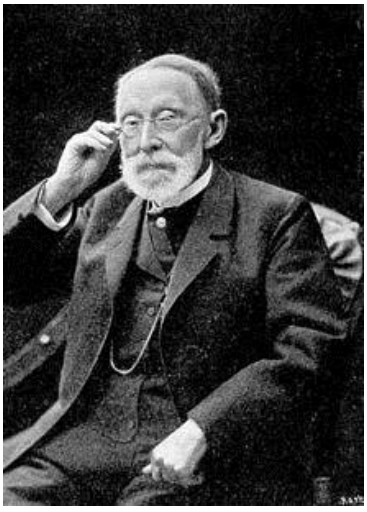
国立がんセンターがん情報，2014
〔http://www.ncc.go.jp/jp/〕

血液内科の疾患分布



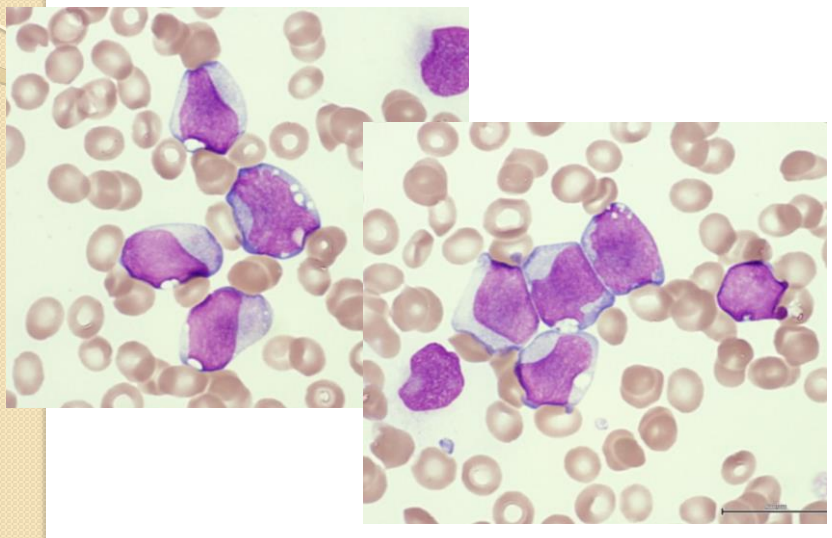
AL :Acute Leukemia（急性白血病）
MDS :Myelodysplasic syndrome（骨髄異形成症候群）
ML :Malignant Lymphoma （悪性リンパ腫）
CML :chronic myeloid leukemia （慢性骨髄性白血病）
ET :Essential thrombocytosis （本態性血小板血症）
PV :Polycytemia Vera （多血症）
MM :Multiple Myeloma （多発性骨髄腫）
ITP :idiopathic thrombocytopenic
(Immune thrimbocytopenia) （特発性血小板減少性紫斑病）

2013. Meiwa

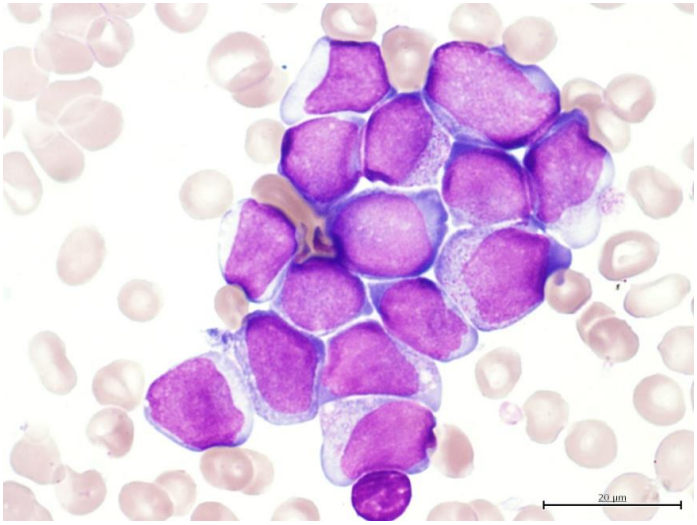


Virchow, R.:
Weisses Blut Milztumoren.1. Med Ztg.,
157, 163, 1846

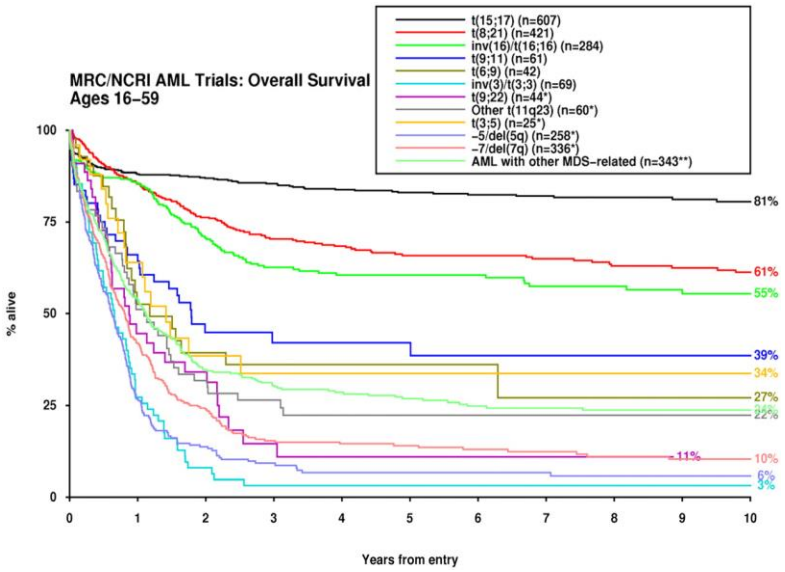
末梢血



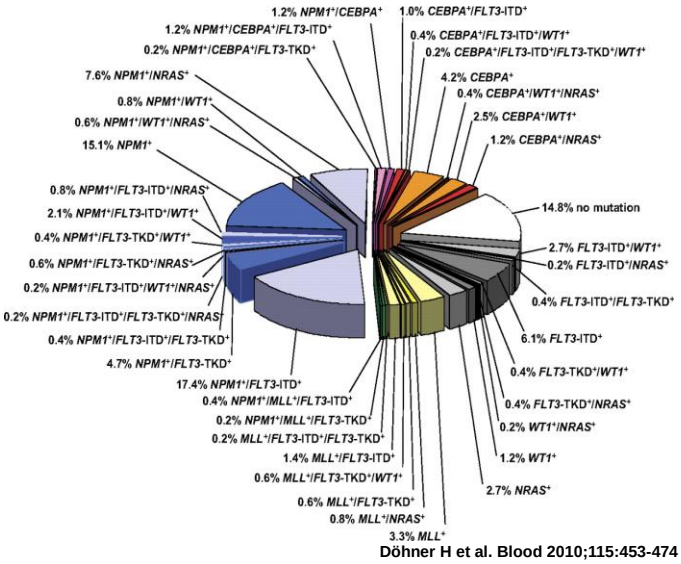
骨髓



Cytogenetic impact on survival

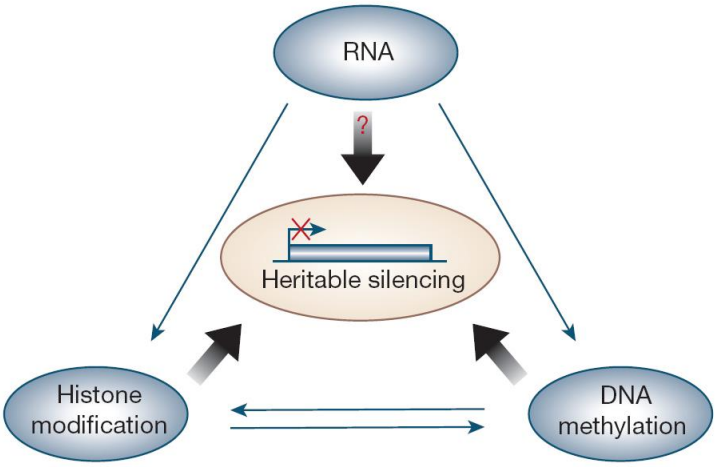


the molecular heterogeneity of cytogenetically normal AML



Döhner H et al. Blood 2010;115:453-474

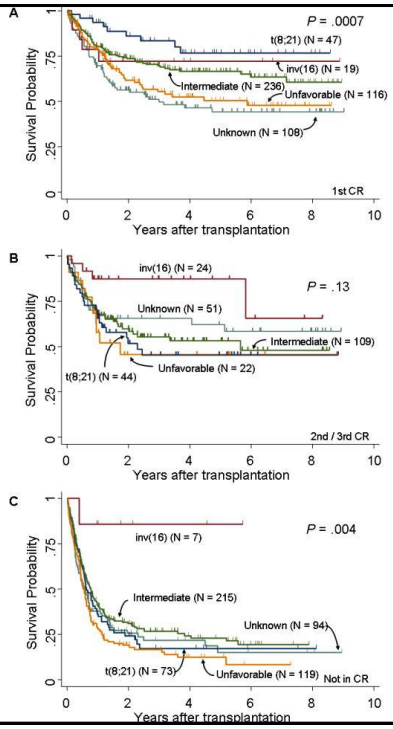
Epigenetic mutation



AML移植の適応

	予後分類	他家移植			自家移植
		HLA適合同胞	HLA適合非血縁	臍帯血	
第一寛解期	低リスク	GNR	GNR	GNR	Dev
	標準リスク	S	CO	GNR	Dev
	高リスク	S	S	CO	Dev
第二以降の寛解期		S	S	S	GNR
再発進行期・寛解導入不応期		CO	CO	CO	GNR

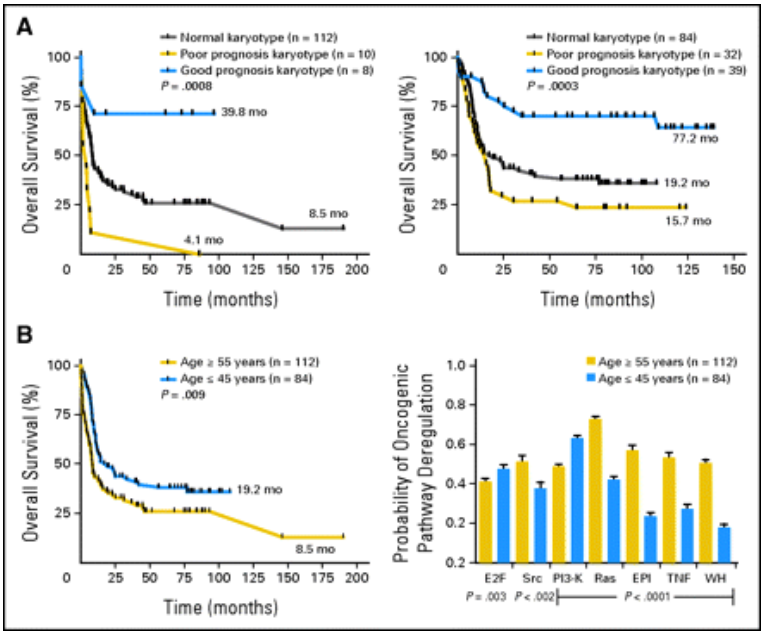
GNR : generally not recommended
S: as the standard of care
CO: clinical option



1st CR で移植

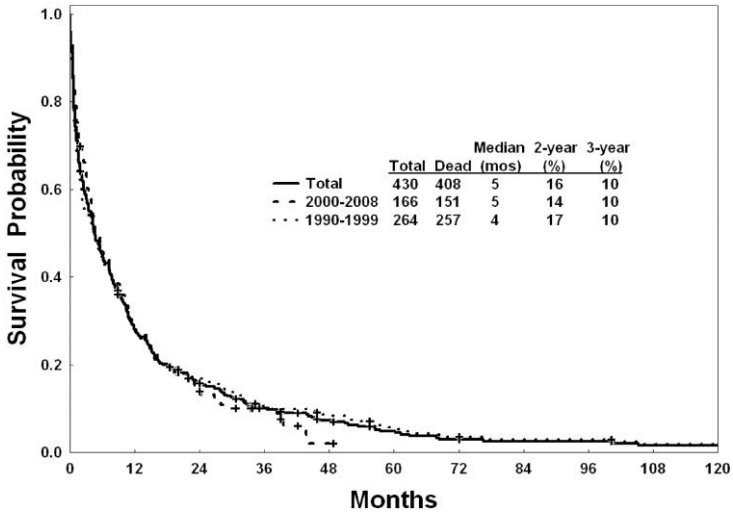
2nd CRで移植

非寛解で移植



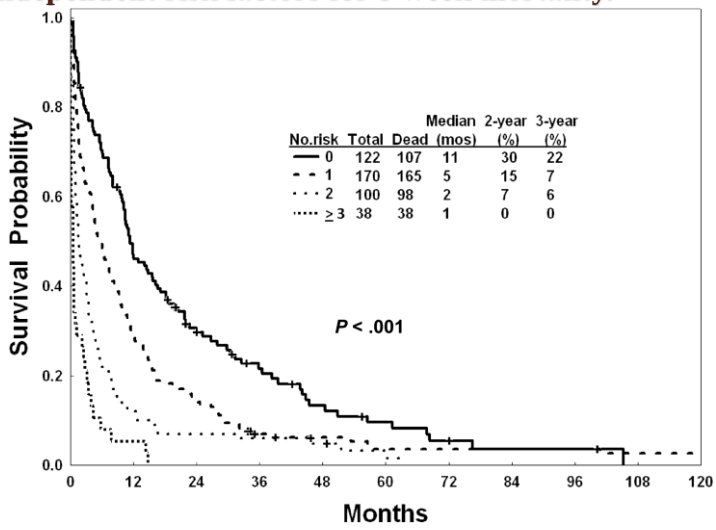
JCO VOLUME 27 NUMBER 33 , 2009

Survival of 430 elderly patients with AML, excluding CBF leukemias, by year of therapy.



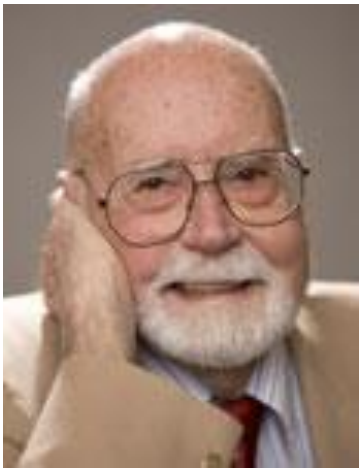
Kantarjian H et al. Blood 2010;116:4422-4429

Survival of 430 elderly patients AML by number of independent risk factors for 8-week mortality.



Kantarjian H et al. Blood 2010;116:4422-4429

E. Donnall Thomas, M.D, 1990 Nobel Laureate
Pioneering bone marrow transplants to cure leukemia



BONE MARROW TRANSPLANTATION – PAST, PRESENT AND FUTURE

Nobel Lecture, December 8, 1990

by E. DONNALL THOMAS

PAST

歴史１.

1. 1957 IO. E.D. Thomas, H.L. Lochte, Jr., W.C. Lu and J.W. Ferrebee, N. Engl. J. Med. 257, 491-496 (1957).:
   Intravenous infusion of stem cells
2. 1959 *identical twin*,
   supralethal irradiation後、血液学的回復
   しかしLeukemiaは再発。
3. 1958 *MTXがGVHD*を抑制する。
4. 1959 1. Yugoslavian radiation accident
   J Clini Intern-----*recurrence*
   2. lethal radiation------*GVL*
   3. *GVHD*

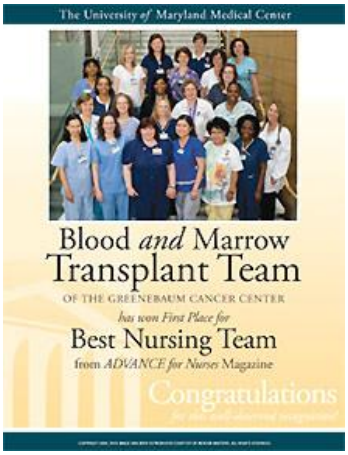
歴史 2.

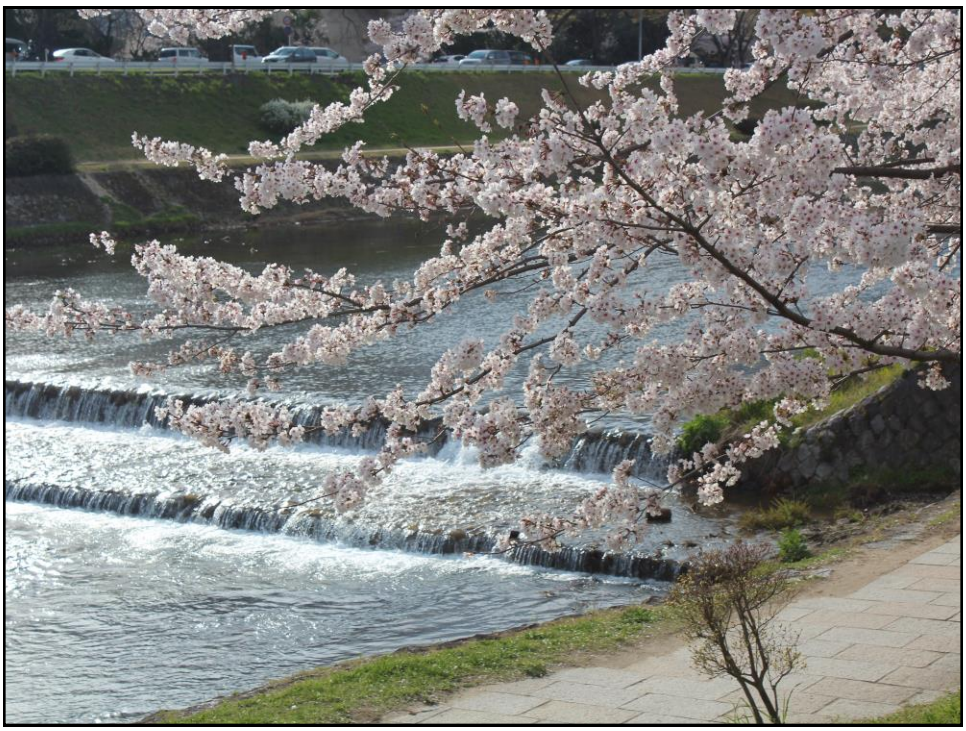
5. 1960 *AutoSCT* success in dog
6. 1962 移植細胞は*凍結保存*できる。

7. 1971 犬での移植成功は*DL-A matching*(HLA)

8. 1968 免疫病の児童、*Matched sibling*から移植
   に成功。
9. 1968. A team of nurses
10. 1969 HLA matched sibling ,
    進行したAMLに移植
11. 1977 a plateau in Kaplan-Meier 6/54 ----cured
    about 50% 0f 299 ---------cured
    ALL of children--------40% plateau

Nursing team





1980ノーベル賞医学生理学賞

1960 年代：Baruj B. Benacerraf、
Hugh O. McDevitt：
MHCクラII分子の多型

1950年代：Jean B. C. Dausset、
ヒトのHLA

1930年代: George D. Snell,
Peter A. Gorer:
マウス H-2

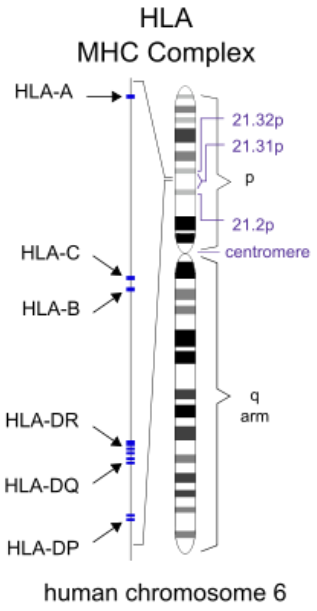
HLAについて

HLA（Human Leukocyte Antigen＝ヒト白血球抗原）は1954年、白血球の血液型として発見され、頭文字をとってHLA。HLAは白血球だけにあるのではなく、ほぼすべての細胞と体液に分布していて、組織適合性抗原(ヒトの免疫に関わる重要な分子)として働いていることが明らかになりました。

クラスⅠa抗原：HLA-A、B、C、
クラスⅡ抗原：HLA-DR、HLA-DQ、HLA-DP

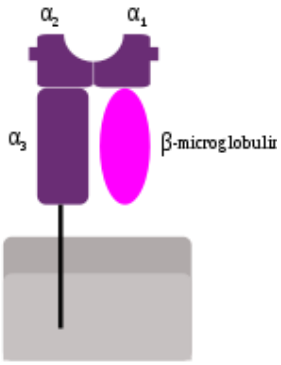
6番染色体

MHC=major histocompatibility complex in Humane



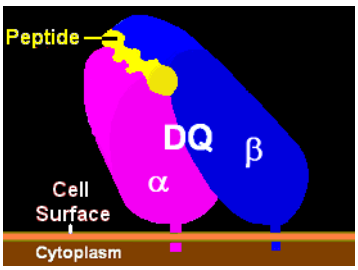
MHCのClass

Major HLA Class Ⅰ



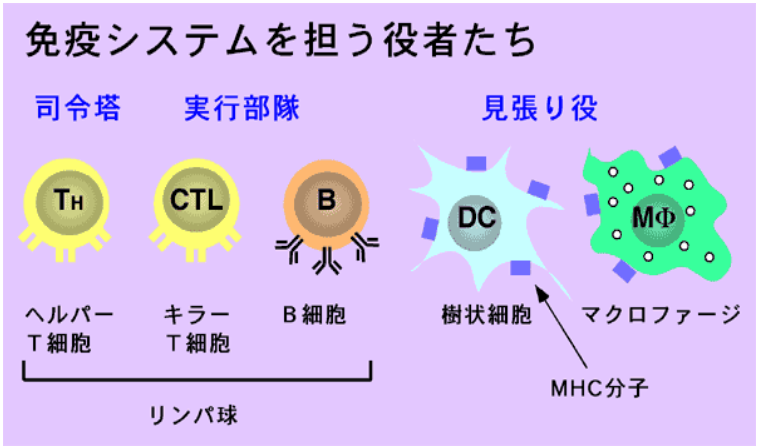
HLA−A, HLA−B, HLA−C
体のほとんどの細胞表面

Major MHC Class Ⅱ

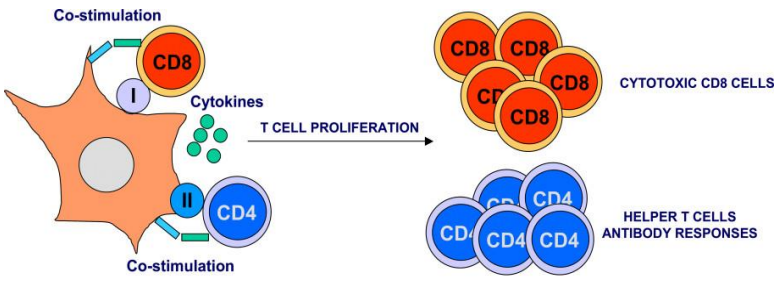


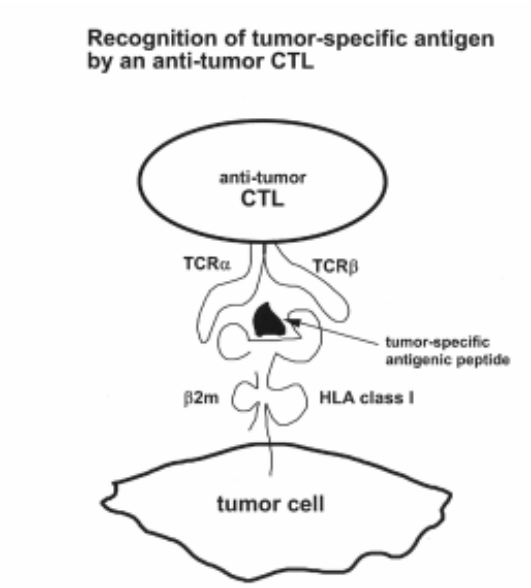
HLA−DP, HLA−DG, HLA−DR
樹状細胞、マクロファージ、B細胞

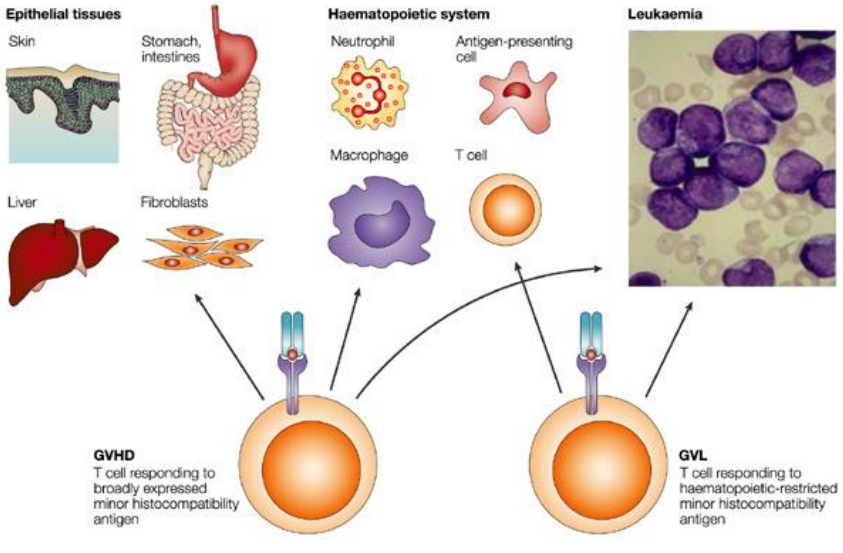
免疫細胞



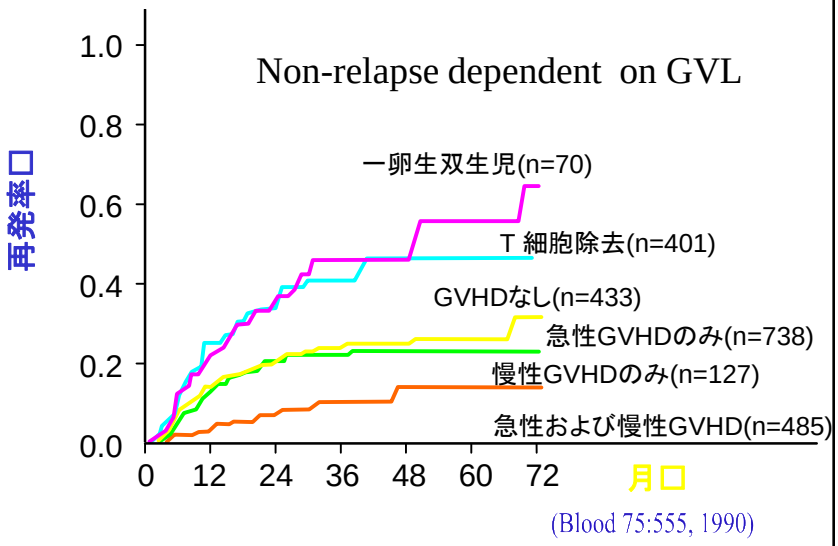
APC とCD4、CD8




Recognition of tumor-specific antigen by an anti-tumor CTL
anti-tumor CTL
TCRα
TCRβ
tumor-specific antigenic peptide
β2m
HLA class I
tumor cell


Epithelial tissues
Skin
Stomach, intestines
Liver
Fibroblasts
Haematopoietic system
Neutrophil
Antigen-presenting cell
Macrophage
T cell
Leukaemia
GVHD
T cell responding to broadly expressed minor histocompatibility antigen
GVL
T cell responding to haematopoietic-restricted minor histocompatibility antigen
Nature Reviews | Cancer

Actuarial probability of relapse after BMT



(Blood 75:555, 1990)

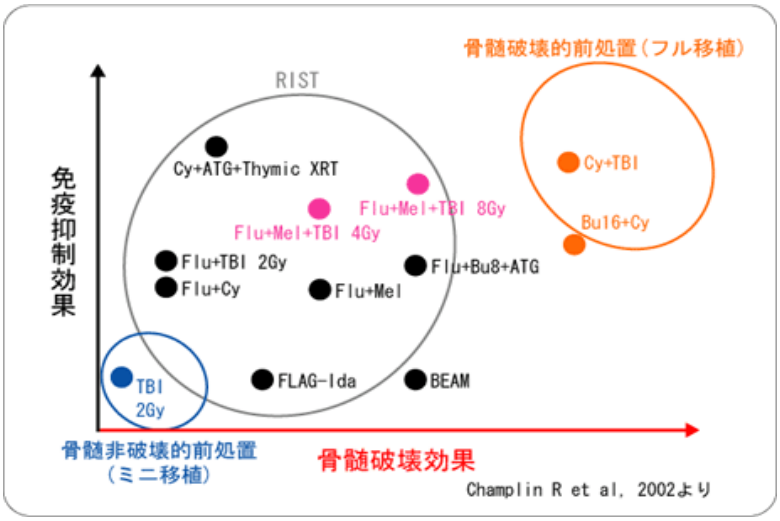
移植の歴史から分かったこと

1. 腫瘍細胞は高容量の抗腫瘍剤では根絶できない。

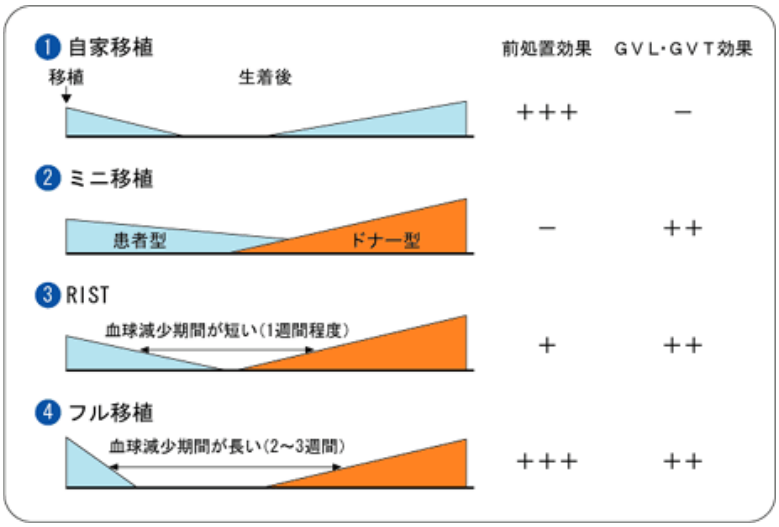
2. 治癒は移植片がもたらす抗腫瘍作用によって
もたらされる。

3. 移植片-宿主の混合キメラ
(a state of mixed donor-host chimerism)は
治癒の状態をもたらす。

前処置



前処置と抗腫瘍効果



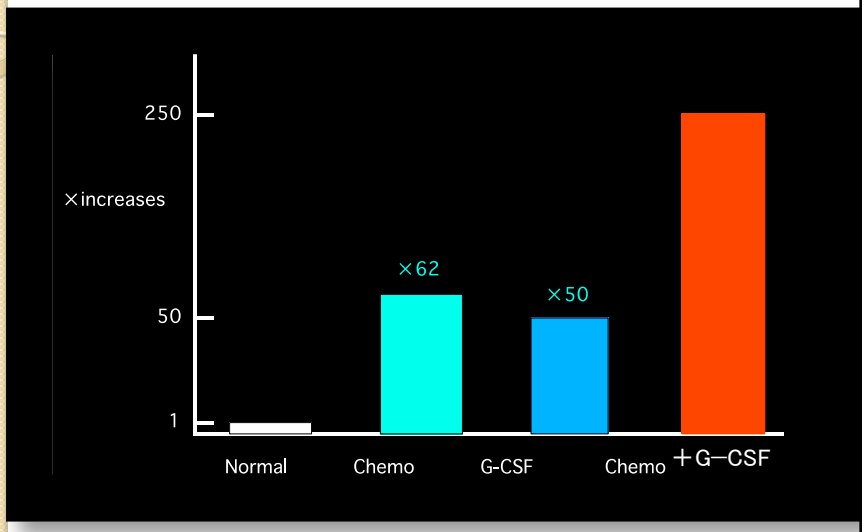
PBSCTの歴史

1970年 Thomas CY/TBIによるBMTを実施
1971年 Mc Credie；末梢血にわずかに幹細胞がある
1976年 Richman；乳がん・卵巣癌の化学療法後に一時末梢血に幹細胞が増加
1980年前半 日本でBMTの成功率高まる
1986年以降 PBSCTの臨床応用
1988年 PBSCTの臨床開始(日本)

1992年12月PBSCH
1993年7月PBSCT for ALL (於　星ヶ丘厚生年金病院)

1994年4月PBSCT保健医療に。

Harvest cells of PBSC



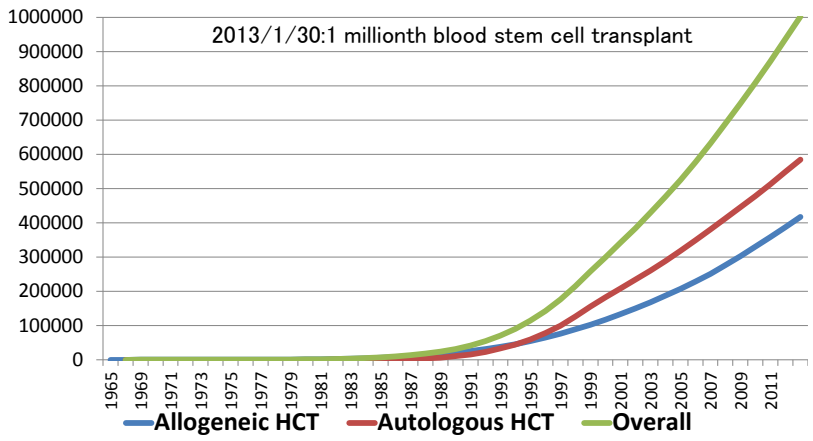
PRESENT

Bern, Switzerland, Jan. 30, 2013
The Worldwide Network for Blood and Marrow Transplantation (WBMT)

The collaborative work of medical scientists and physicians across the globe has resulted in a major medical milestone: the world's 1 millionth blood stem cell transplant, a procedure that has become a proven and essential therapy for many patients battling blood cancers like leukemia and lymphoma, as well as other critical diseases.

Estimation of Global Transplant Numbers

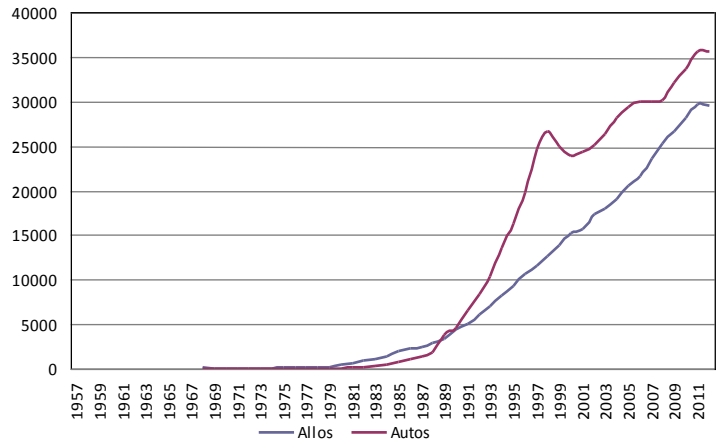
Allogeneic and autologous



not for publication

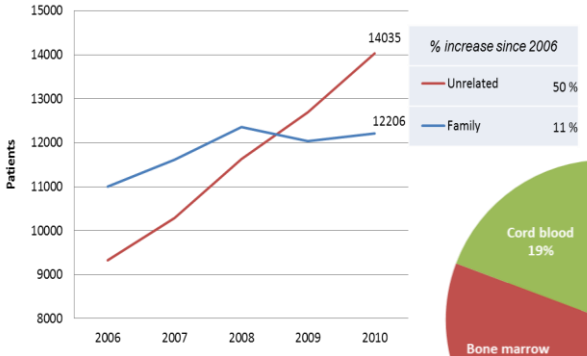
Global Transplant Numbers

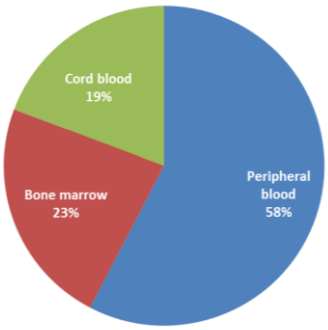
Allogeneic and autologous 1957 – 2012



not for publication

Trend over 5 years : Donor type





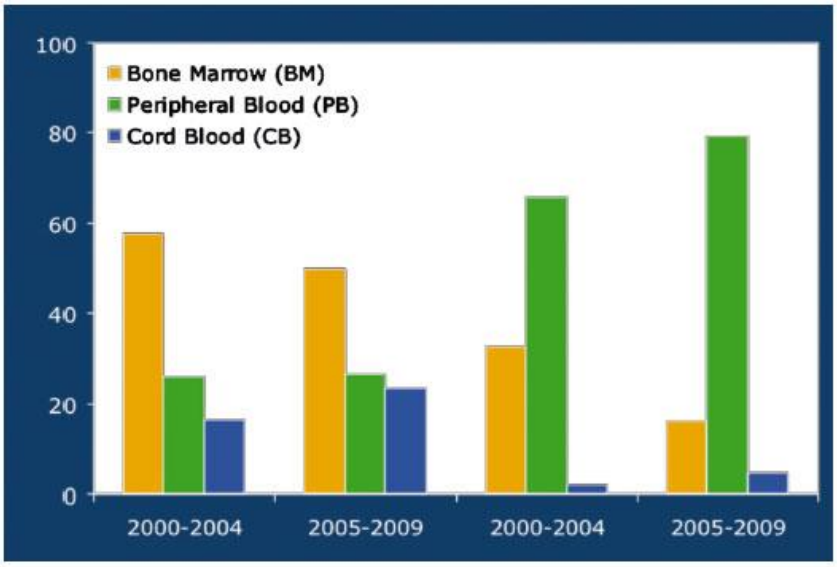
09/10 preliminary data

Unrelated stem cell source

not for publication

Worldwide Network for Blood and Marrow Transplantation
NGO in official relations with the World Health Organization

Stem cell 別



FUTURE

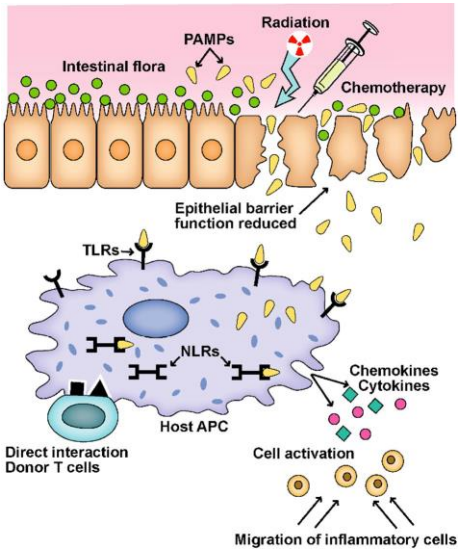
移植の課題

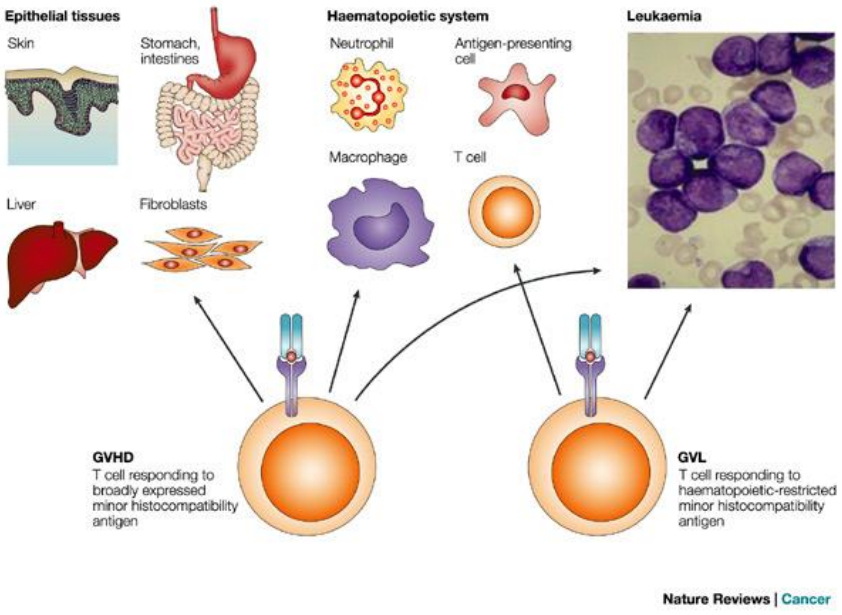
1. Rejection（拒絶）
   Graft-versus-host disease（GVHD）
   Immunosuppresuive agents
   6MP, Immuran, CPM, CyA、ATG

2. Recurrence（再発）

3. Infection（感染症）

GVHD initiation





GVHD対策

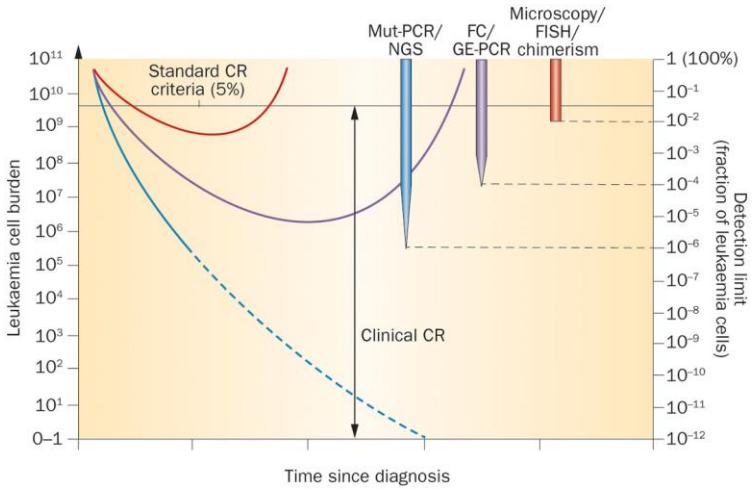
1. T cell depletion (Perugia)
   (ex vivo)

2. Post transplantation CY
   Experimanal ?(USA)

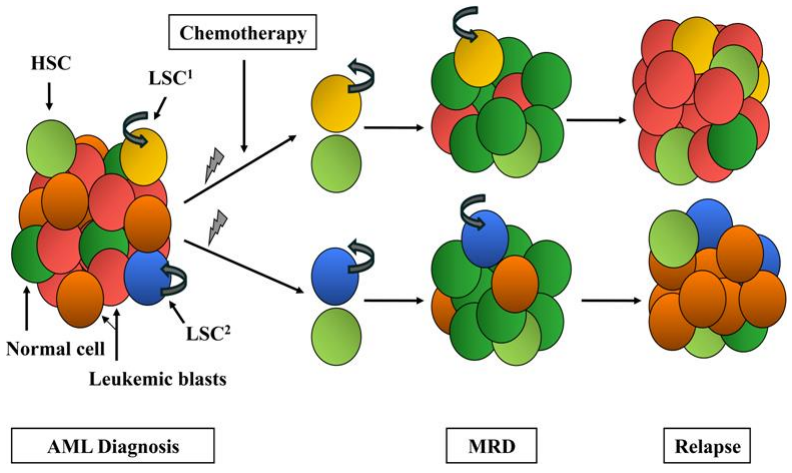
3. High dose ATG (China Korean)
   (in vivo depletion)

4. Low dose ATG+mPSL (Hyogo)

Detection thresholds of various MRD modalities compared to traditional clinical complete remission



Hourigan, C. S. & Karp, J. E. (2013)
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.100



Christopher S. Hourigan & Judith E. Karp
Nature Reviews Clinical Oncology 10, 460-471

Barrierを超えて

HLA=Barrier
matched SCT

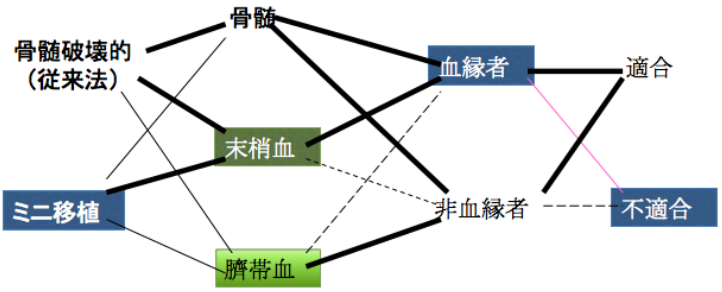
HLA=Stepping-stone
Haplo SCT

#new technical developments
1. Mesenchimal Stem Cells
2. new agents
移植の夢に向かって

SCTの見直し

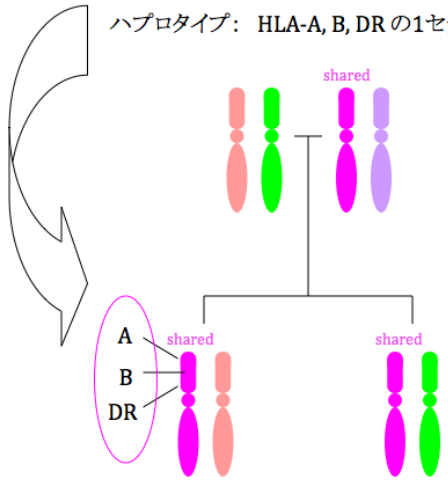
造血幹細胞移植(SCT)治療
移植方法の種類

前処置　幹細胞源　ドナー　HLA



2 X 3 X 2 X 2＝24通り

Haplo-identical Donor

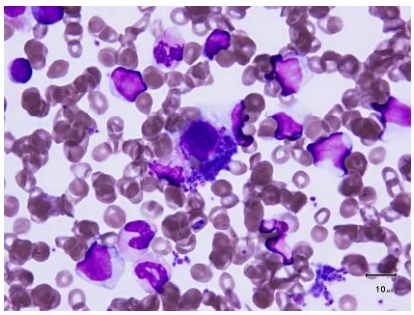


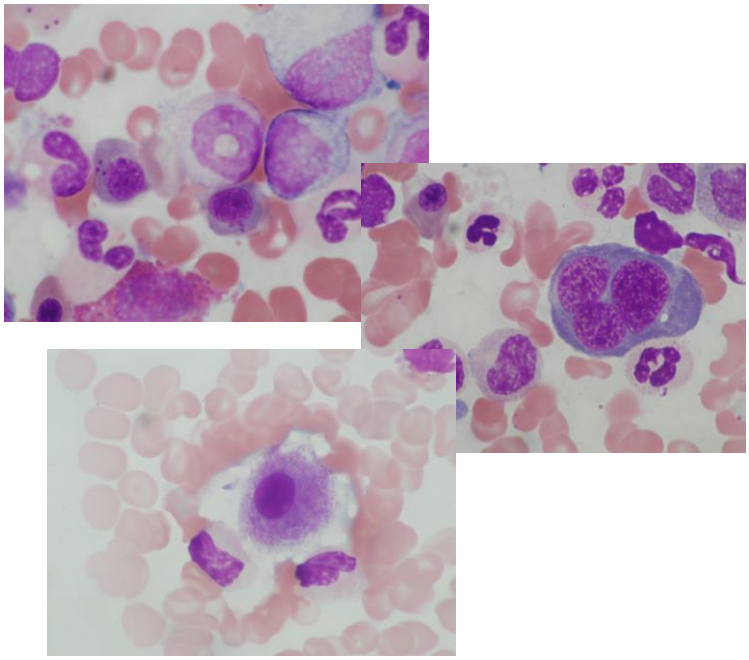
ハプロ移植： haploidentical donor からの移植

「以下、HLA-haploidentical を、HLA半合致と呼ぶことにする」

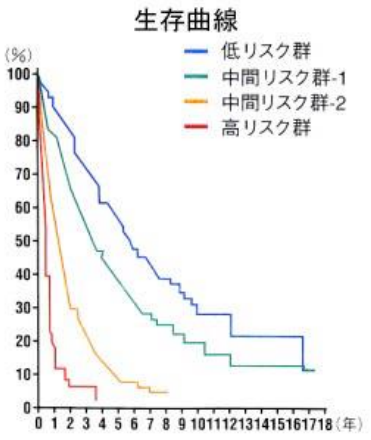
（兵庫医大 血液内科）

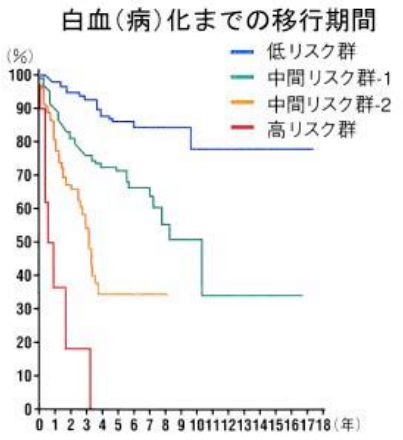
Case : 6x y.o.. Male
Peripheral blood :
WBC : Hb : Platelet = 6100 : 7.6 : 35.1*10E4
Bone marrow : NCC 4.8, Mgk 15, M/E=26.2,
blast 25.6% > 20%
CD 7 83.2, CD13 96.2, CD33 82.6, CD 75.5,
HLA-DR 86.6
WT1=33000
46, XY, t(4;12)(q12;p13)[20]



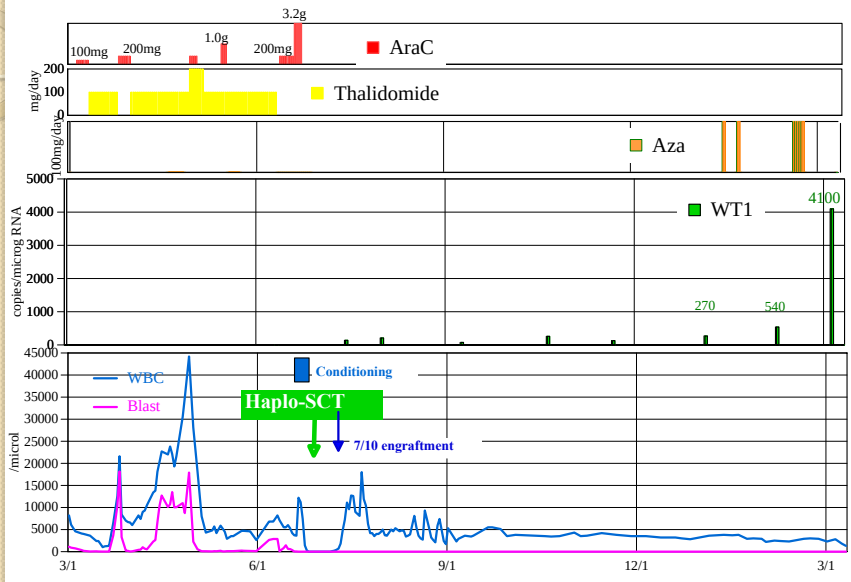


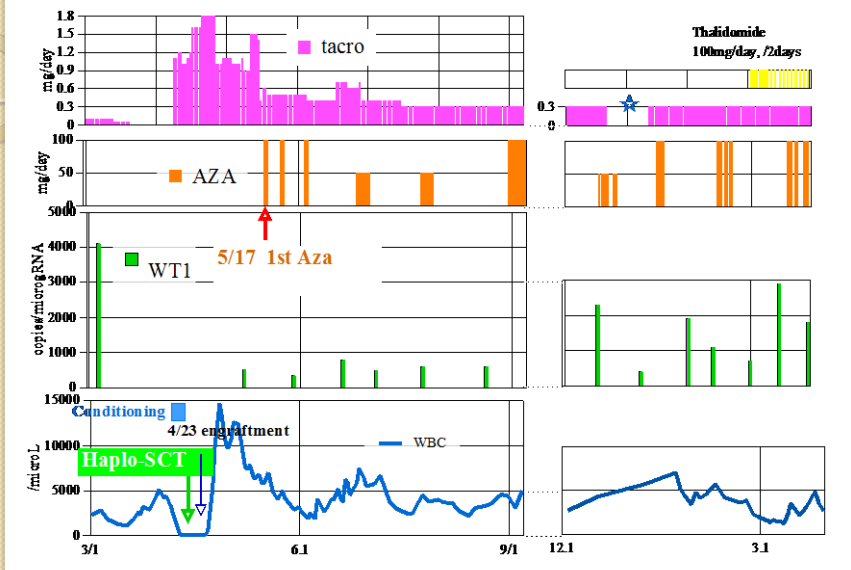
MDS IPSSによる予後と白血病化





Haplo-SCT


3.2g
100mg
200mg
1.0g
200mg
AraC
mg/day
200
100
0
Thalidomide
100mg/day
Aza
5000
4000
3000
2000
1000
0
copies/microg RNA
WT1
4100
270
540
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
/microl
WBC
Blast
Conditioning
Haplo-SCT
7/10 engraftment
3/1
6/1
9/1
12/1
3/1


1.8
1.5
1.2
0.9
0.6
0.3
0
mg/day
tacro
Thalidomide
100mg/day, /2days
0.3
0
100
50
0
mg/day
AZA
5000
4000
3000
2000
1000
0
copies/microgRNA
WT1
5/17 1st Aza
15000
10000
5000
0
/microL
Conditioning
4/23 engraftment
Haplo-SCT
WBC
3/1
6/1
9/1
12/1
3/1

Neutropeniaと細菌感染

Neutropenia

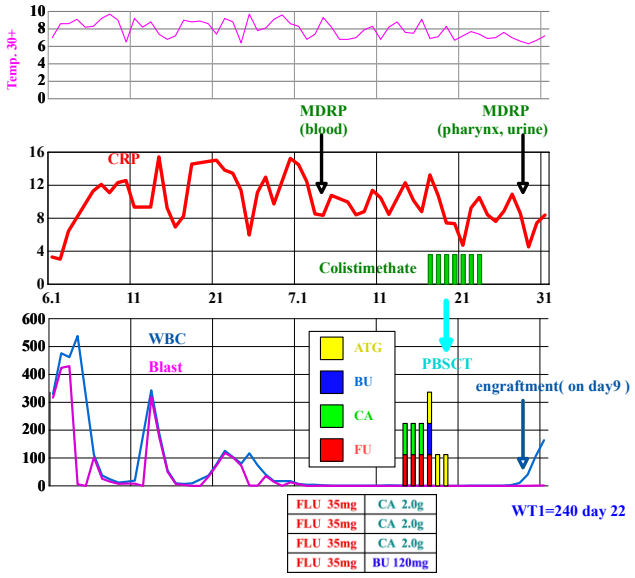
less than 100、 Blood stream infection 11--25%

Infected germes at Netropenia

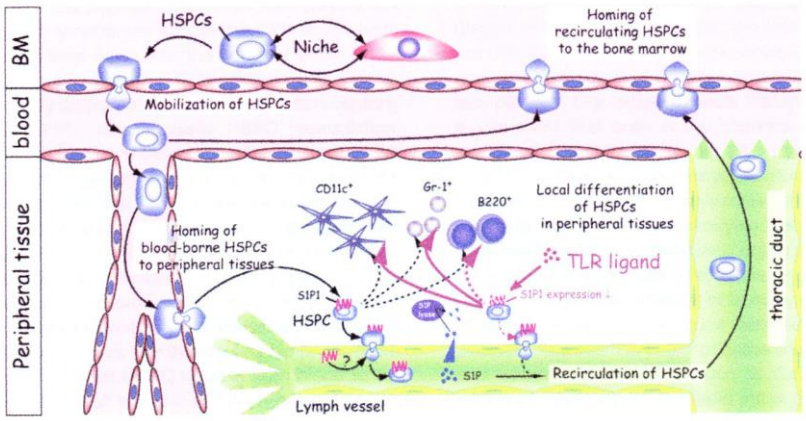
1. **Staphylocuccus**
   - **Coagulase negative, oxacillin-resistant 31.8%**
   - **Coagulase negative, oxacillin-sensitive 14.7%**
2. **S.aureus 7.2%**
3. **E.coli 25%**
4. **Enterobacteriacea 15%**
5. **Pseudomonas aeruginosa 3.8%**
   Reduced susceptibility to CAZ, CFPM & MEPM
   11～33%

(Infection and Drug Resistance 2010:3 53-61)

Haplo SCT of 1st relapse AML

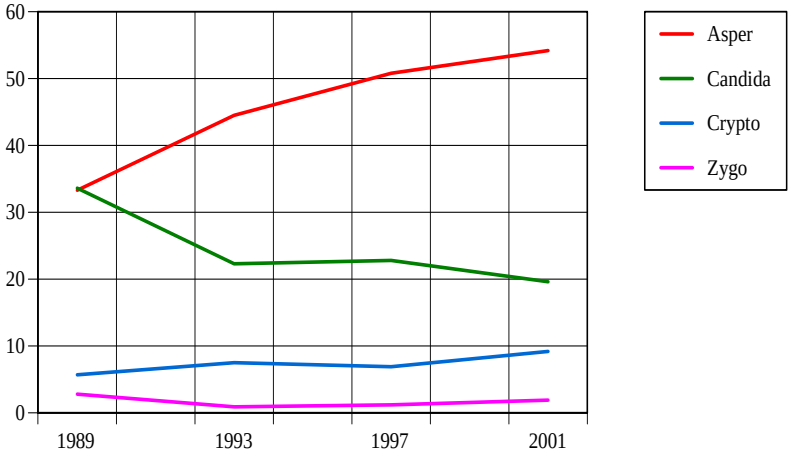


Innate Immunity

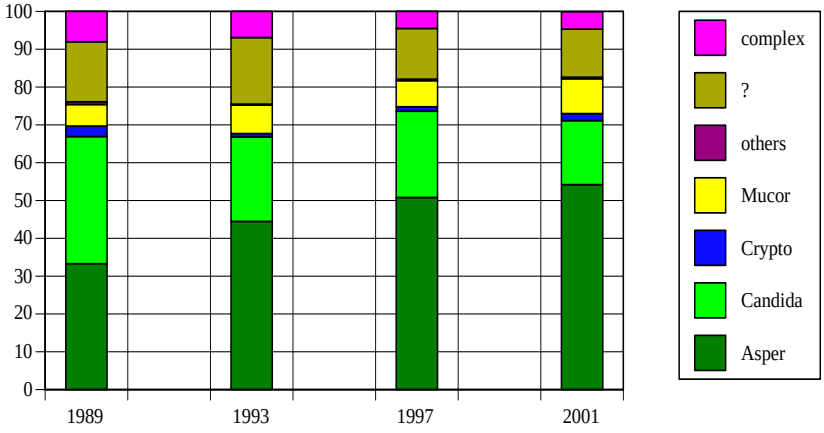


Steffen M. et.al. Cell 131,2007

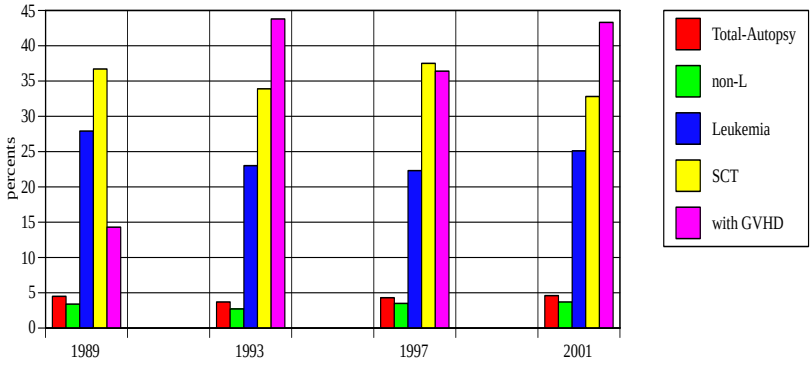
白血病剖検例における起因真菌の占める割合（重複感染・起因菌不明を除く）



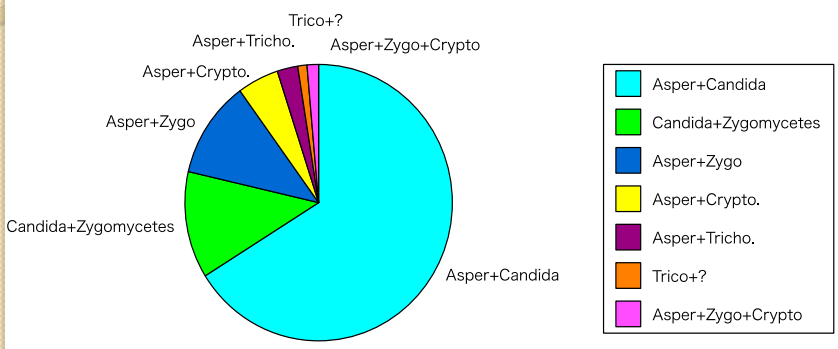
起因真菌別頻度



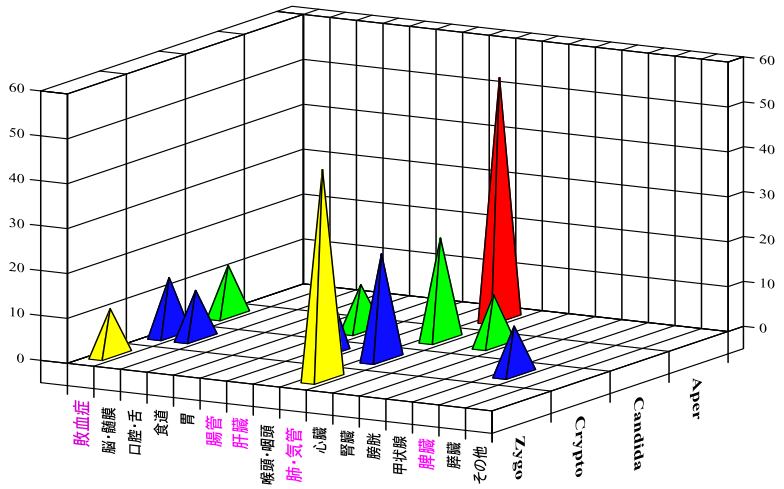
Fungal Infections
内蔵真菌症の発生頻度



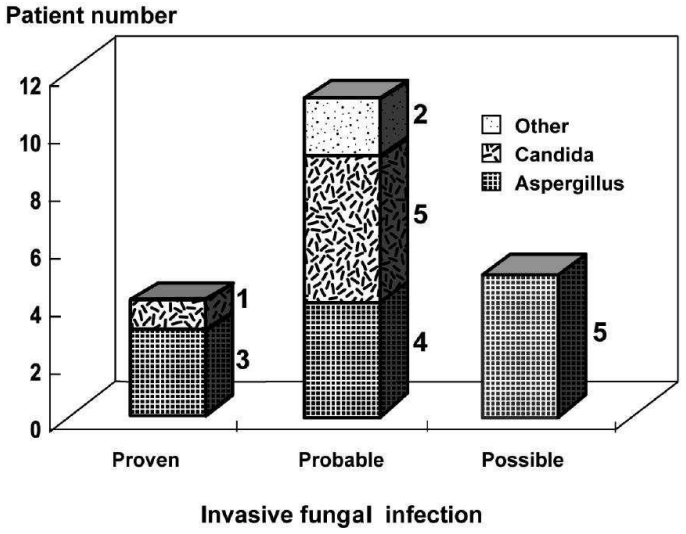
重複感染症の起因真菌別内訳



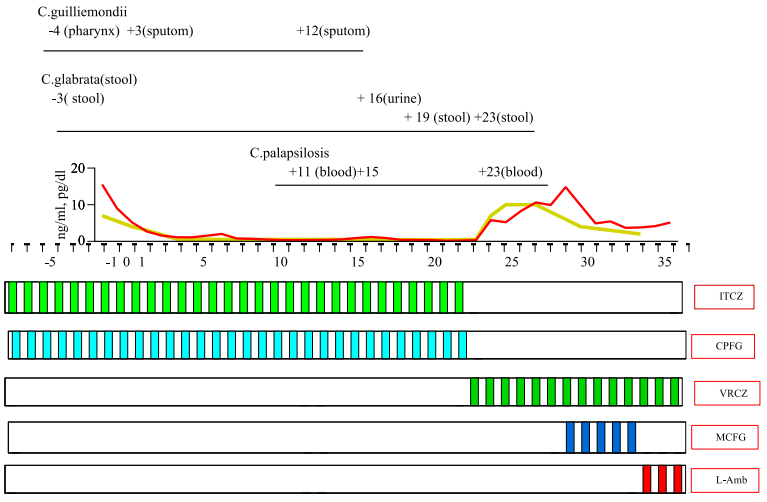
起因真菌別にみた罹患臓器別頻度（単独真菌感染例）



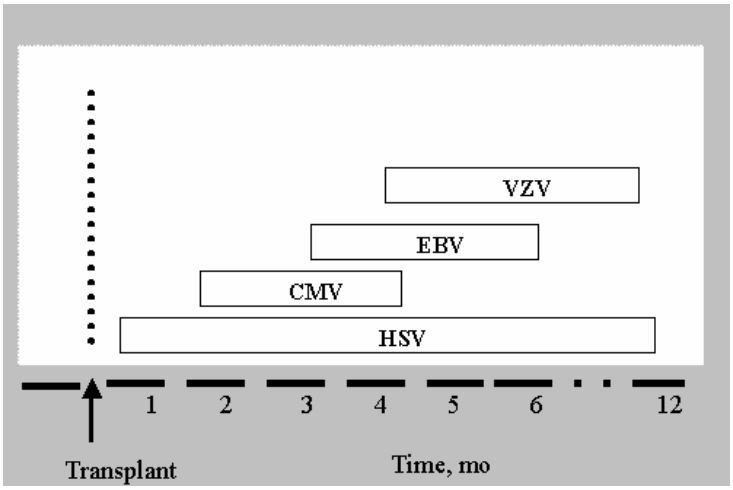
診断カテゴリー



invasive fungal infectionの例



The reactivation of herpesviruses



The triangular model of infectious disease

Agent or microbe
causes the disease

Envirnoment
allow disease transmission
cytokine, chemokine
pharmacological E.

Host
genetic susceptibility
nutritional status
resiliency

未来へ

minimizing pain,
maximizing gain

Marie-Térèse Little and Rainer Storb
Fred Hutchinson Cancer Research Center