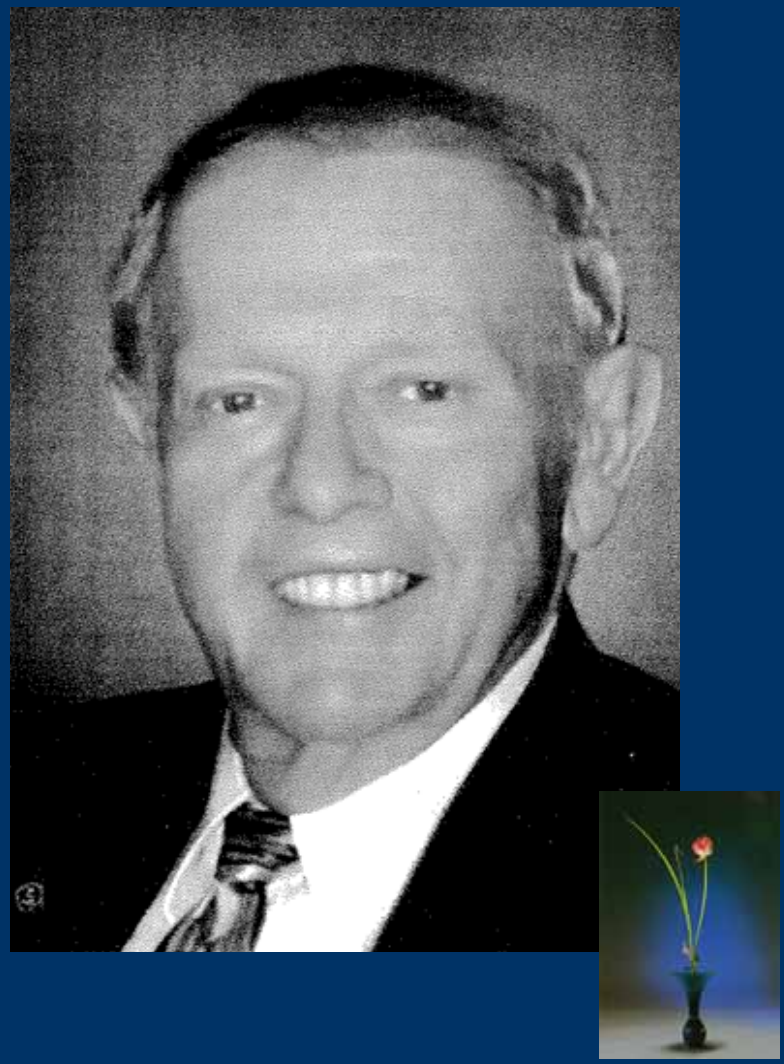
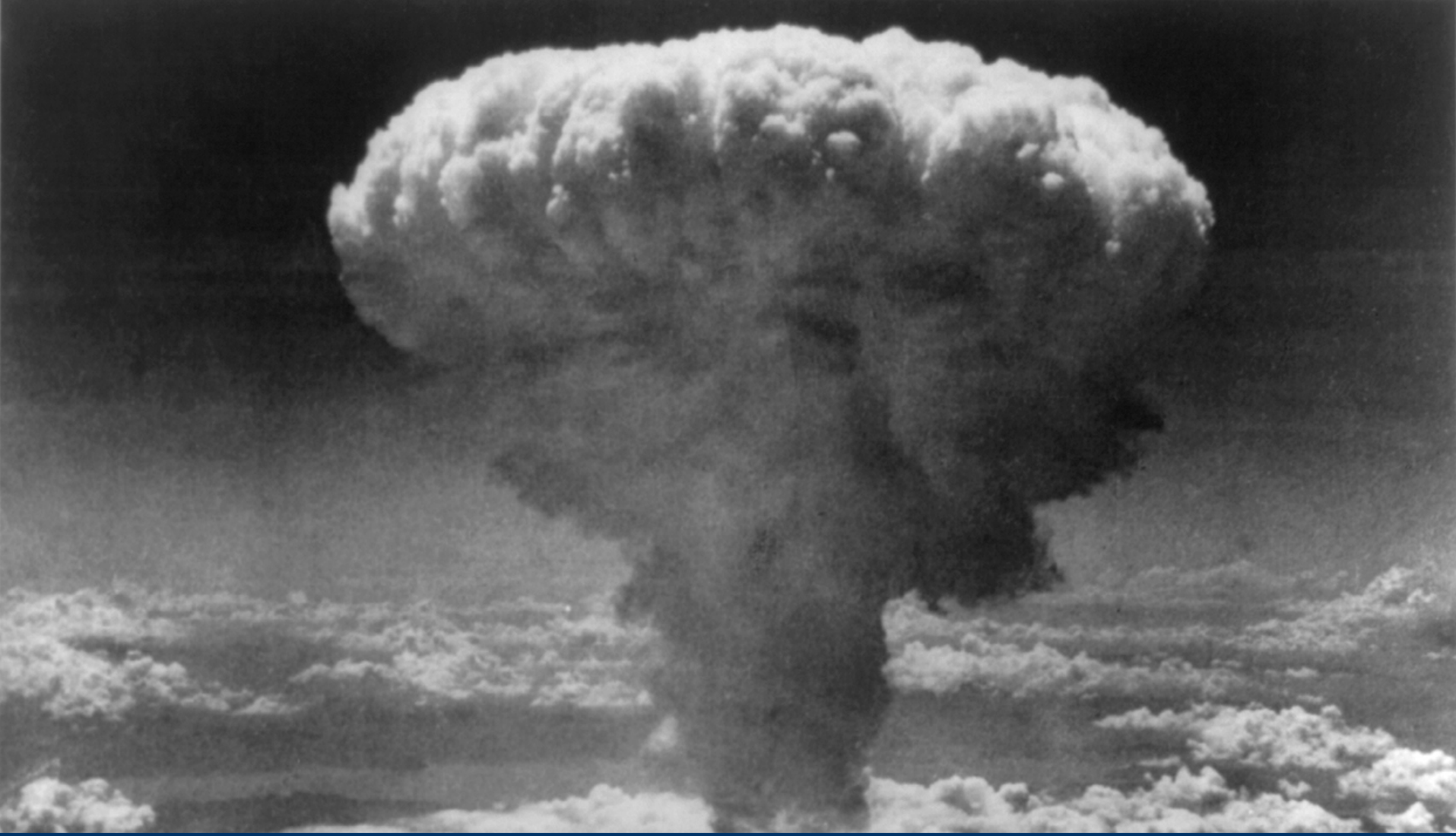
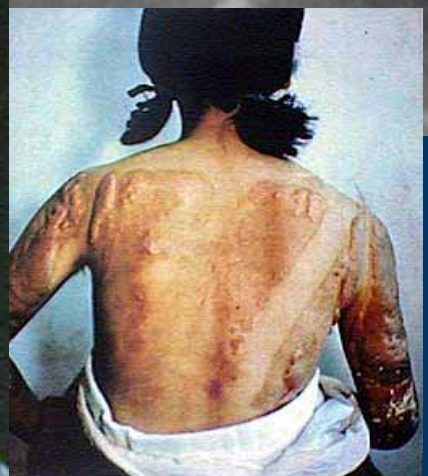
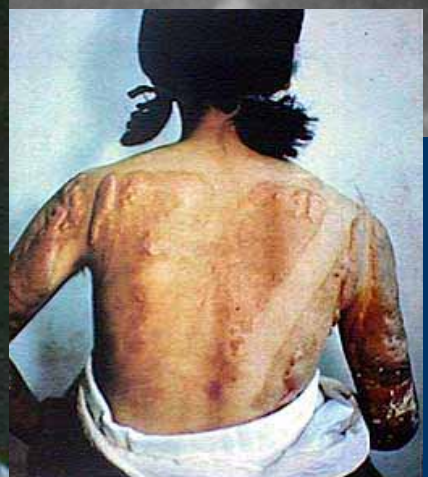


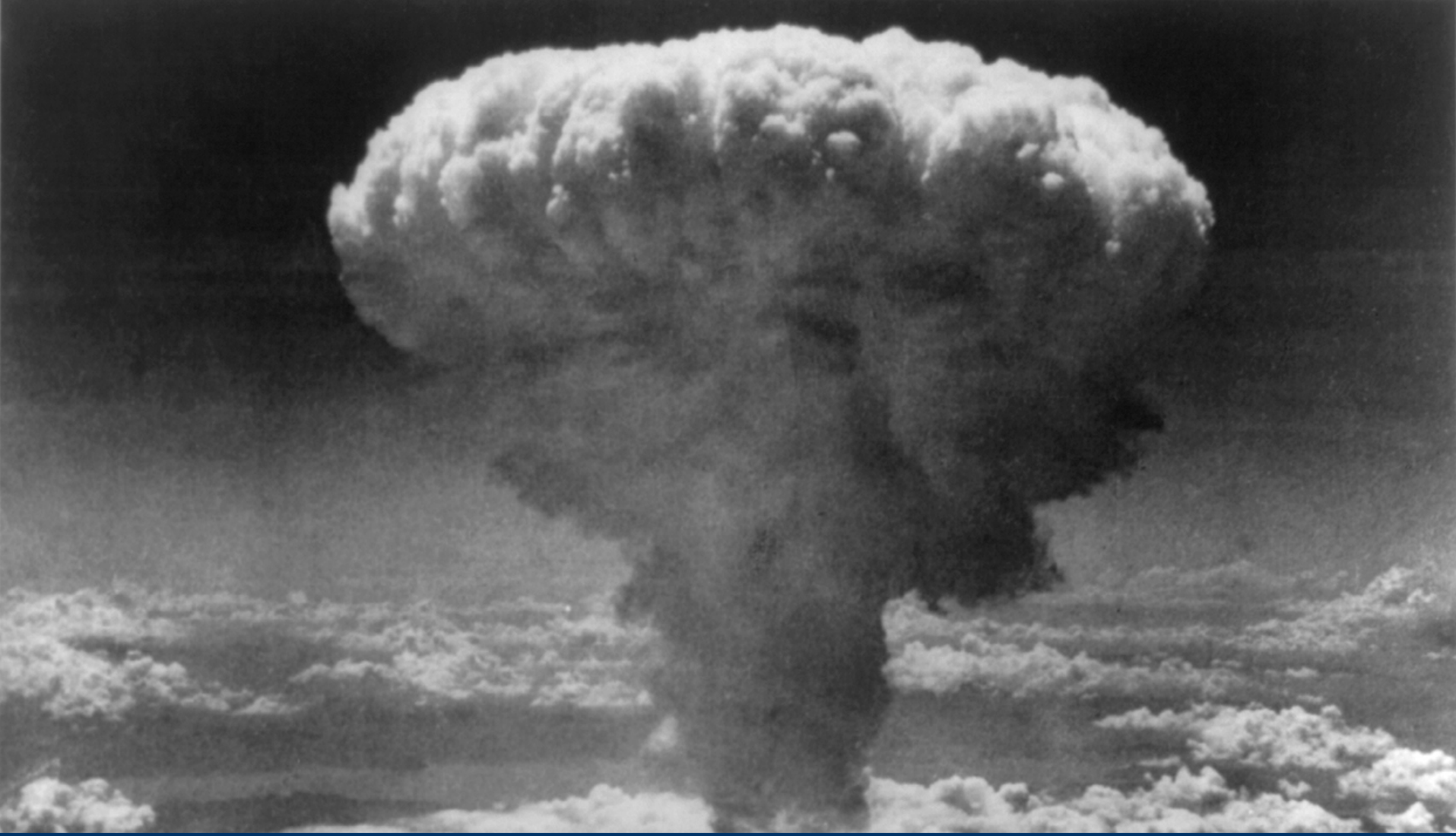
Dedicated
to
Gordon

Stem Cell Transplantation: The Journey

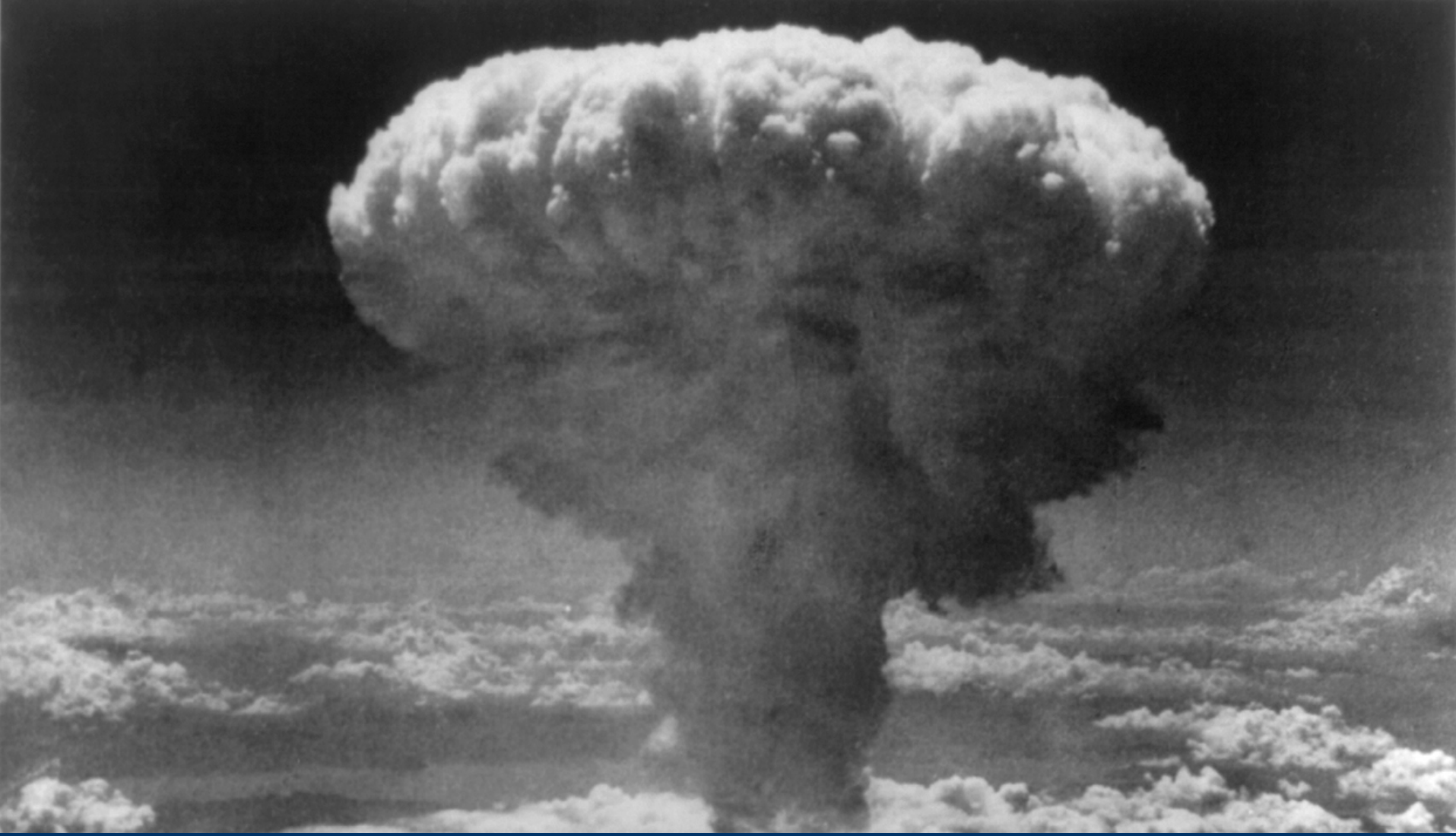




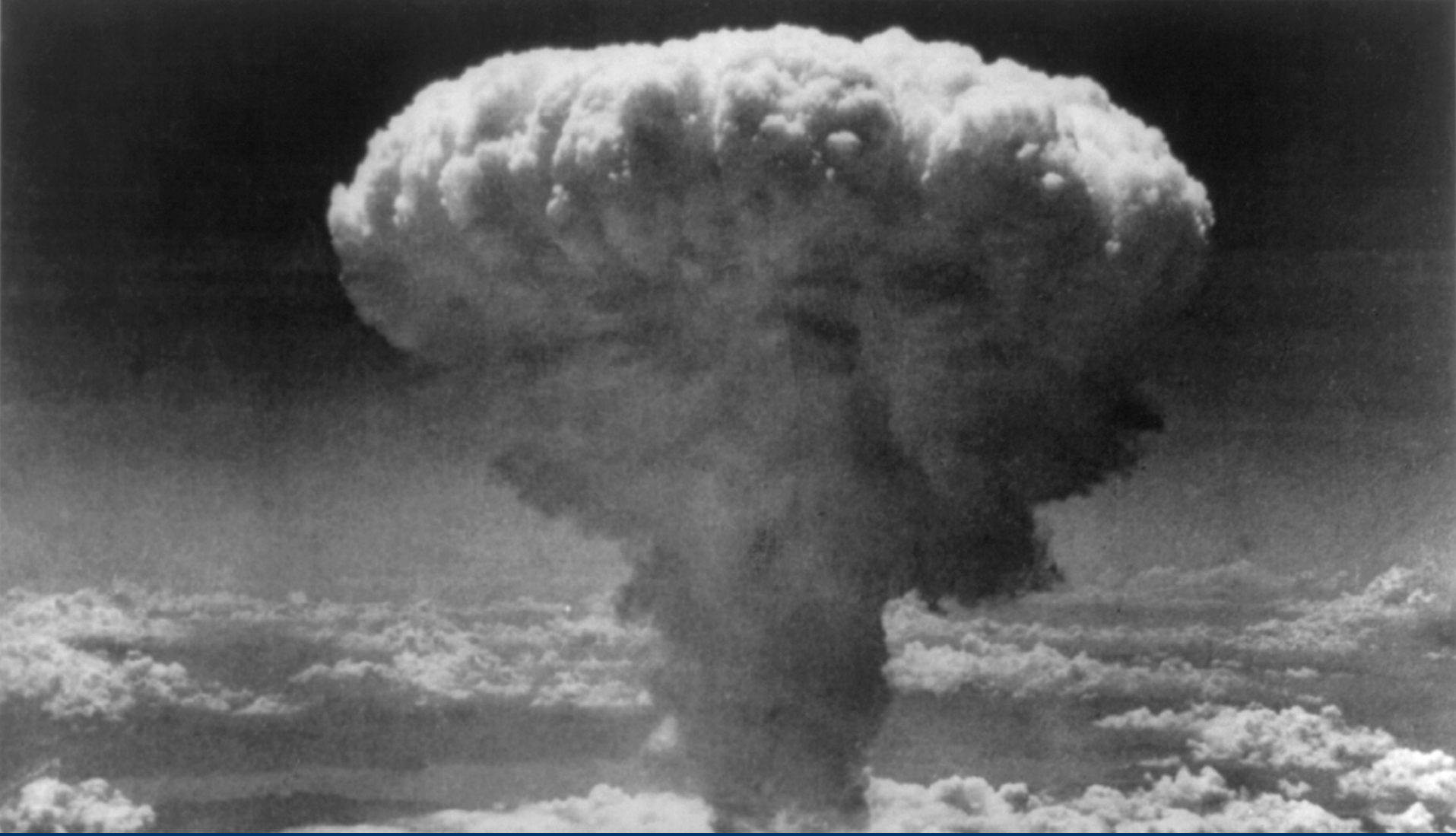




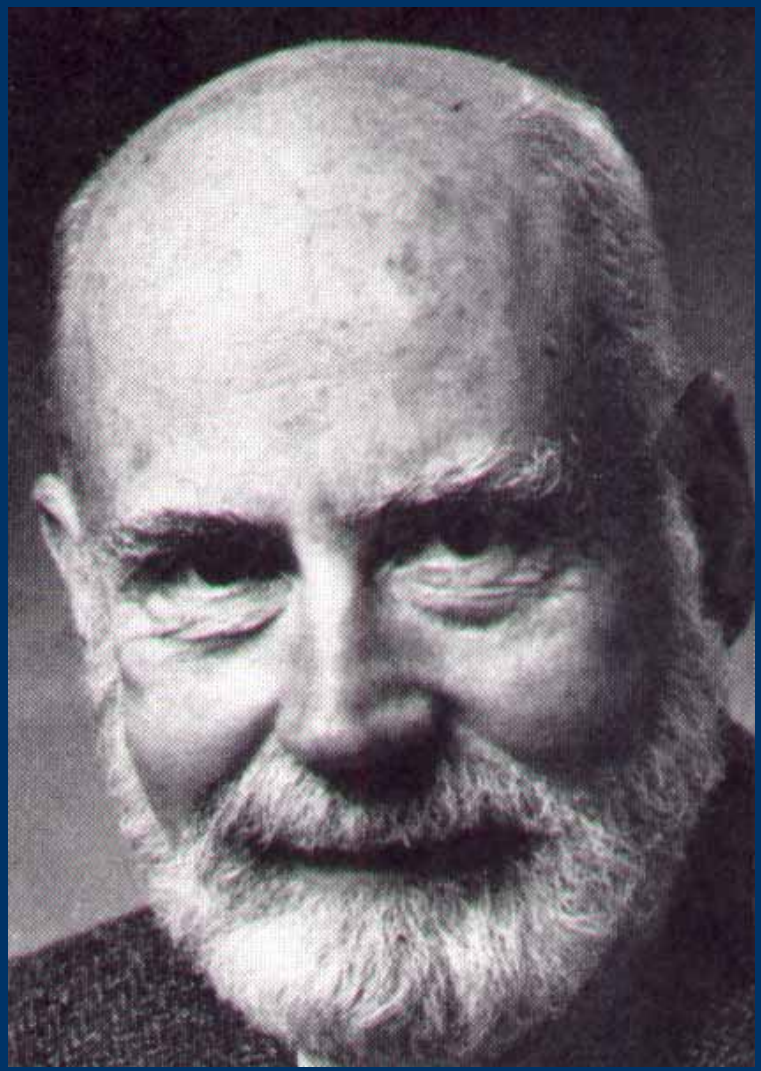
1949 Jacobson et al: Radioprotection by lead shielding of the spleen of a lethally irradiated animal



1951 Lorenz et al: Radiation protection of lethally irradiated animals by marrow and spleen cells from non-irradiated animals of the same strain

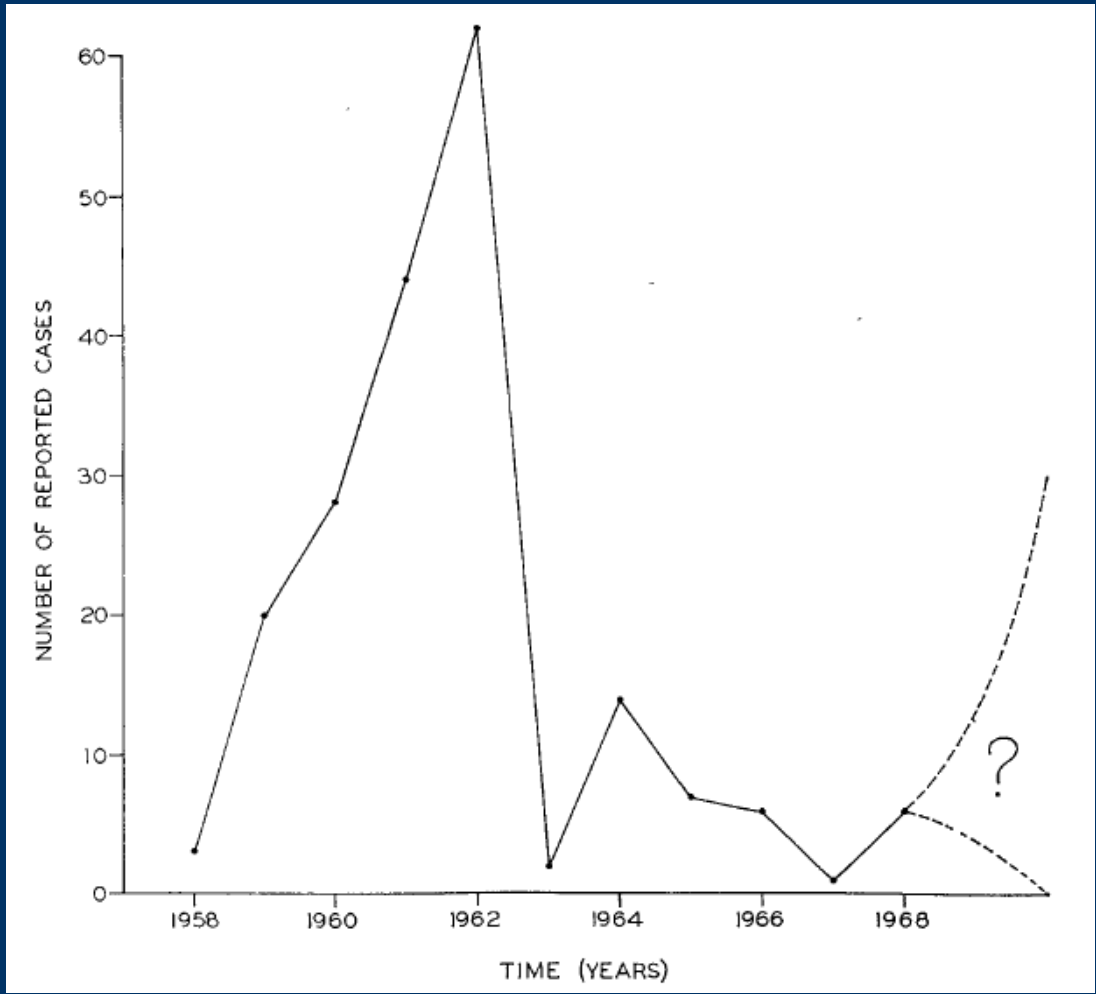


1956 Barnes et al: Successful treatment of leukemia in mice after lethal irradiation followed by injection of normal marrow cells

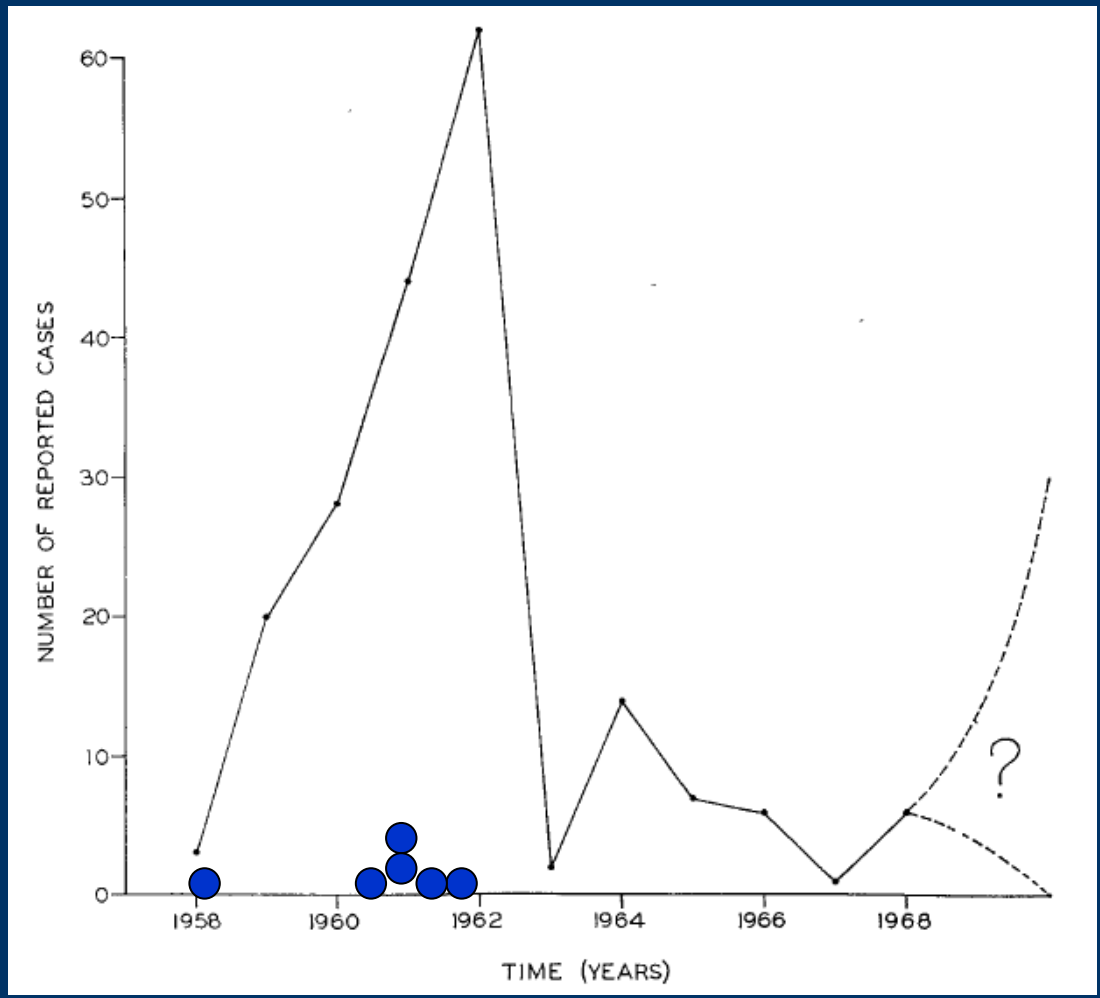


Donnell E. Thomas

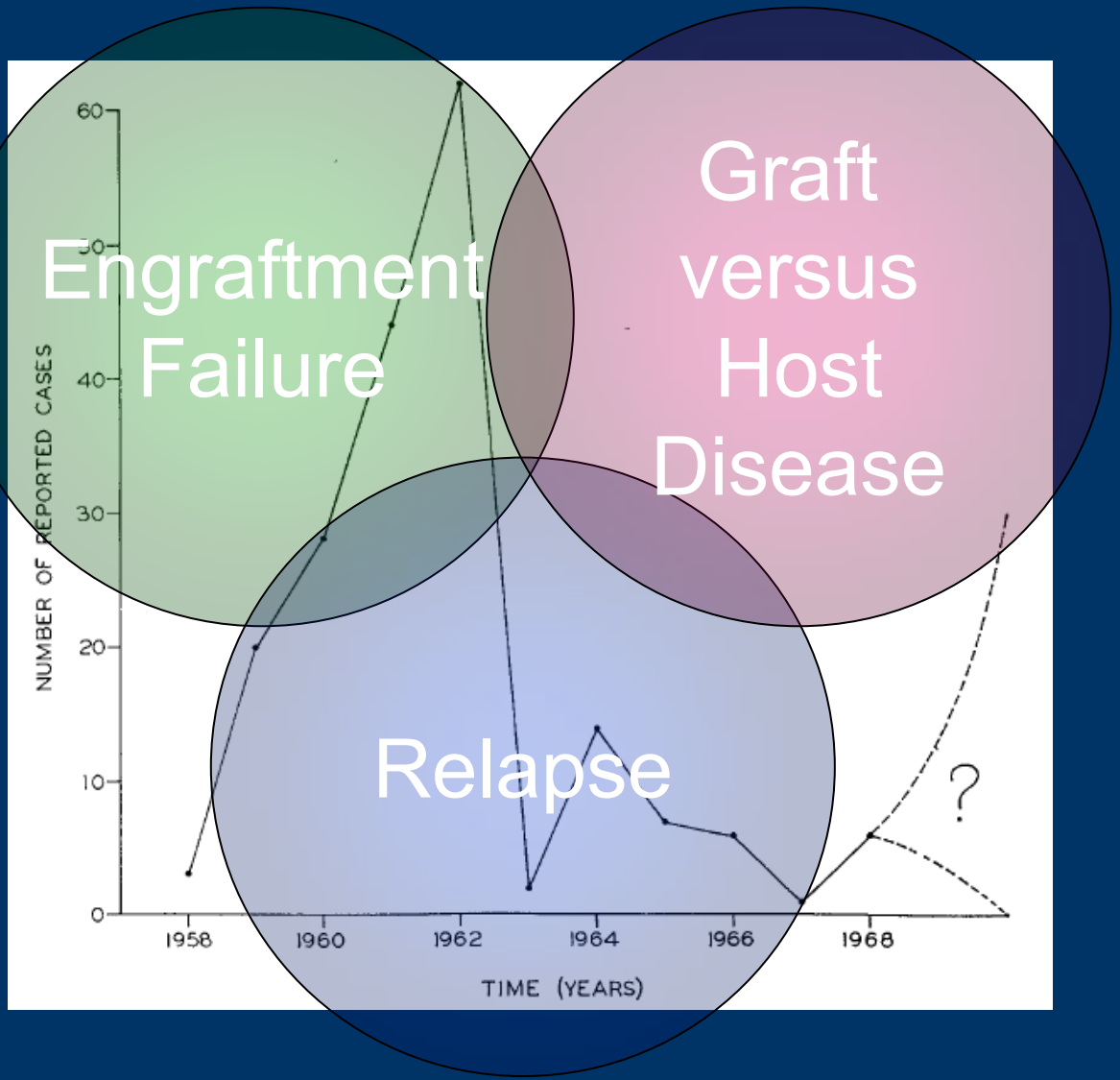
The first wave of transplants



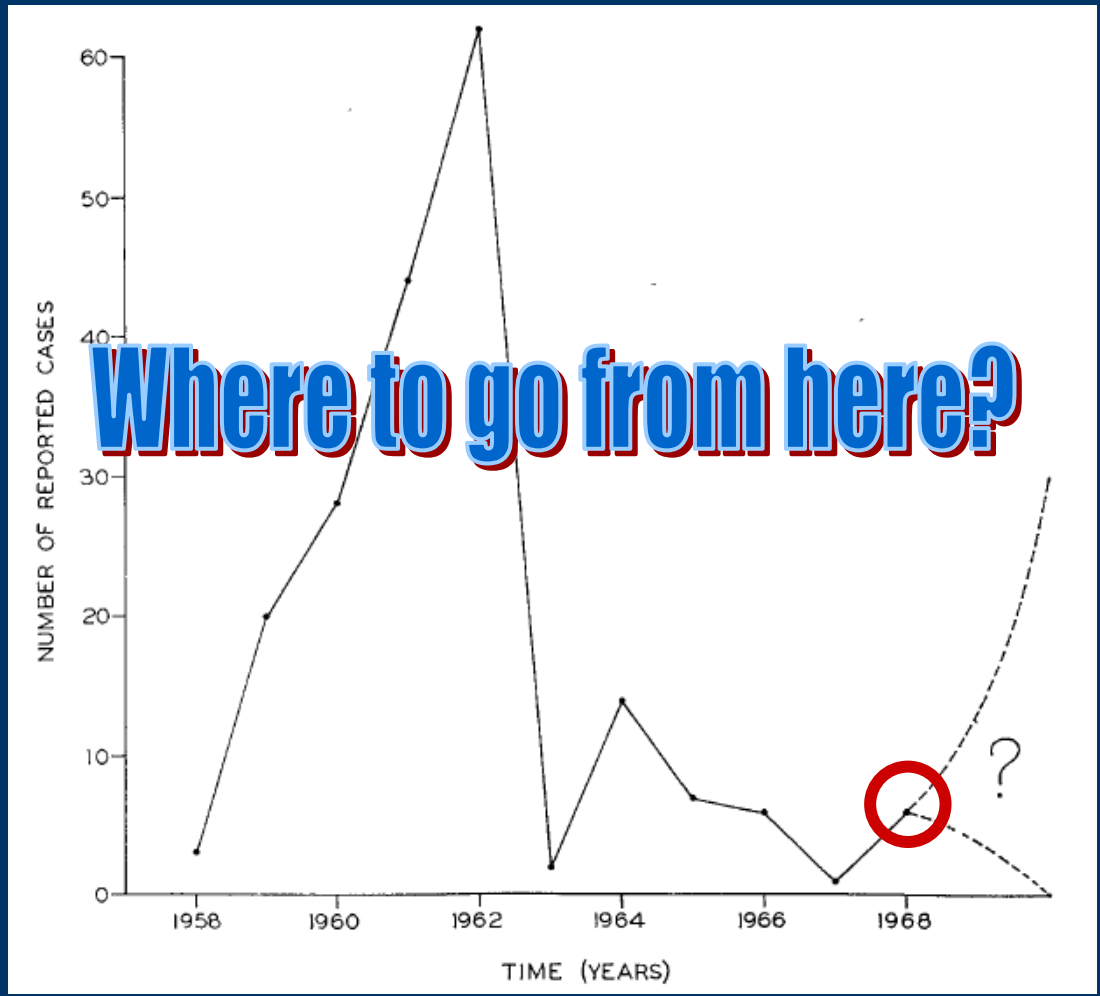
The first wave of transplants



The first wave of transplants



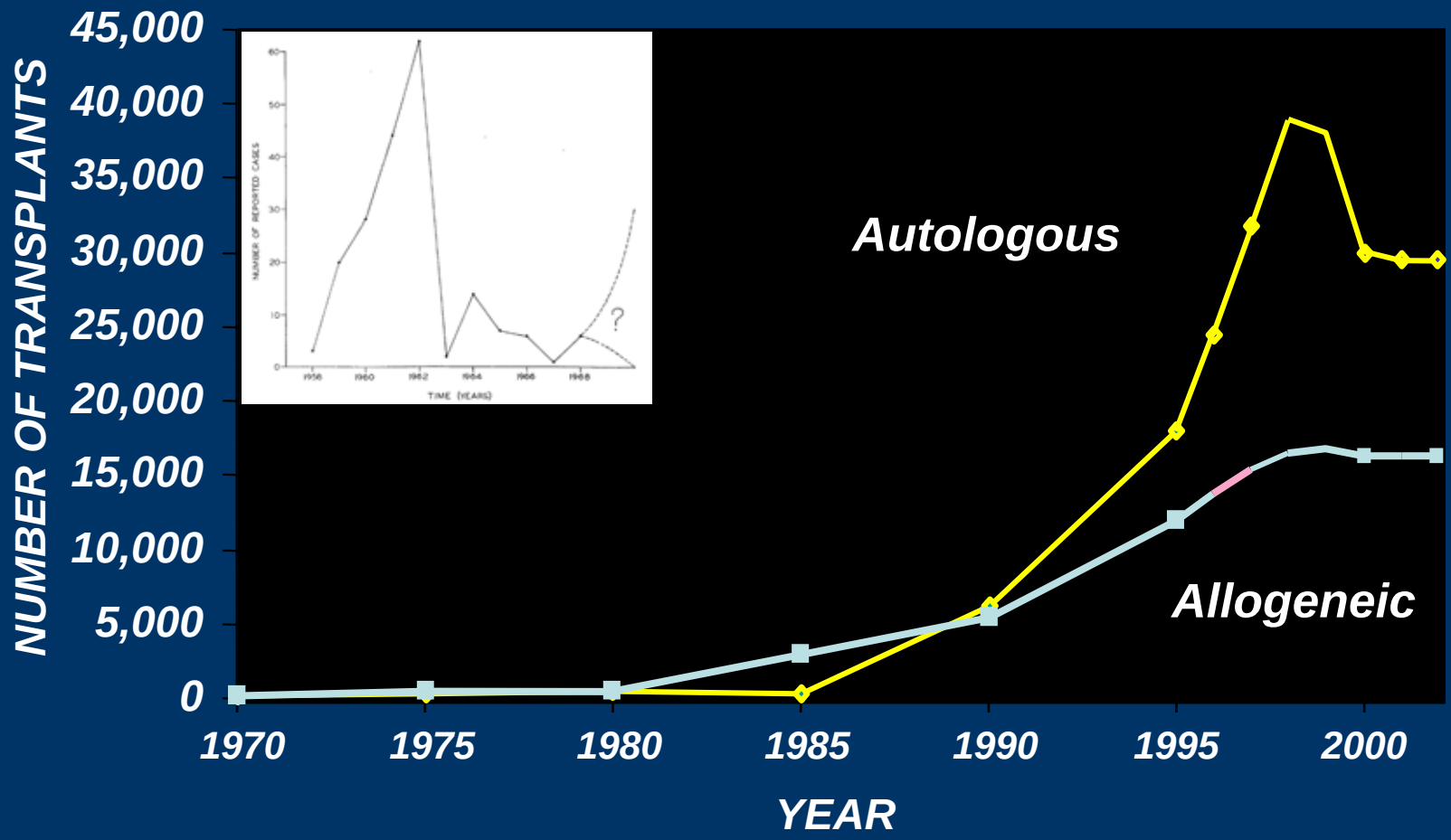
The first wave of transplants



Establishment of principles : The pillars of modern transplantation

- HLA typing
- Stem cell biology
- Transplant immunology
- Supportive care

The second and sustained wave of transplants



Emerging complexity of the HLA-system

HLA-A alleles N=6

HLA-B alleles N=6

1968

Locus	Number of alleles	Locus	Number of alleles
HLA-A	209	HLA-DRB8	1
HLA-B	414	HLA-DRB9	1
HLA-C	101	HLA-DQA1	21
HLA-E	6	HLA-DQB1	45
HLA-F	1	HLA-DPA1	19
HLA-G	15	HLA-DPB1	93
HLA-DRA	2	HLA-DOA	8
HLA-DRB1	273	HLA-DOB	8
HLA-DRB2	1	HLA-DMA	4
HLA-DRB3	30	HLA-DMB	6
HLA-DRB4	10	TAP1	6
HLA-DRB5	15	TAP2	4
HLA-DRB6	3	MICA	51
HLA-DRB7	2		

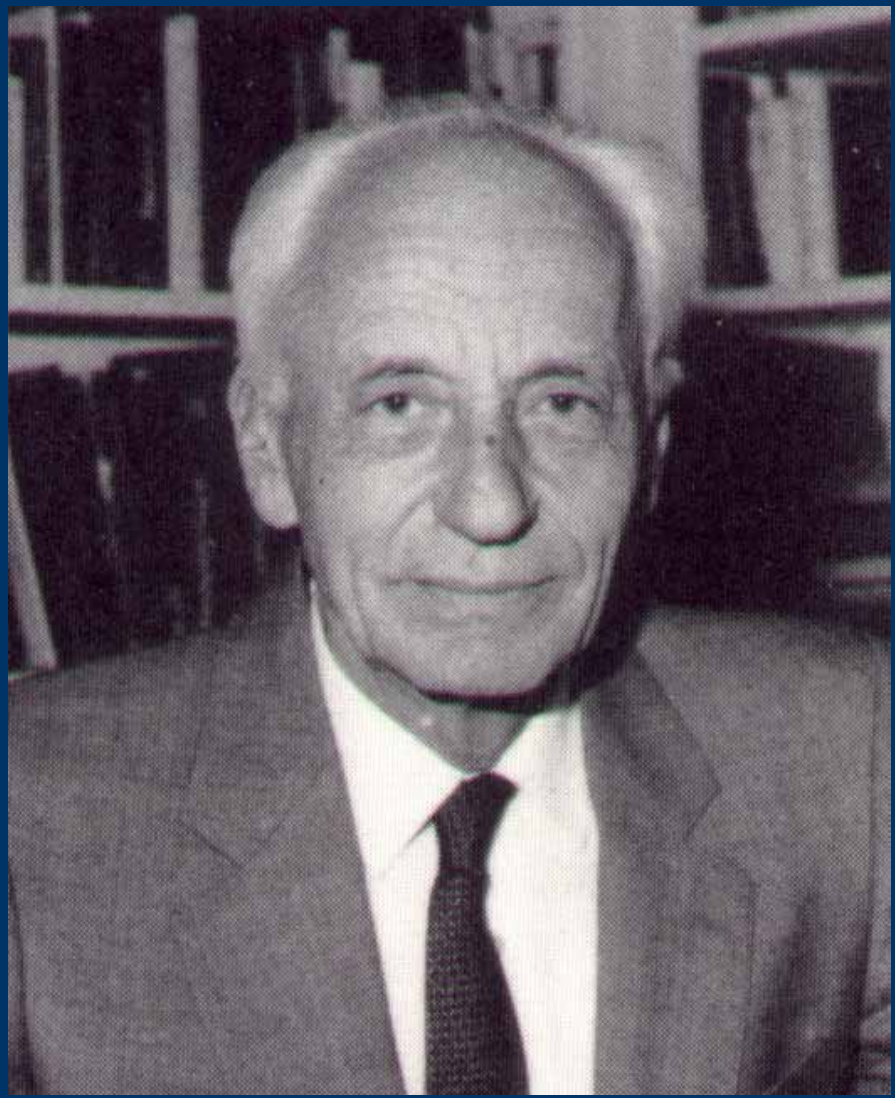
Emerging complexity of the HLA-system

HLA-A alleles N=6

HLA-B alleles N=6

1968

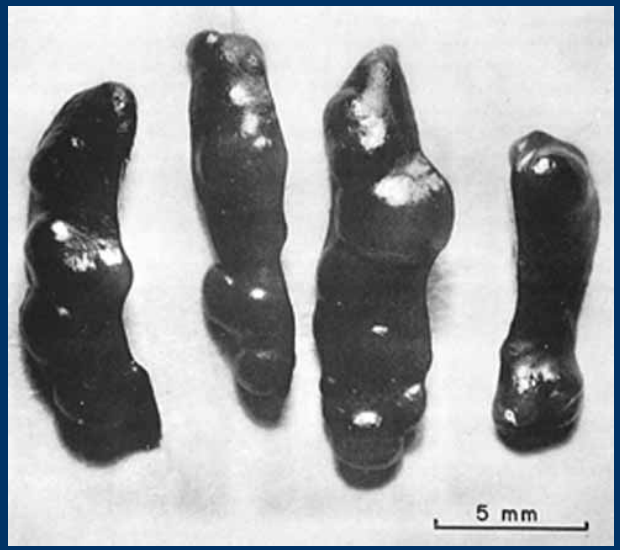
Locus	Number of alleles	Locus	Number of alleles
HLA-A	209	HLA-DRB8	1
HLA-B	414	HLA-DRB9	1
HLA-C	101	HLA-DQA1	21
HLA-E	6	HLA-DQB1	45
HLA-F	1	HLA-DPA1	19
HLA-G	15	HLA-DPB1	93
HLA-DRA	2	HLA-DOA	8
HLA-DRB1	273	HLA-DOB	8
HLA-DRB2	1	HLA-DMA	4
HLA-DRB3	30	HLA-DMB	6
HLA-DRB4	10	TAP1	6
HLA-DRB5	15	TAP2	4
HLA-DRB6	3	MICA	51
HLA-DRB7	2		

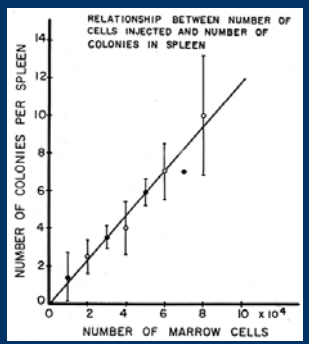


Jean Dausset

Hemopoietic Stem Cells

Stem Cells: A PMH Tradition





Reprinted from Radiation Research, Volume 14, No. 2, February 1961

RADIATION RESEARCH 14, 213-222 (1961)

A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells[1]

J. E. TILL AND E. A. McCULLOCH

Department of Medical Biophysics, University of Toronto, and the Divisions of Biological Research and Physics of the Ontario Cancer Institute, Toronto, Ontario

INTRODUCTION

Evidence is accumulating that the proliferative capacity of mammalian cells has a uniformly high radiation sensitivity regardless of the species and tissue of origin. The evidence derives from experiments on fresh explants and established cell lines in tissue culture (*1–4*), and on transplantable tumors *in vivo* (*5*) where single-cell techniques have been applied. Further, experiments using an indirect technique to measure the sensitivity of normal mouse bone marrow indicated that these cells have a radiation sensitivity of similar magnitude (*6*). In the present report a direct method of assay for these cells with a single-cell technique will be described.

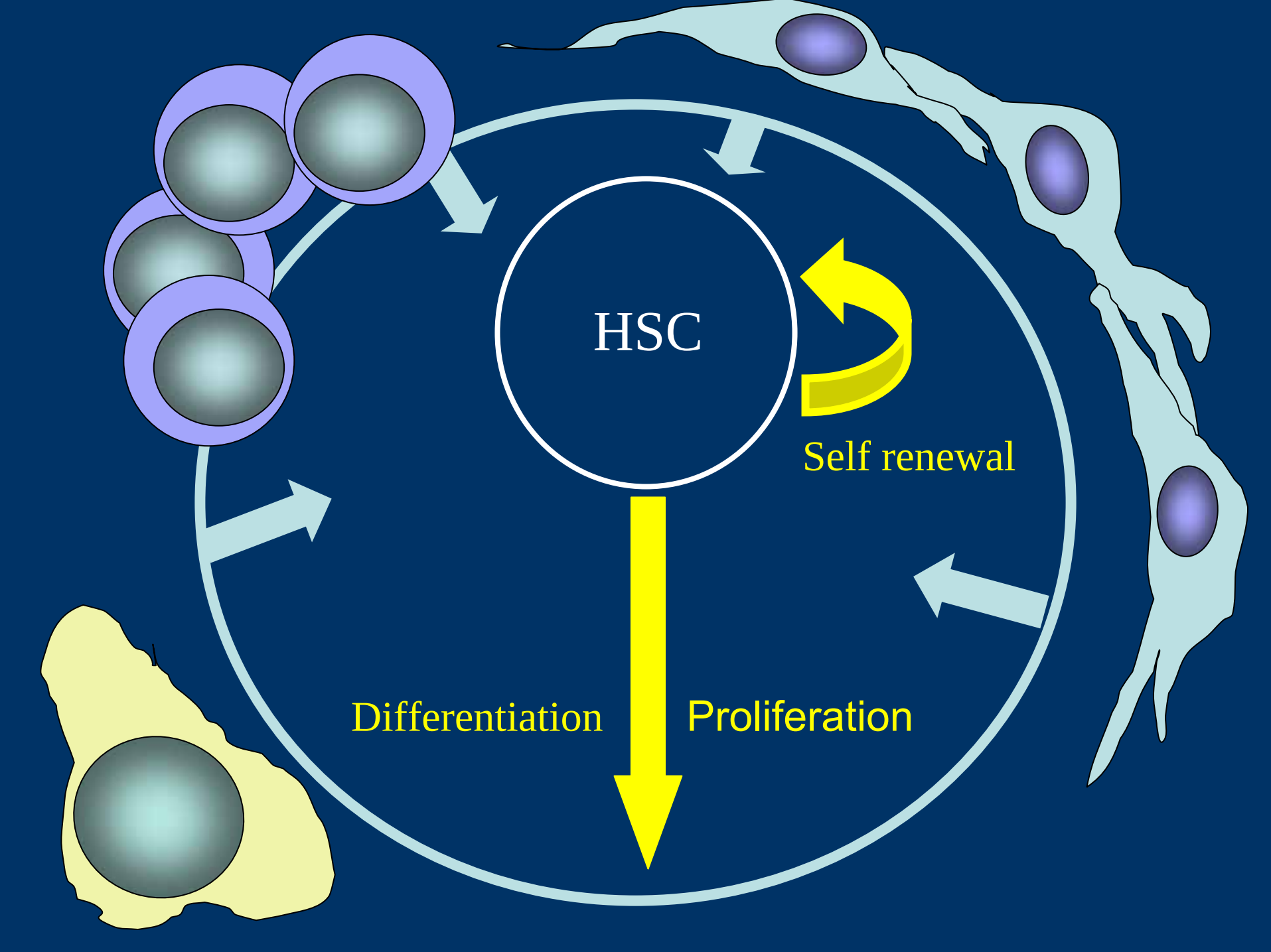
The method is based on the fact that the intravenous injection of an appropriate number of marrow cells into isologous hosts previously exposed to supralethal total-body irradiation leads to the formation of colonies of proliferating cells in the spleens of these animals. These colonies appear as gross nodules in the spleen, which may readily be counted. The relationship between the number of cells injected and the number of colonies appearing in the spleen has been determined and used to study the sensitivity to radiation of the proliferative capacity *in vivo* of normal adult mouse bone marrow cells irradiated *in vitro*. The results show that normal mouse bone marrow cells have a similar radiation sensitivity to other mammalian cells tested by very different methods.

EXPERIMENTAL PROCEDURES

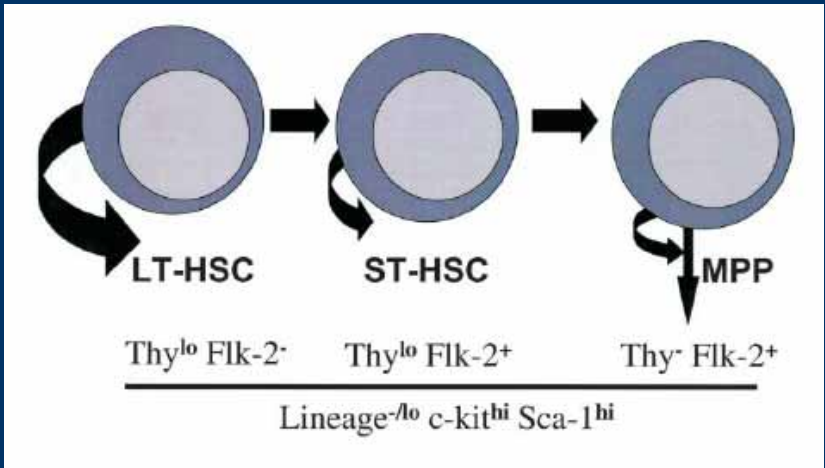
Mice

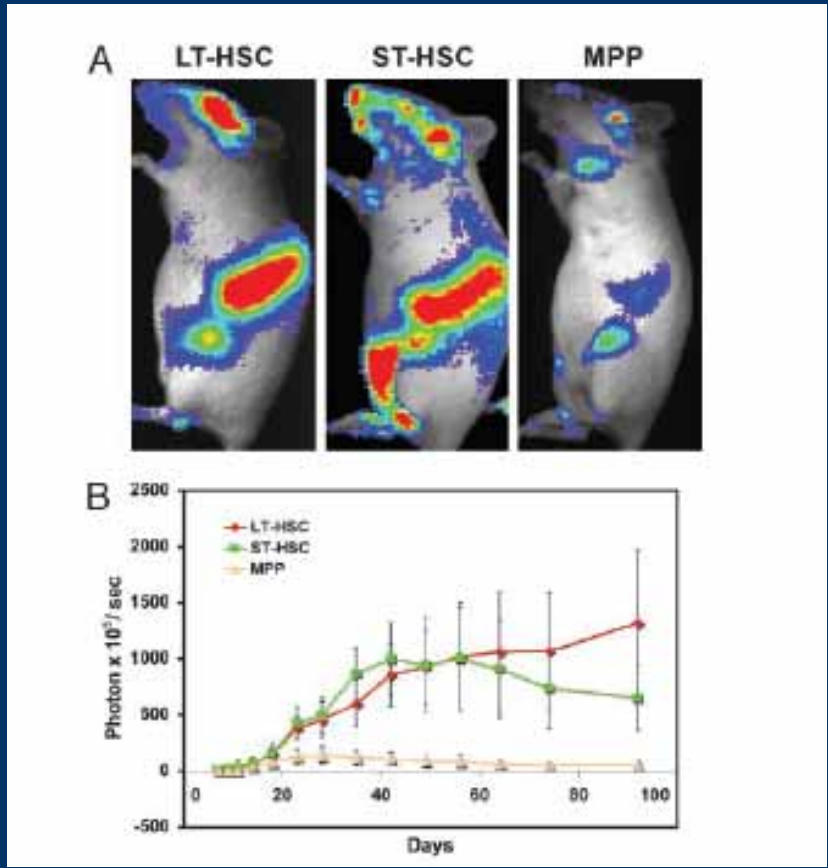
Eight- to twelve-week-old C57Bl/Ha and C3Hf/Ha mice bred in this laboratory were used in the experiments. Each experimental group consisted of 25 mice, with approximately equal numbers of males and females. After irradiation and injection

[1] The research for this paper was supported (in part) by the Defence Research Board of Canada, under Grant DRB 9350-14 (G and C) and (in part) by the National Cancer Institute of Canada.


HSC
Self renewal
Differentiation
Proliferation

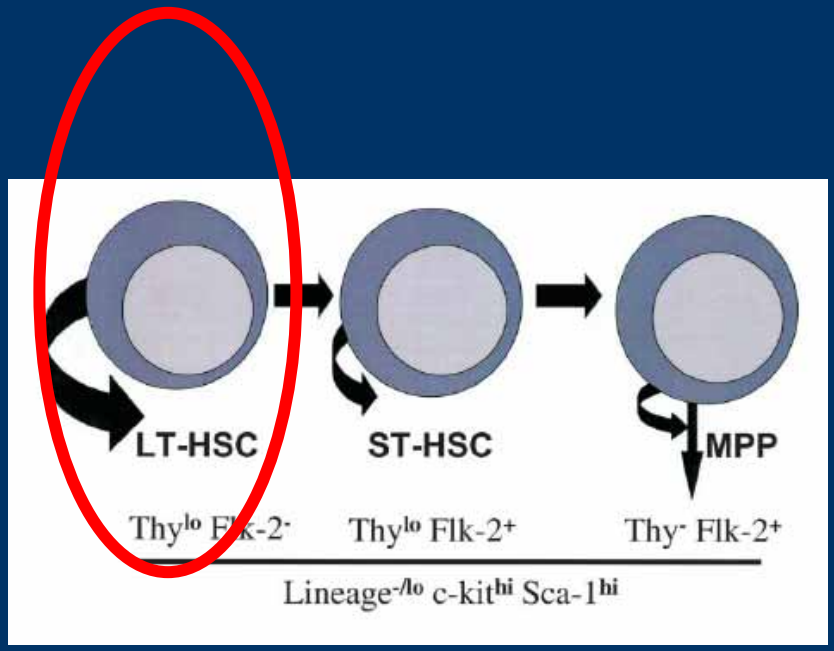
Stem Cell Subpopulations

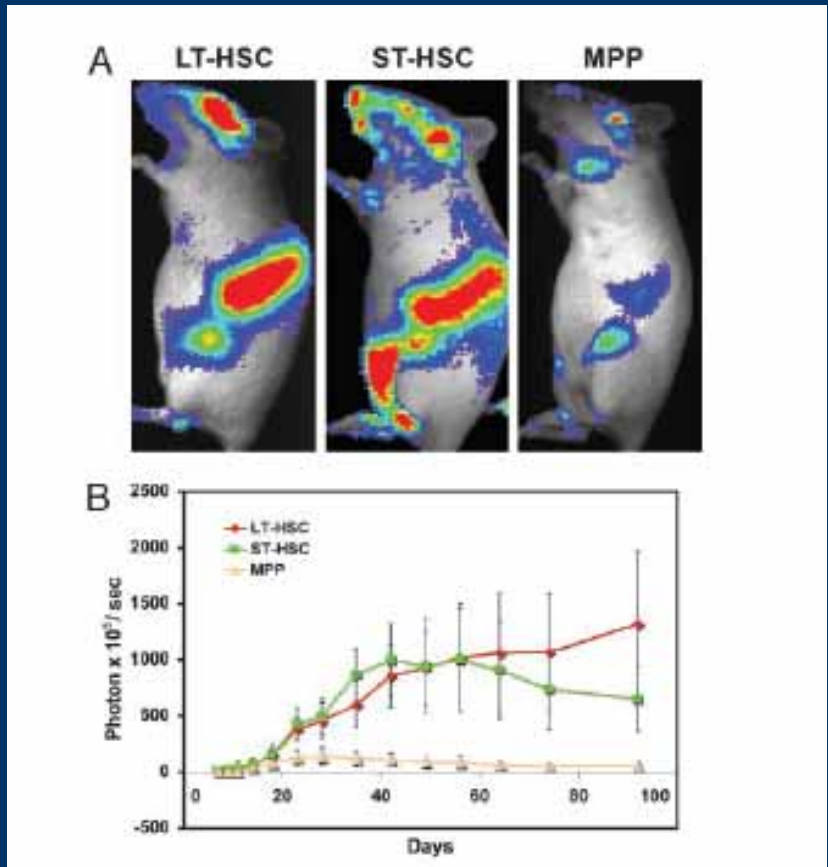




Weissman et al

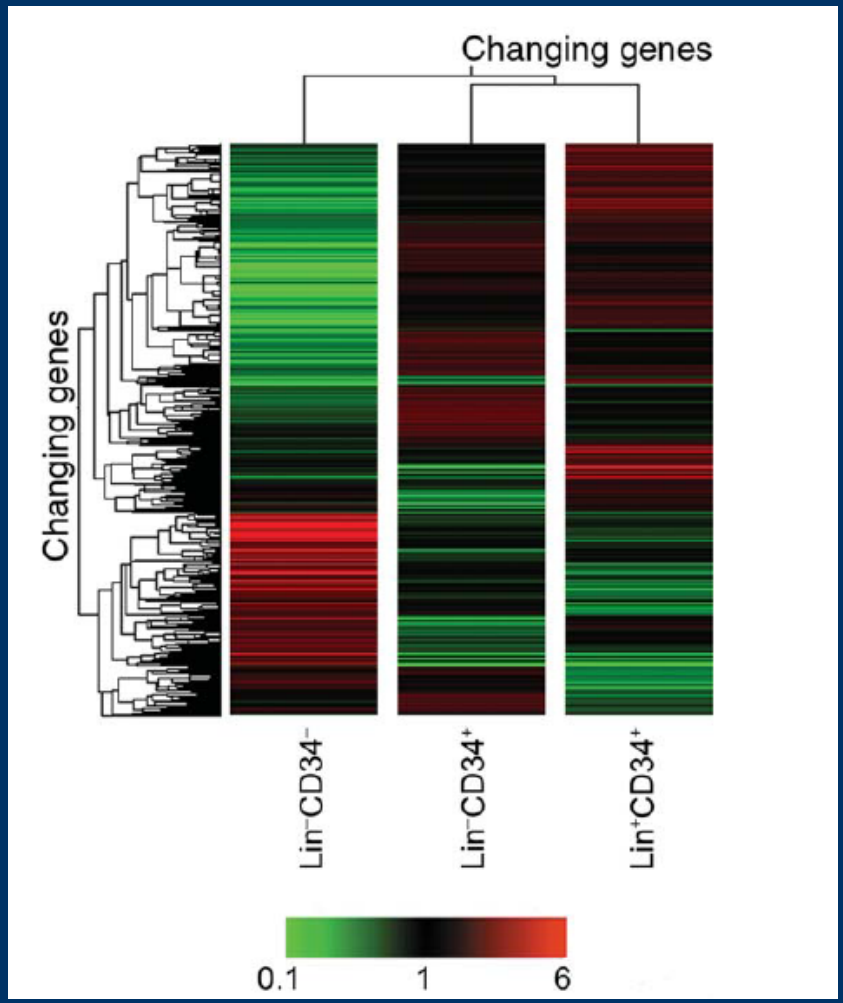
Stem Cell Subpopulations



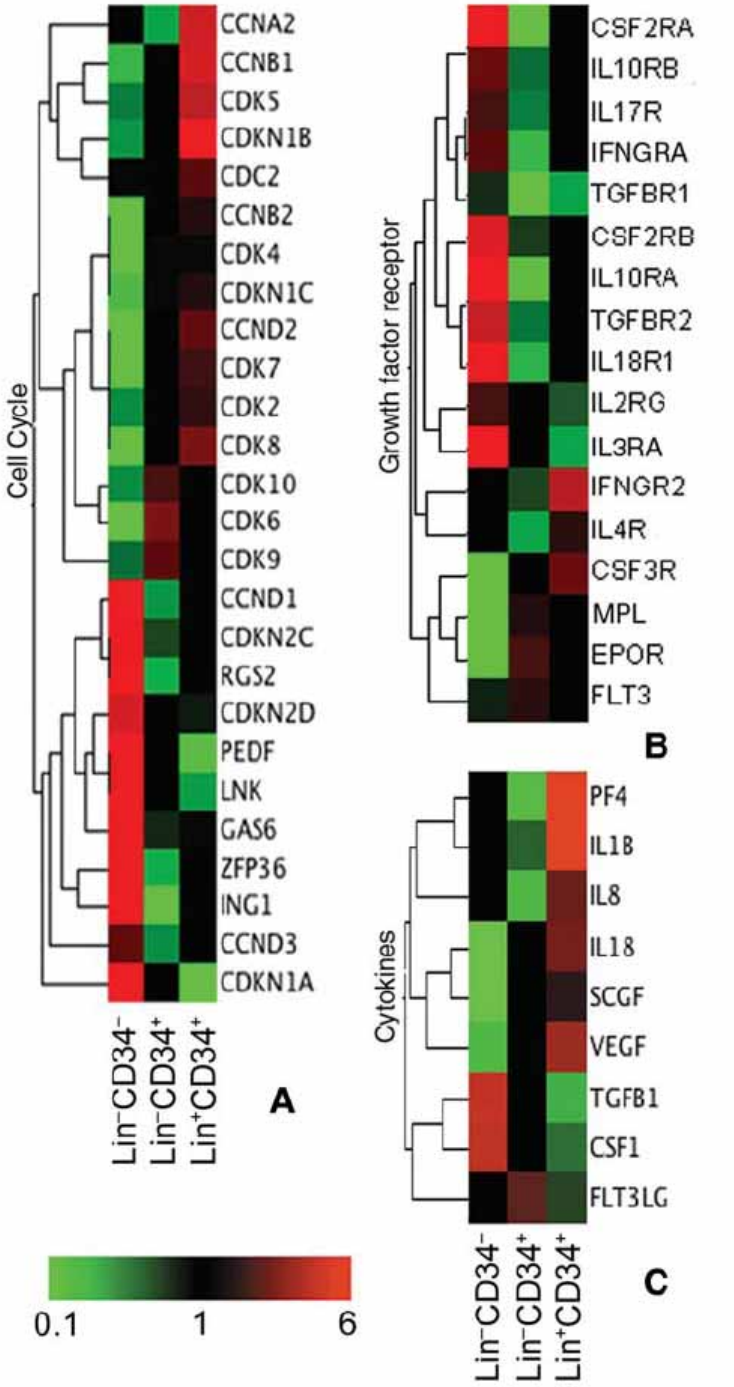


Weissman et al

Gene expression patterns in hemopoietic progenitor cells



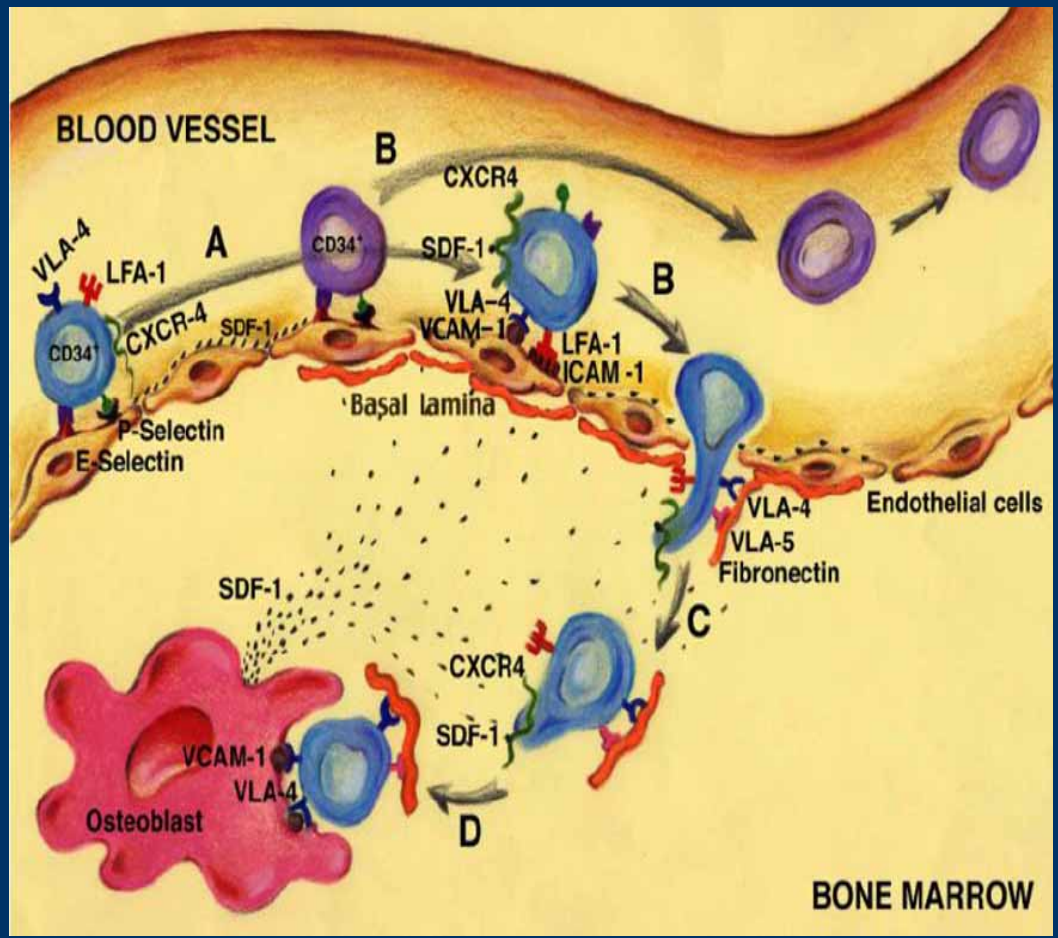
Manfredini R et al Stem Cells 2005; 23: 496 – 506



Gene expression profiles in different hemopoietic progenitor subpopulations

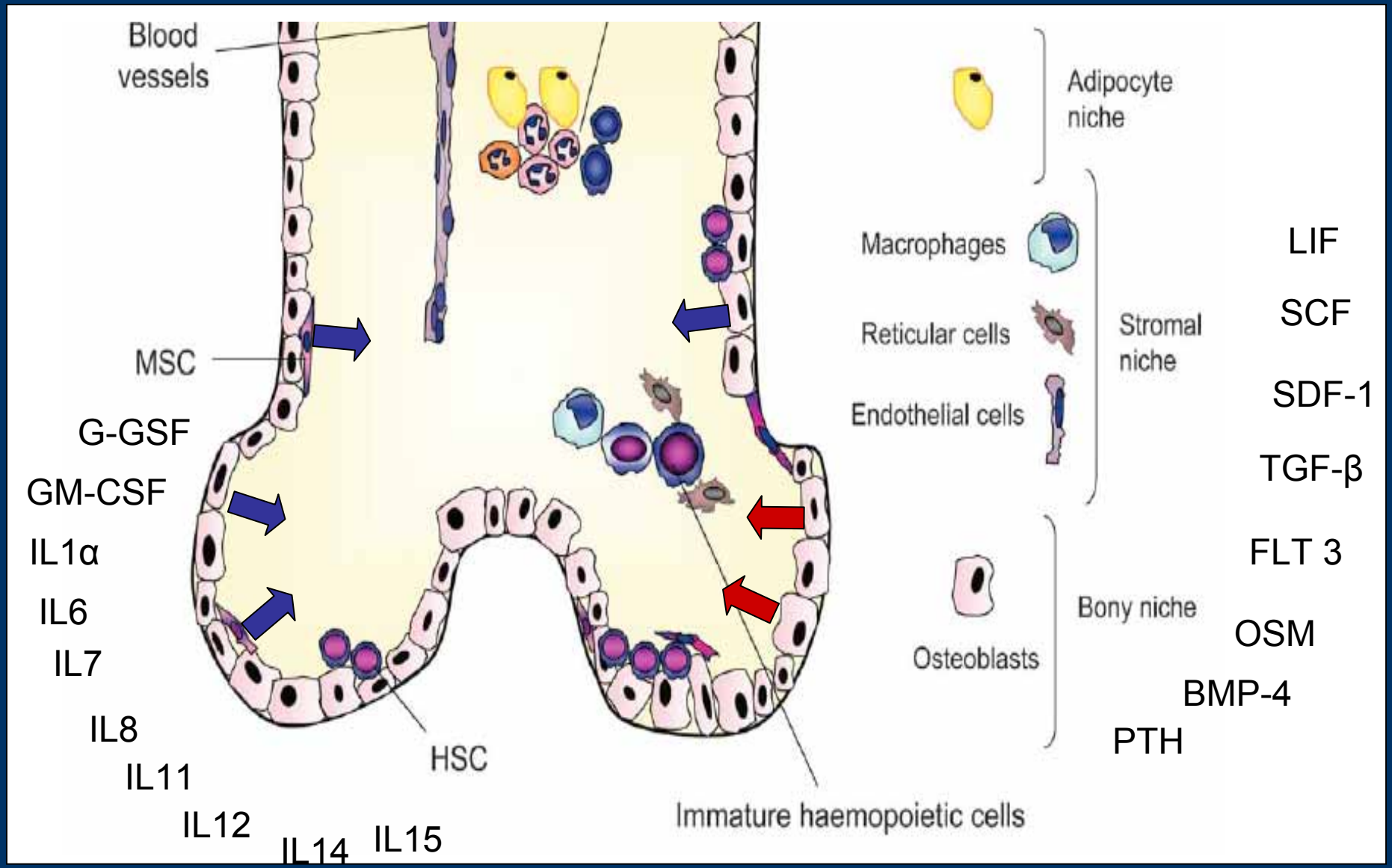
Manfredini R et al
Stem Cells 2005; 23: 496 – 506

Stem cell migration and homing via SDF-1 and CXCR4 interaction



Lapidot T et al 2004

The hemopoietic niche

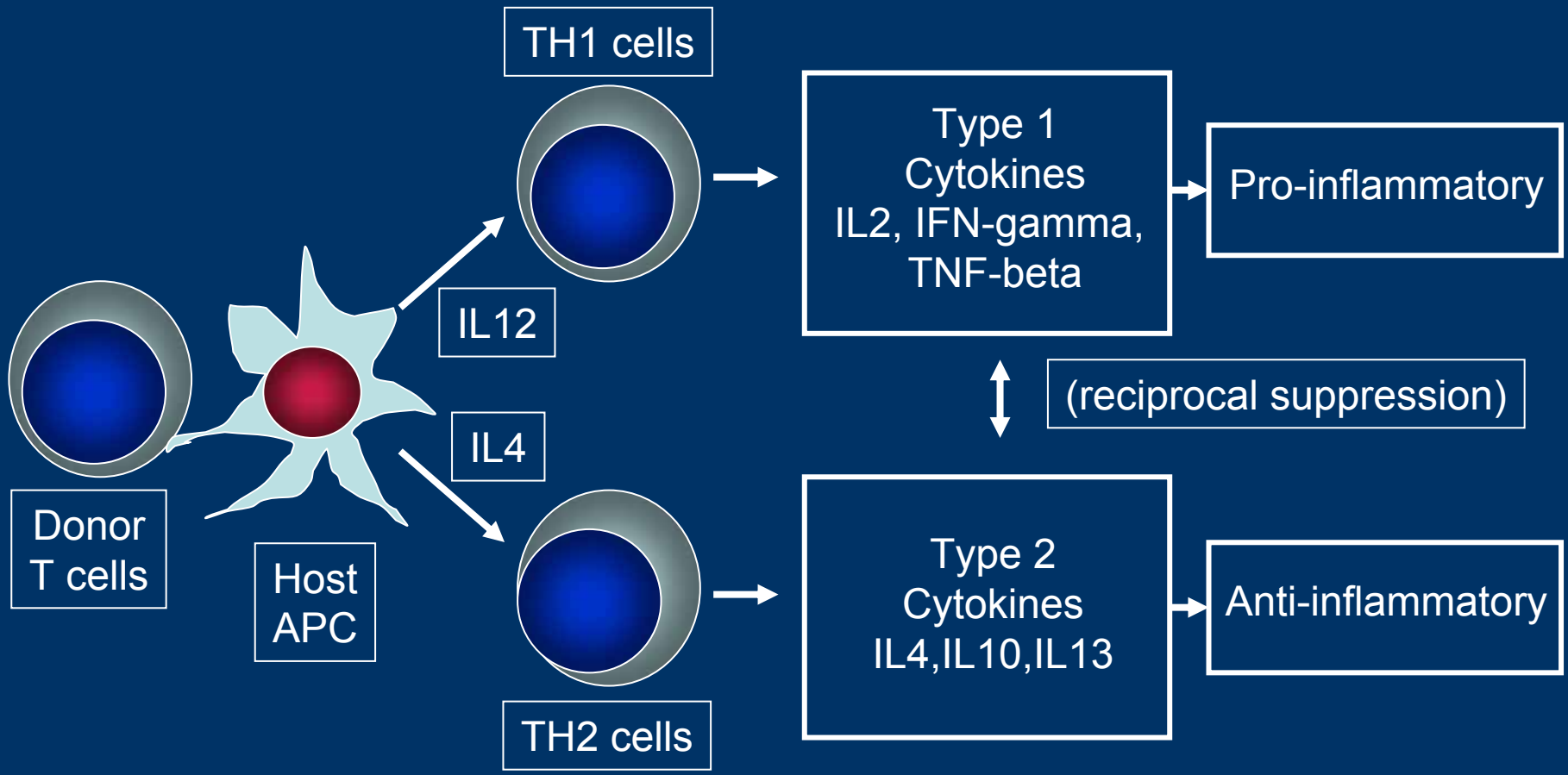


Modified: Dazzi F et al Blood Reviews 2006; 20: 161-171

Transplant Immunology

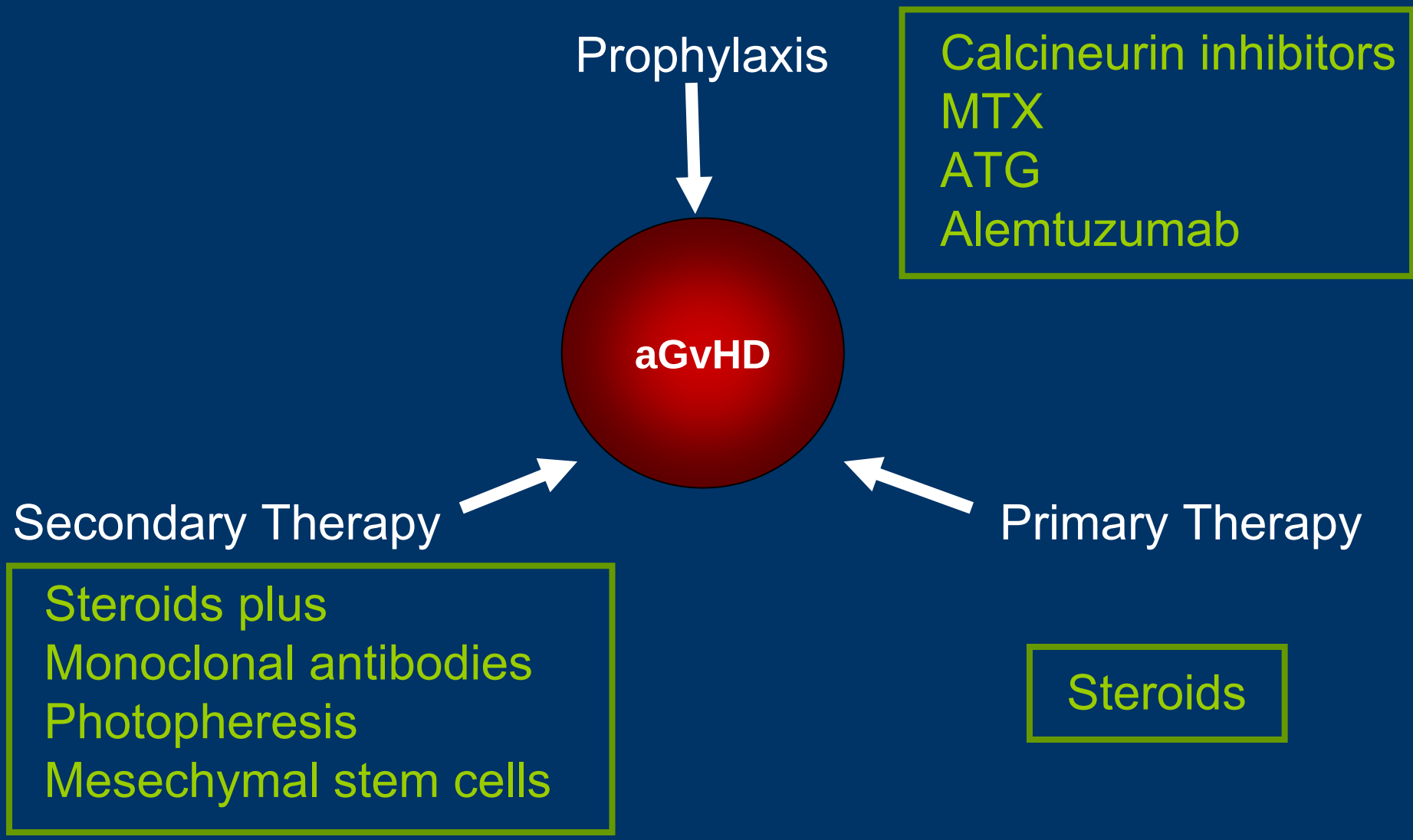
Alloimmune responses by T cells

- Induction phase — Priming
- Expansion phase — Proliferation
- Effector phase — Interaction with cognate AG on host target cells (Perforin, Granzyme, CK)



A7

One of the central problems after allotransplant



A7 Hans Messner, 21/10/2007

Supportive Care

CANADIAN BLOOD SERVICES
SOCIÉTÉ CANADIENNE DU SANG

Transfusion Requirements

Type of Transfusion	Time Interval	Mean (SD)	Maximum
RBC	0 to 60 d	7.26 (6.89)	40
	61 to 120 d	2.82 (5.38)	48
	121 to 180 d	1.55 (3.74)	30
	Total	**11.63 (12.02)**	**68**
Platelets	0 to 60 d	9.93 (10.18)	55
	61 to 120 d	2.57 (6.20)	51
	121 to 180 d	1.28 (4.09)	35
	Total	**13.78 (15.15)**	**81**

What are the Expected Clinical Outcomes after BMT

?

Types of Transplants

- Syngeneic
- Allogeneic
- Autologous

Sources of Stem Cells

- Marrow
- Peripheral blood
- Cord blood

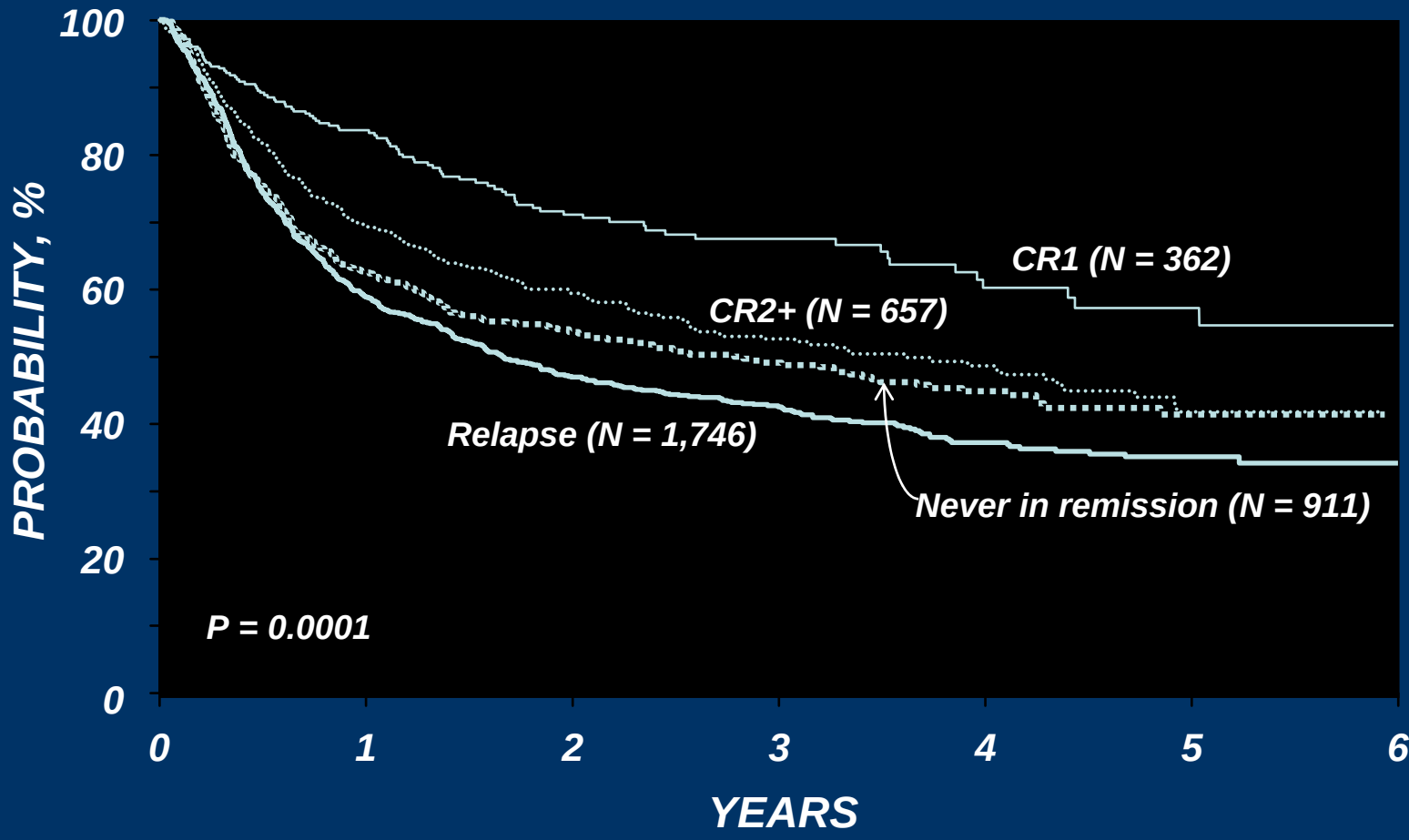
Autologous Blood and Marrow Transplants

- Strategy to use high dose therapy to ablate malignant or autoimmune cell clones
- The problem of residual tumor cells harbored in vivo or in the graft requires attention

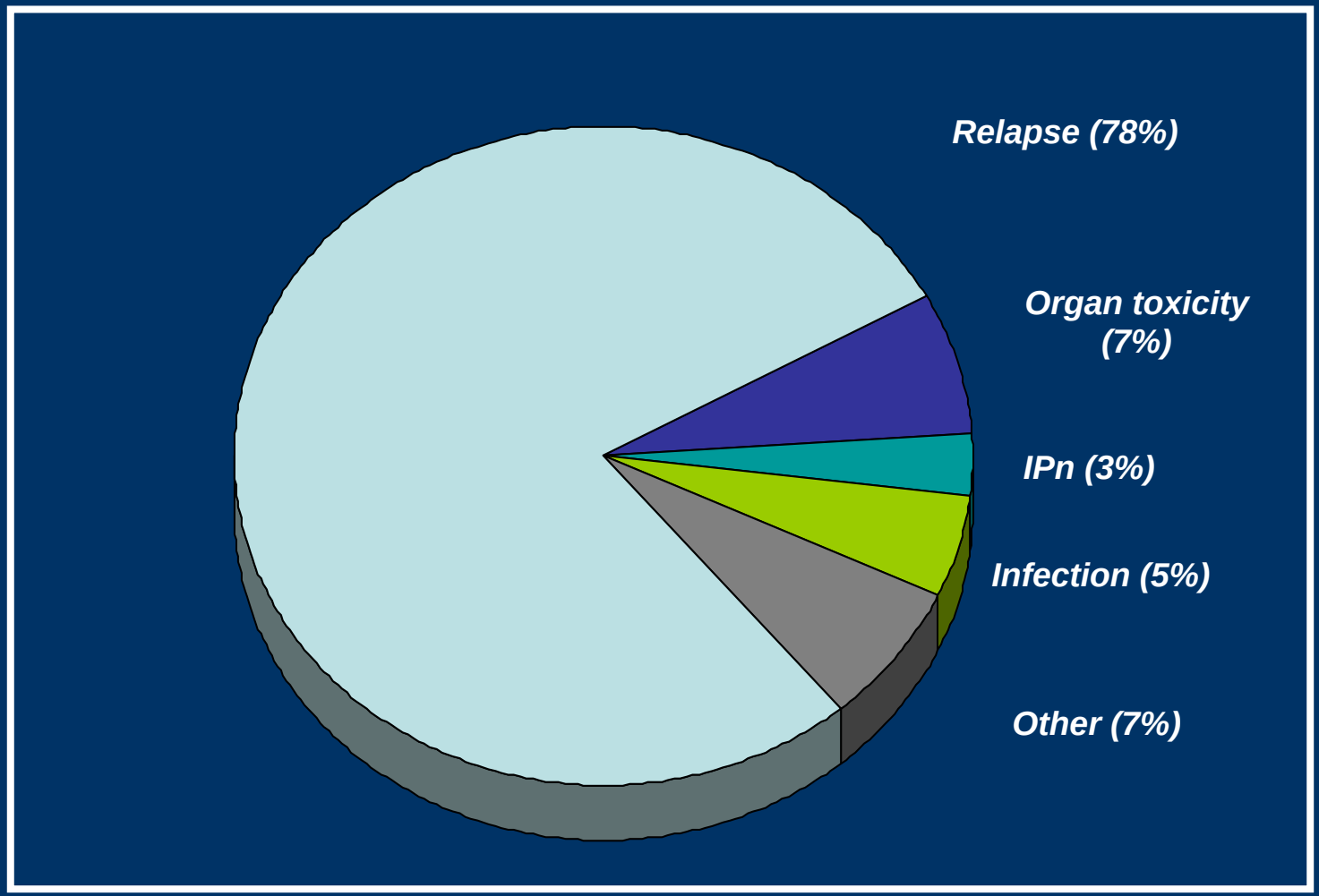
Indications for Autologous Transplants

- Hemopoietic malignancies
- Certain solid tumors
- Autoimmune disorders
- Future potential for tissue repair (e.g. myocardium, liver etc)

PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANTS FOR DIFFUSE LARGE CELL LYMPHOMA



Causes of Death in Auto-BMT



Lessons learned for Autologous Transplants

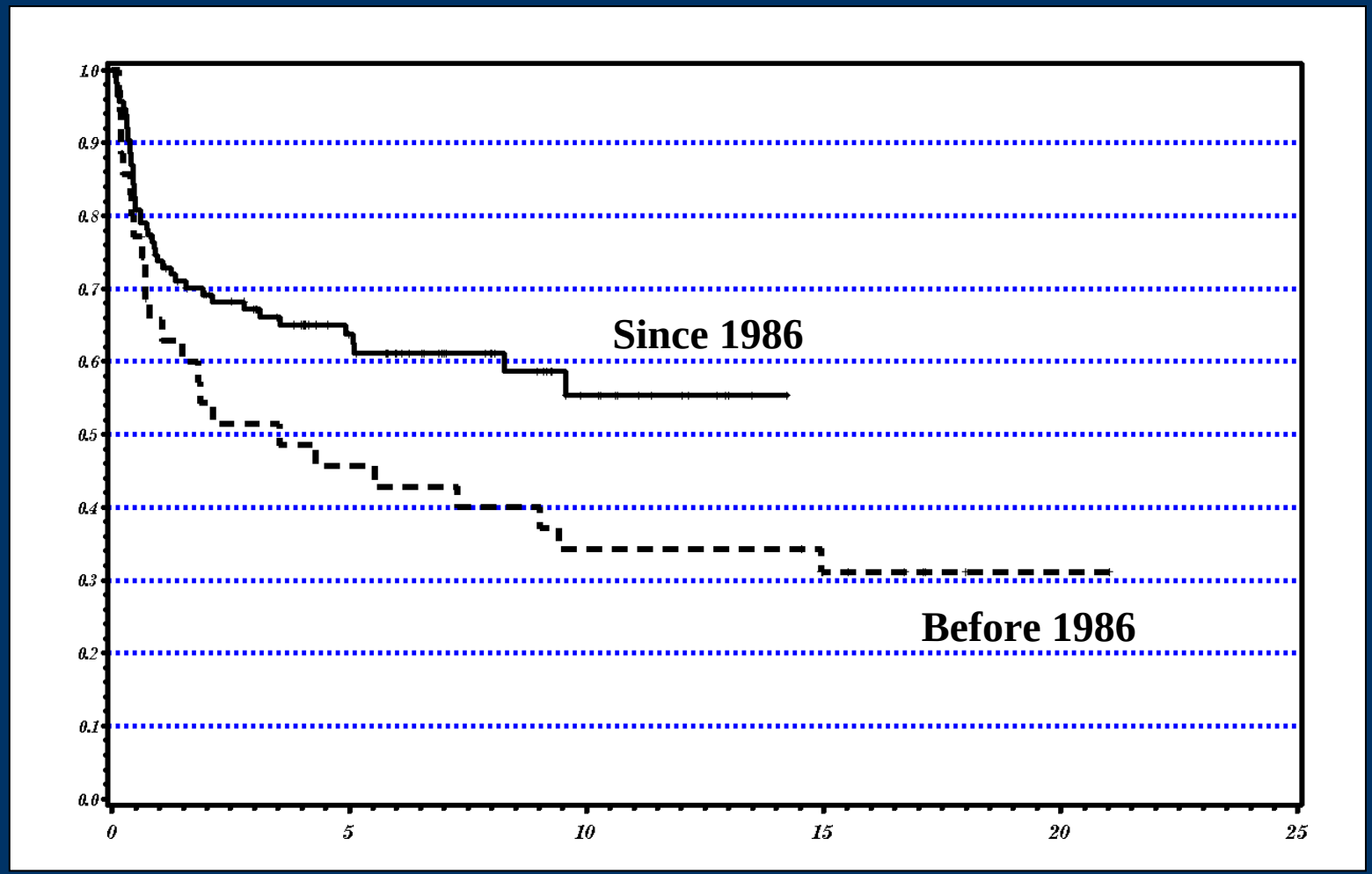
- Low transplant related morbidity and mortality
- High relapse rate
- Relapse may occur through residual disease in the patient or through re-infusion of disease propagating cells present in the graft
- Disease control through administration of dose intensive therapy

Allogeneic Transplants

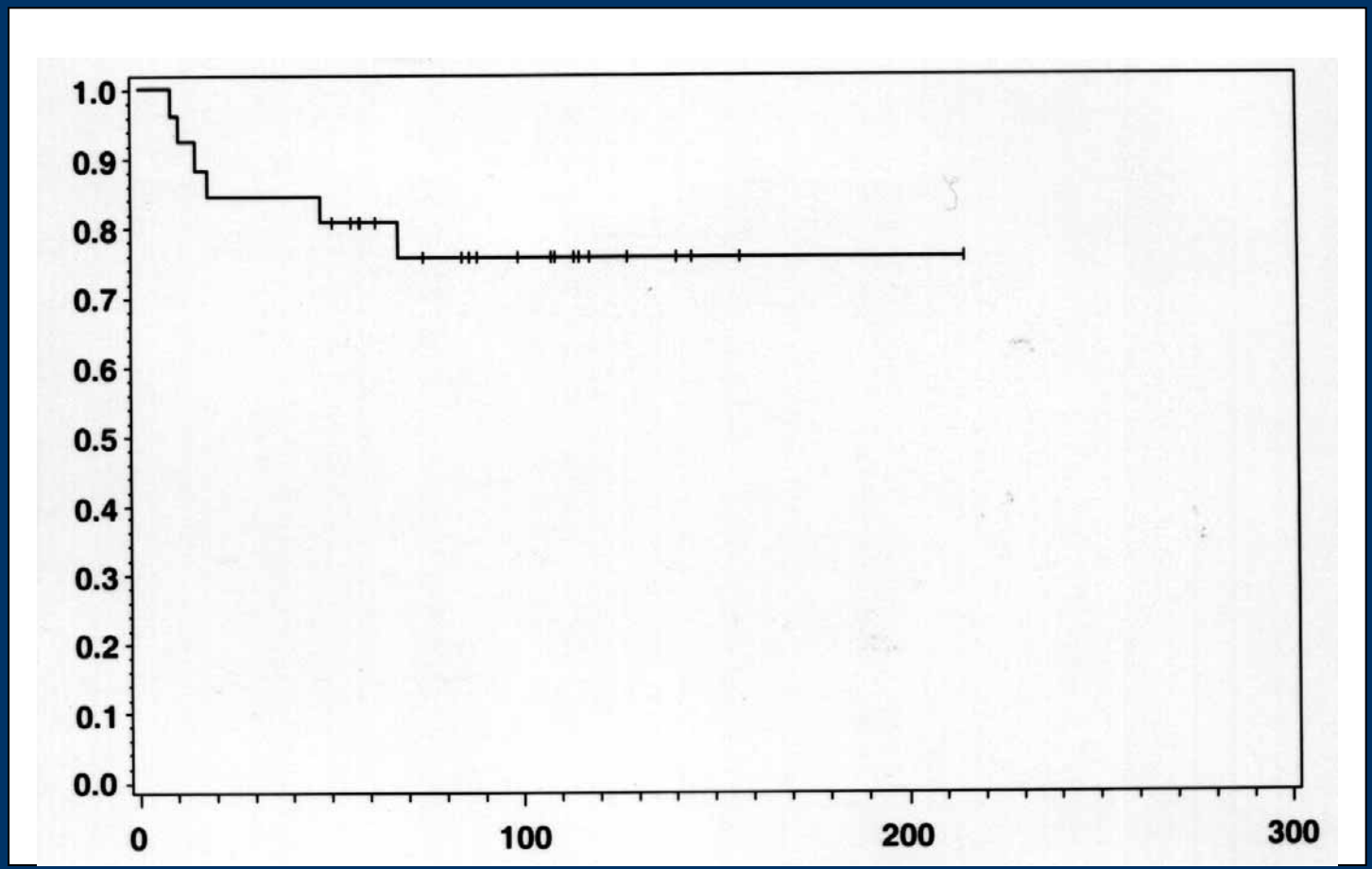
Impact of HLA-typing on Outcome

- Best results are achieved using fully matched donors
- Donors with one antigen mismatched are acceptable but will result in higher mortality
- Transplant from donors with a lesser degree of match are feasible with extensive T cell depletion or other strategies to decrease the immune reactivity of donor derived cells

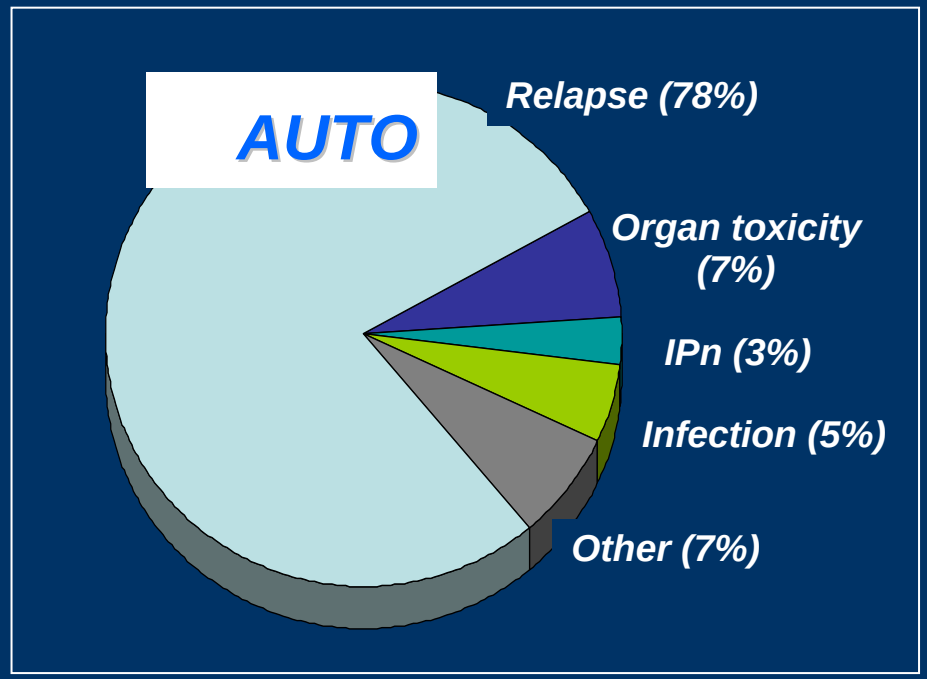
Survival of AML Patients

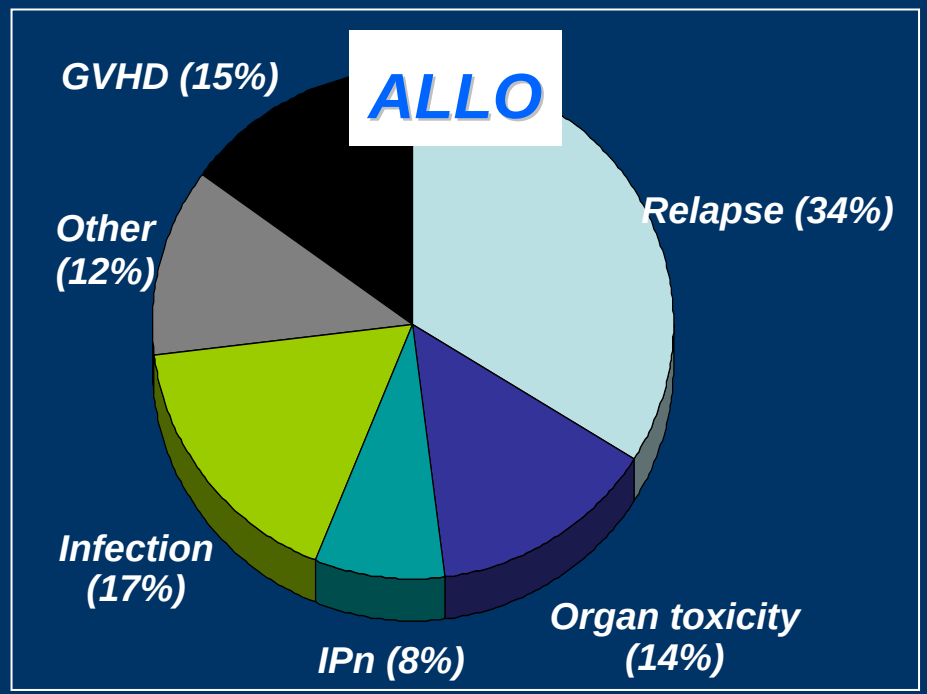


Survival of Patients Transplanted in CR 1



CAUSES OF DEATH AFTER TRANSPLANTS



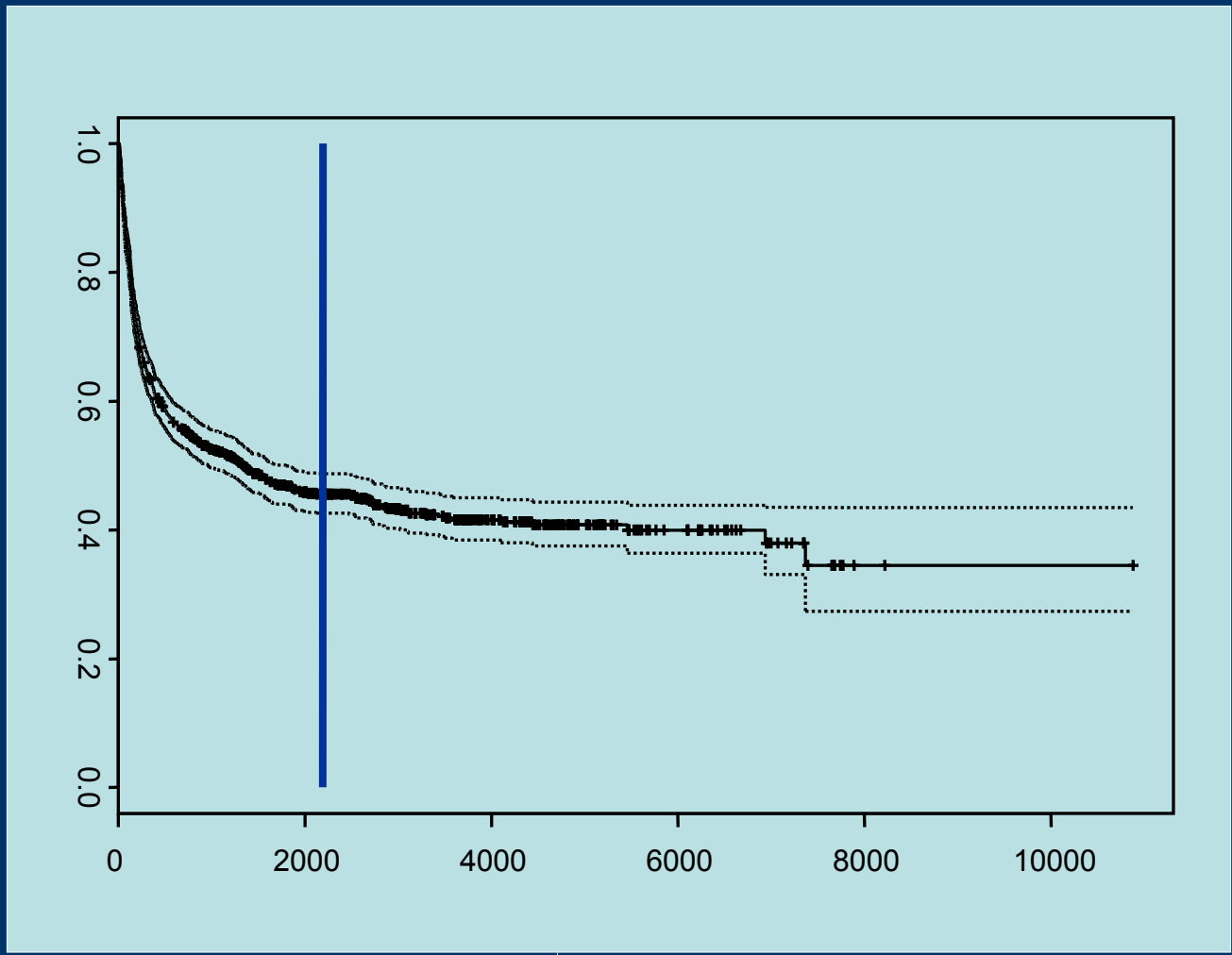


Evidence for Graft vs Malignancy Effects (GvM)

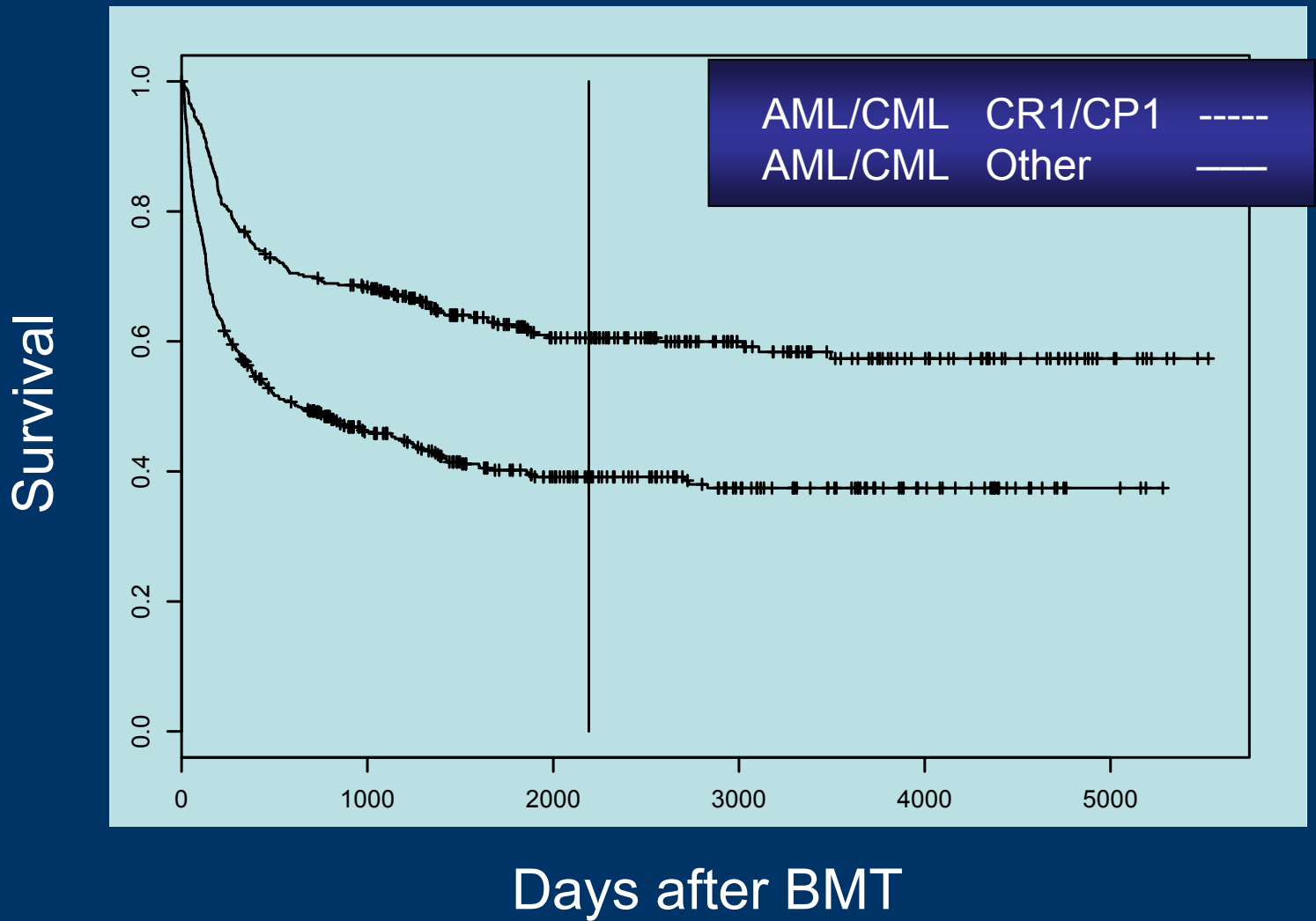
- High relapse rate in syngeneic transplants.
- Increased relapse rate in T cell depleted transplants in some diseases
- Lower relapse rate in patients with GvHD compared to patients without
- Leukocyte Infusions (DLI) in recipients relapsing after a transplant may result in remissions and long-term disease control

Allogeneic transplants: A platform for Cell therapy

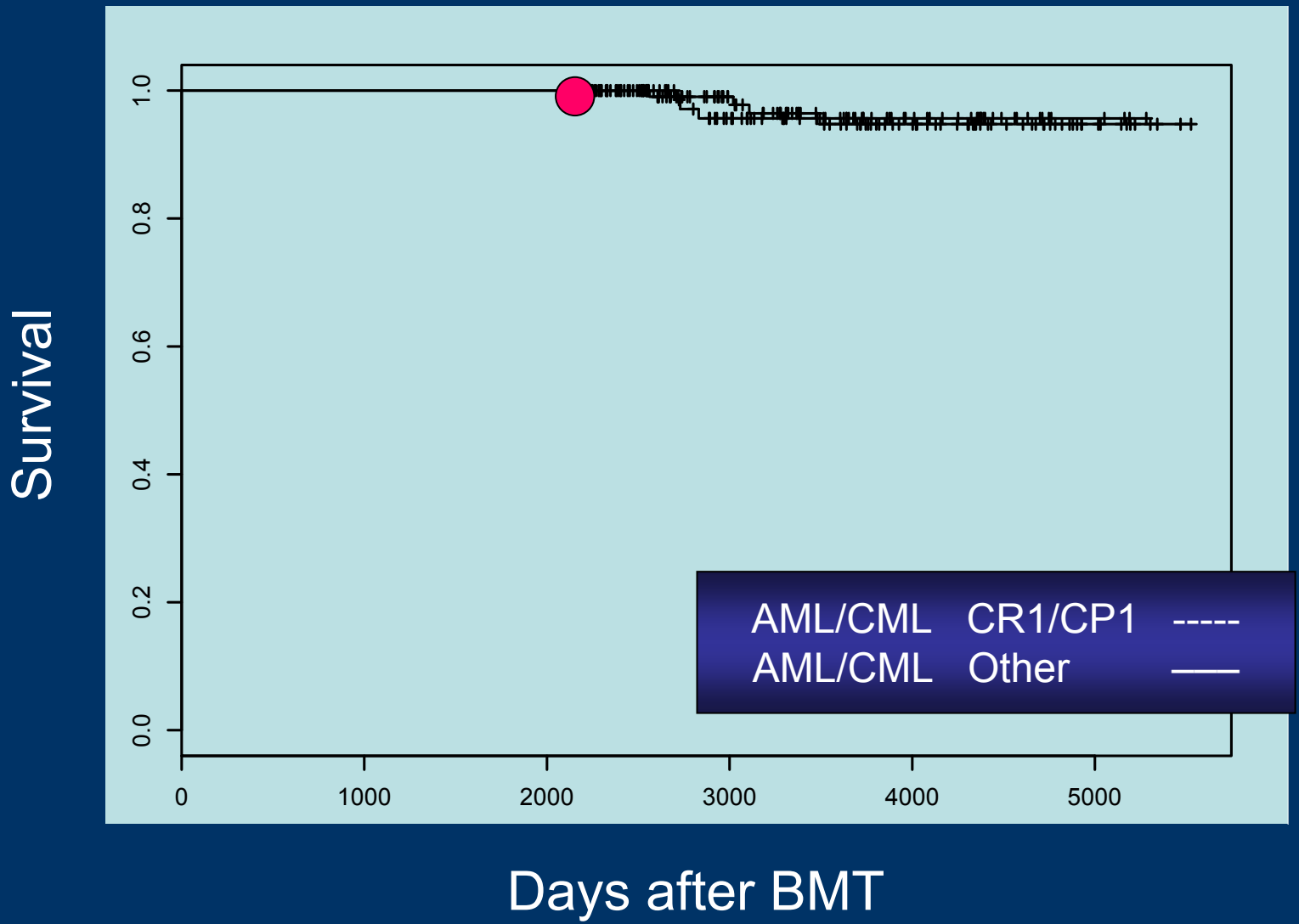
Overall Long-term Survival of all Patients Receiving an Allogeneic BMT at PMH



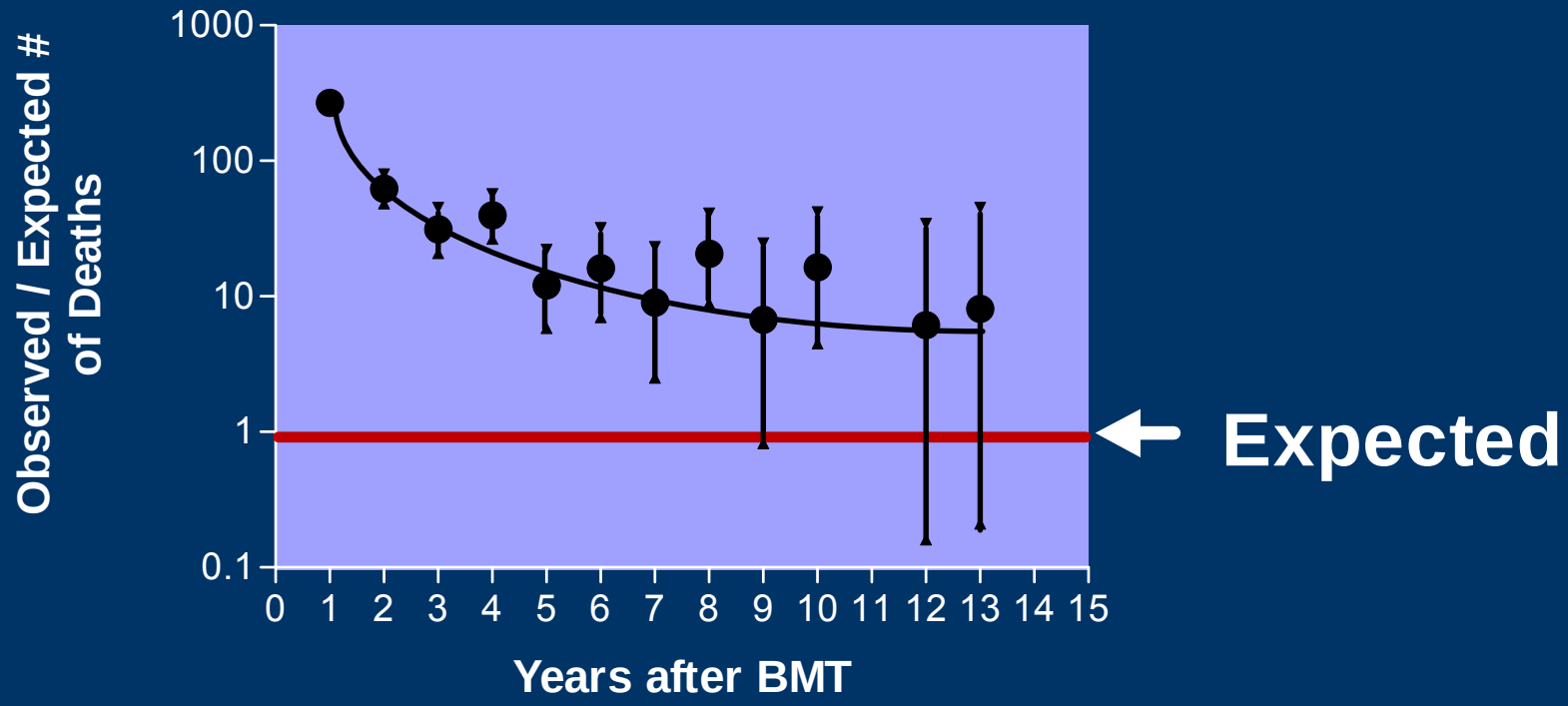
Outcome by Disease Status at BMT in Recipients Transplanted since 1986



Long-term Survival of Patients alive 6 Years by Disease Status at BMT



Observed over Expected Survival after BMT Compared to Survival Expected for the Normativer Population

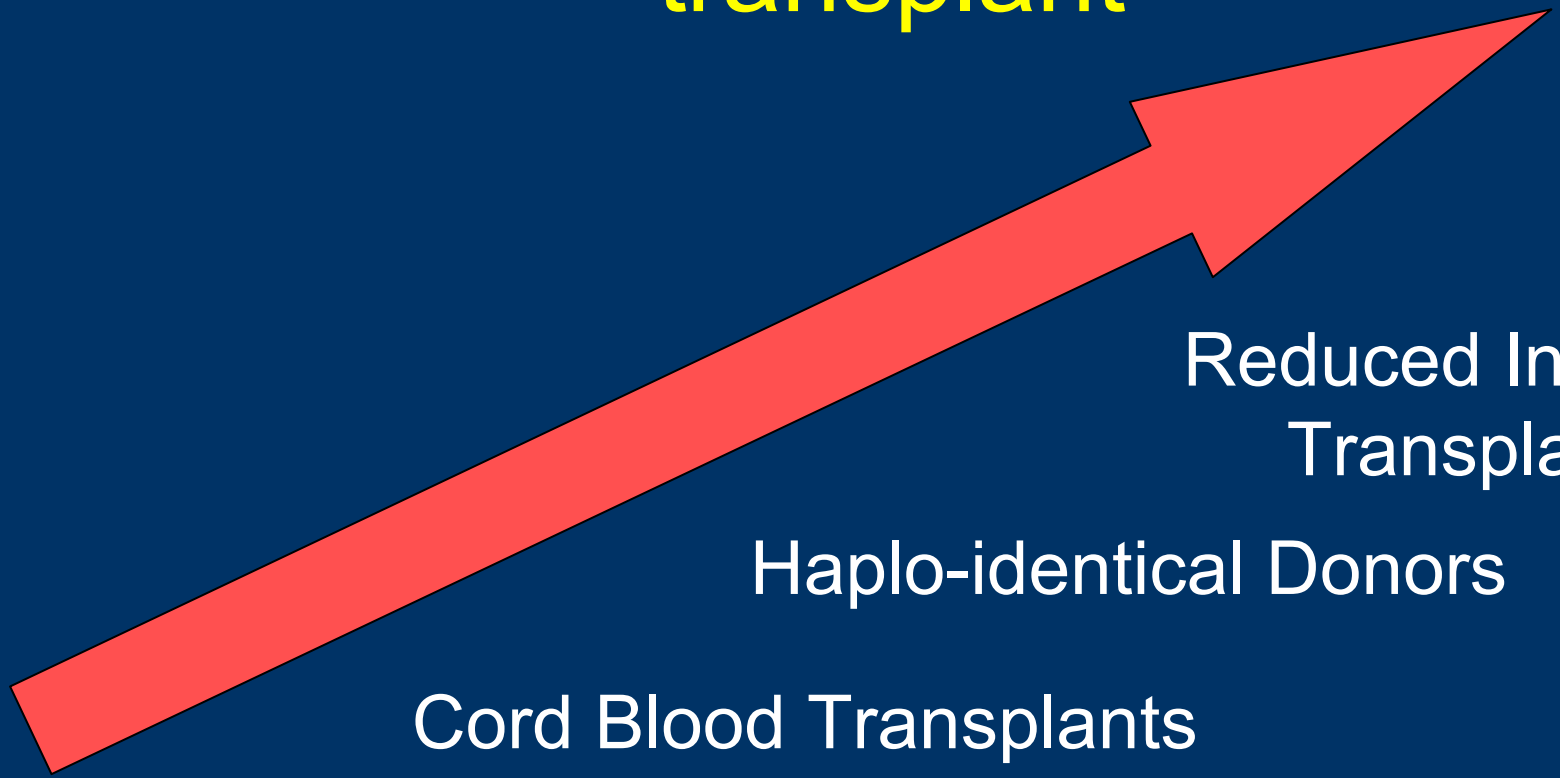


The Probability of Survival Remains lower than that of the Normative Population even more than a Decade after BMT……..

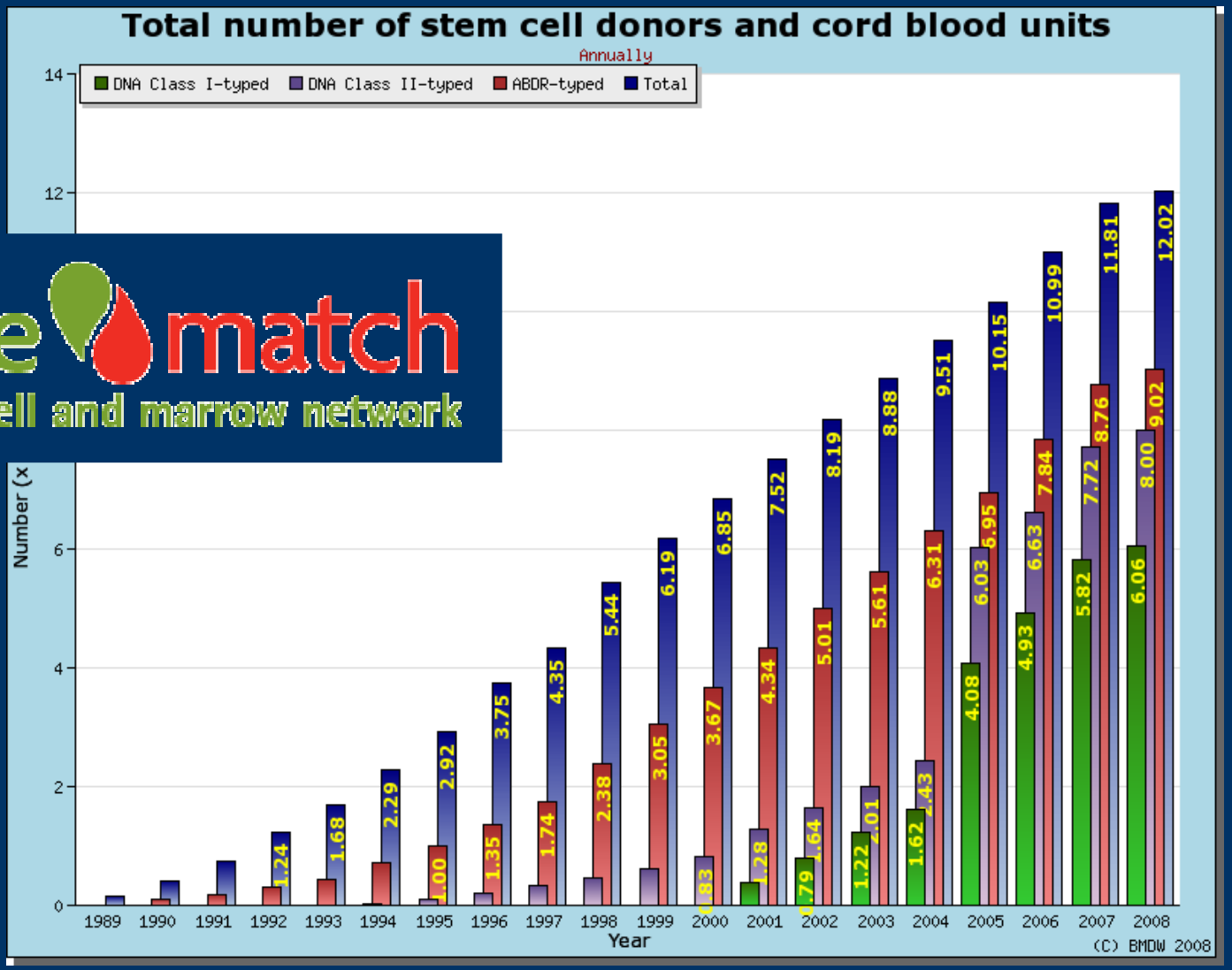
Yet

Transplants may provide the best chance for
long-term survival in patients
with some diseases

Strategies to provide treatment for more patients in need of a transplant

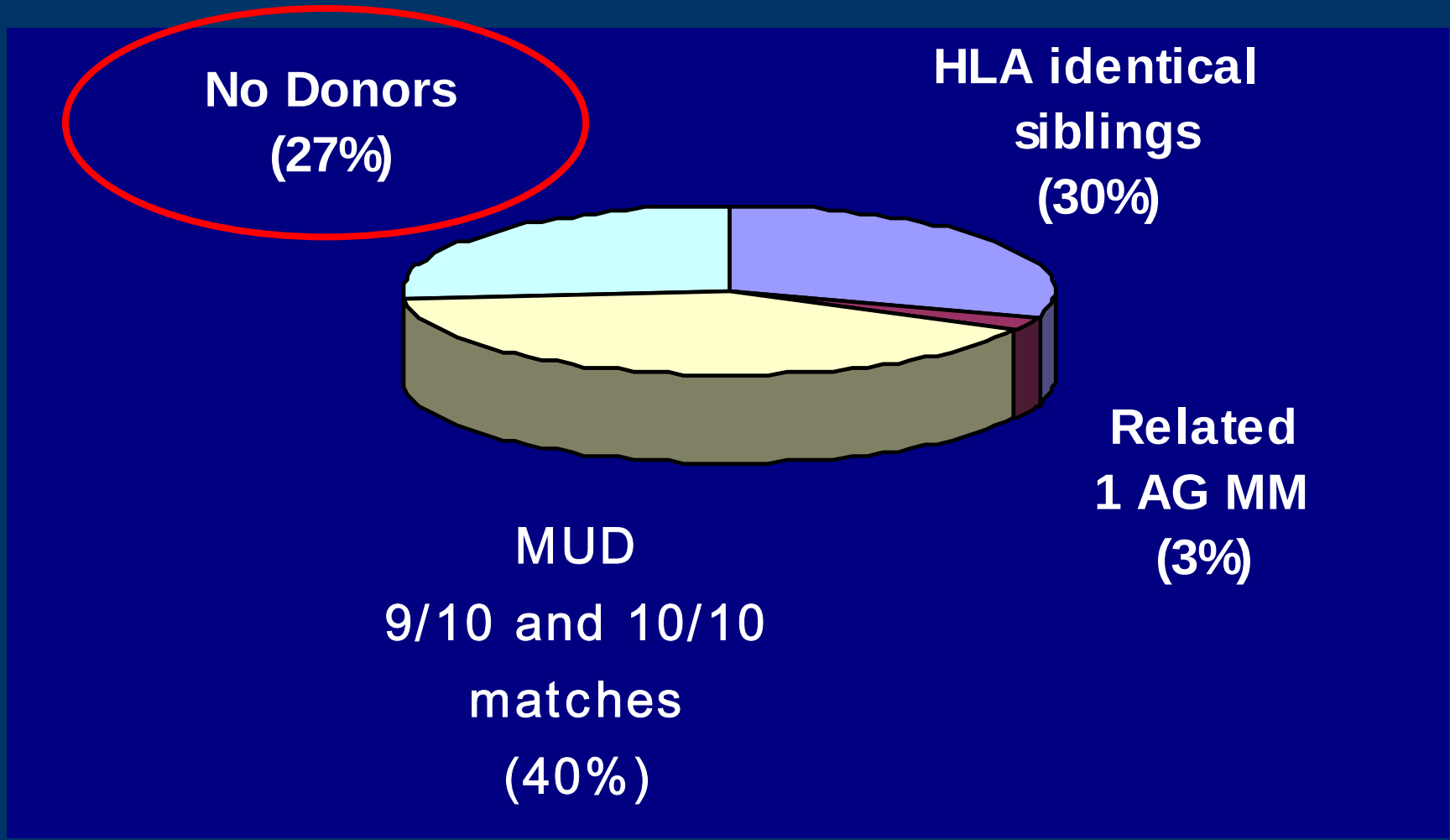


Unrelated donor registries



one match
stem cell and marrow network

Donor availability for allogeneic transplants



(O’Brien TA et al MJA 2006; 184: 407 – 410)

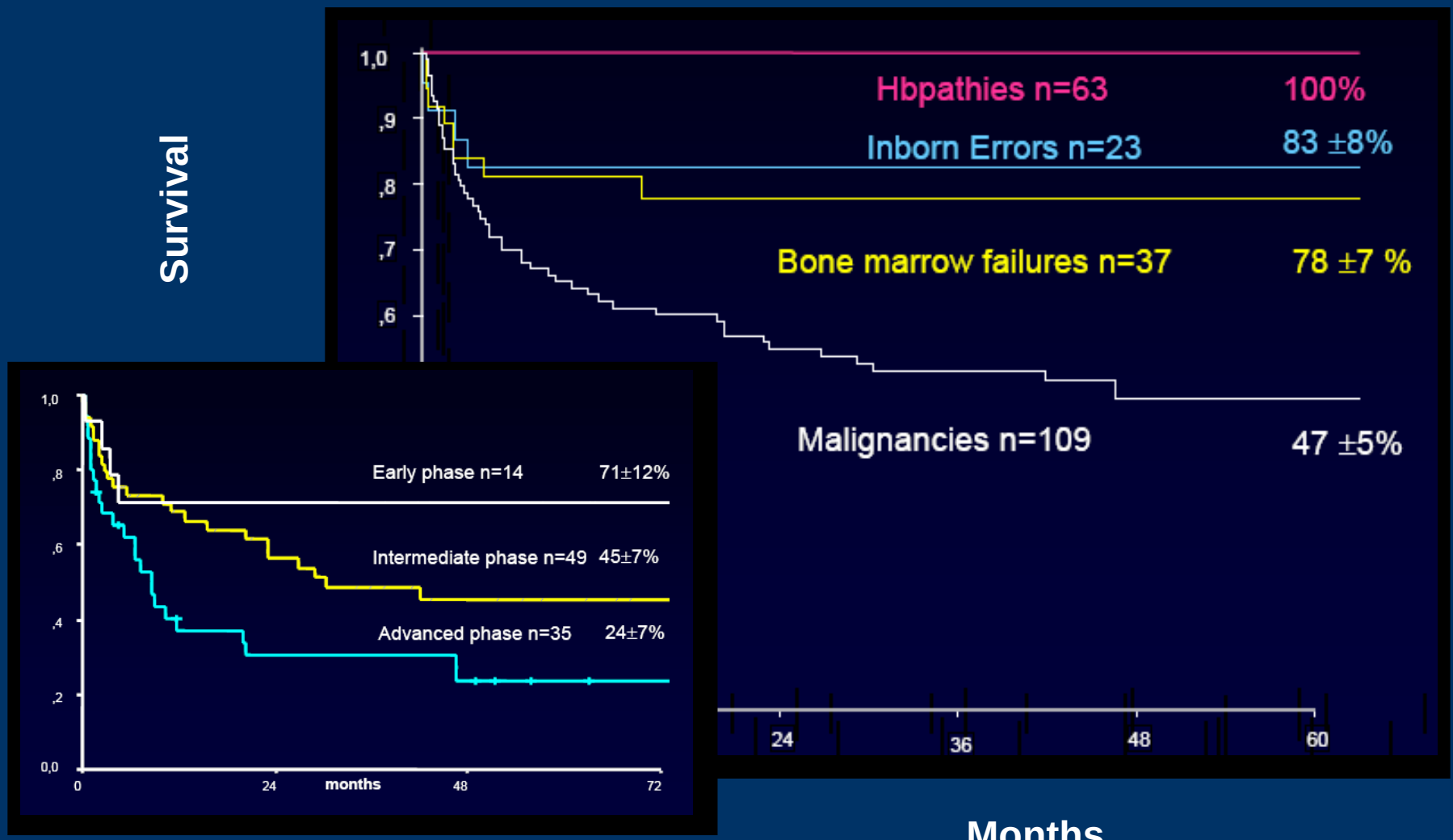
Cord Blood Transplants

Principles:

- Utilization of a waste product
- High proportion of primitive progenitors
- Product readily available

Outcome of CBT from related donors by diagnosis

(Rocha V et al EUROCORD)



Lessons learned

- Cord blood cells are a viable alternative source of hemopoietic progenitor cells
- In the pediatric age group CBT may be preferable because of decreased acute and chronic GvHD and the requirement for a lesser degree of HLA matching
- Cell dose remains a limiting problem particularly for adults

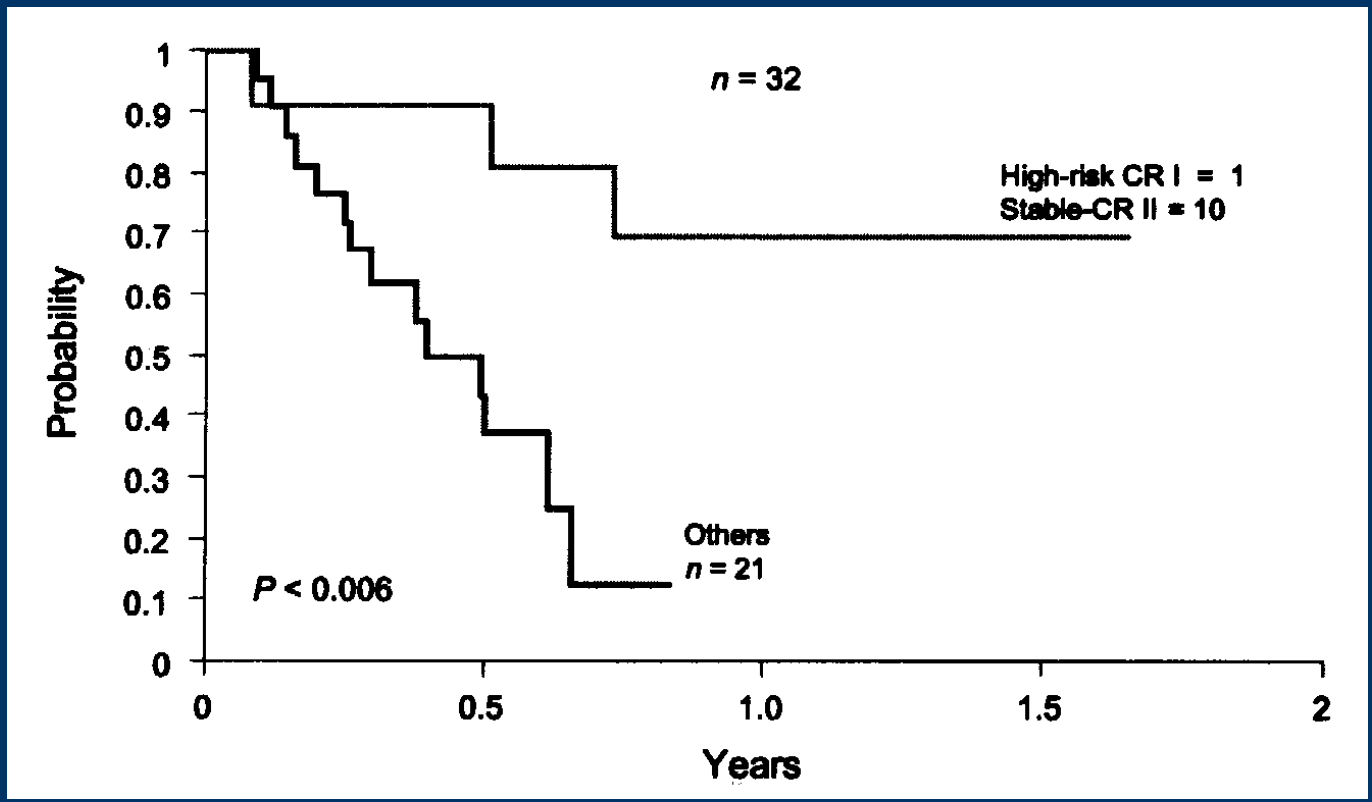
Transplants from Haplo-identical Donors

Principles:

- Intensive preparation
- High stem cell numbers
- Extensive T cell depletion
- Preparation with regimens that maintain regulatory T cell populations
- Availability of donors for nearly everyone

Event-free Survival by Disease Status

Aversa et al RevClinHematol

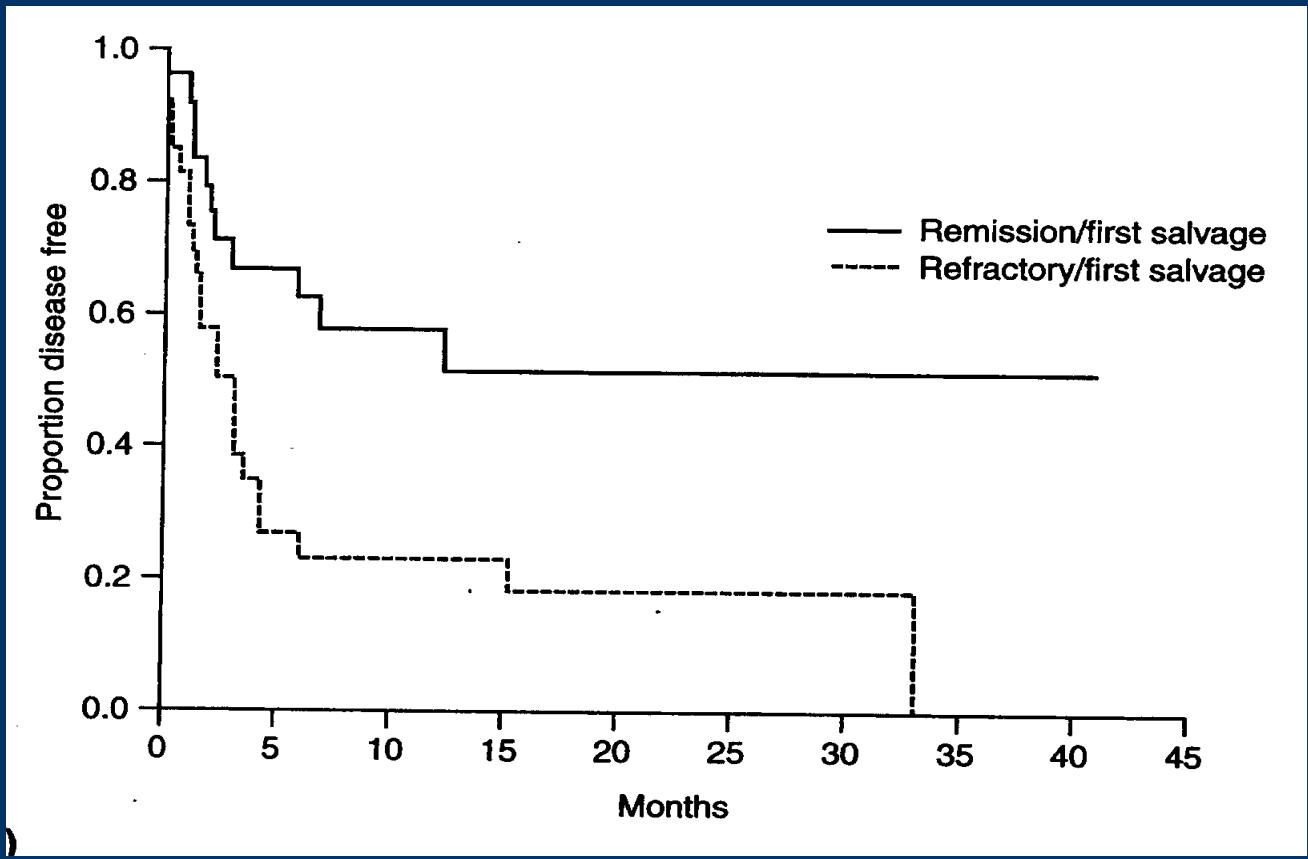


Non-myeloablative Transplants

- Decrease of early transplant related toxicity
- Broadened eligibility to include patients with otherwise non-permissive co-morbidities
- Inclusion of patients with chronic non life threatening diseases
- Reliance on a GvM effect for disease control in patients with malignancies

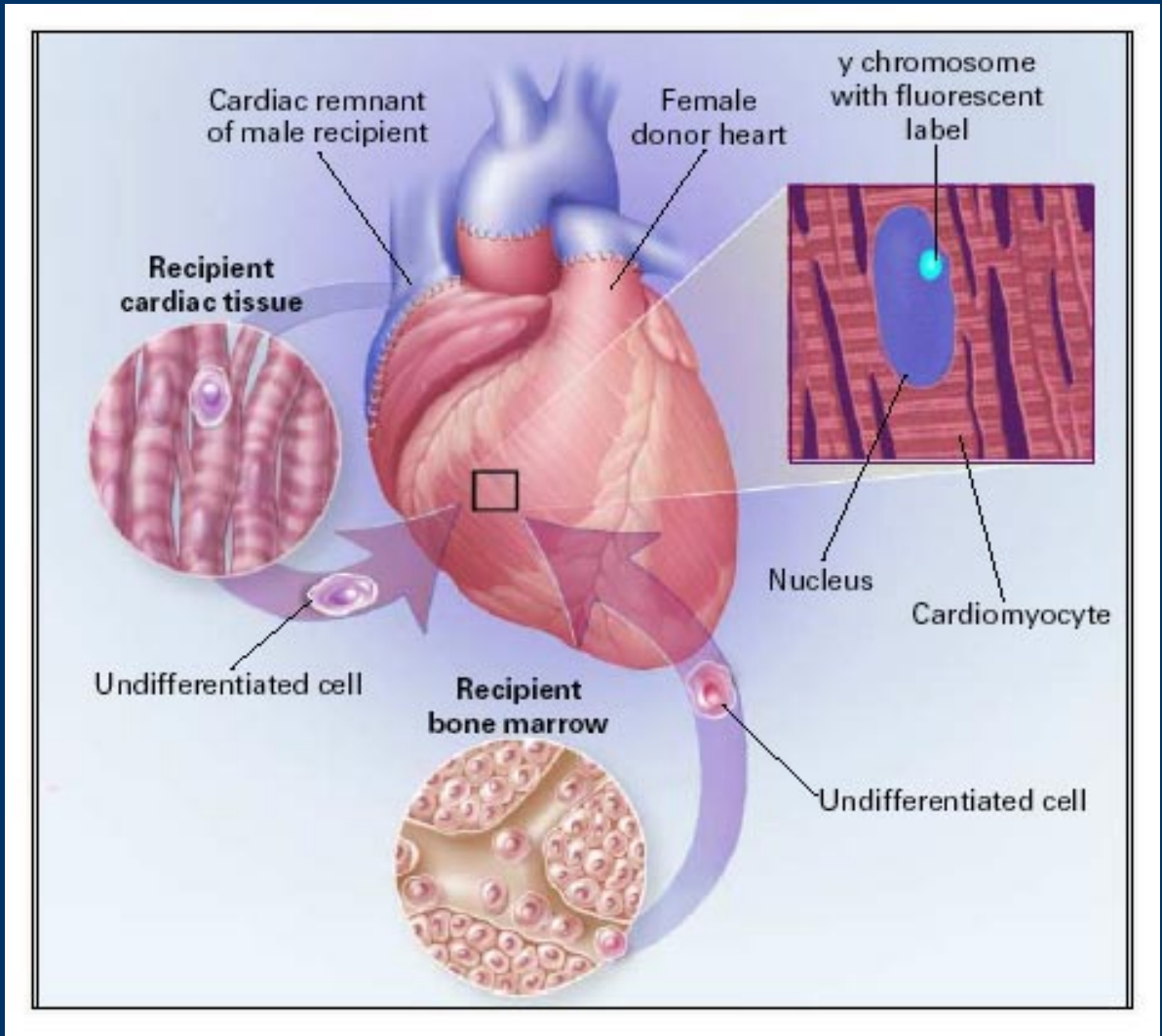
Disease-free Survival of Patients with AML/MDS by Disease Status

Giralt In: NST, 2000



Donor derived Cells after BMT can be found in strange places

- **Myelopoiesis**
- **Lymphopoiesis**
- **von Kupffer cells**
- **Pulmonary alveolar macrophages**
- **Langerhans cells**
- **Osteoclasts**
- **Macro and Microglia**
- **Hepatocytes**

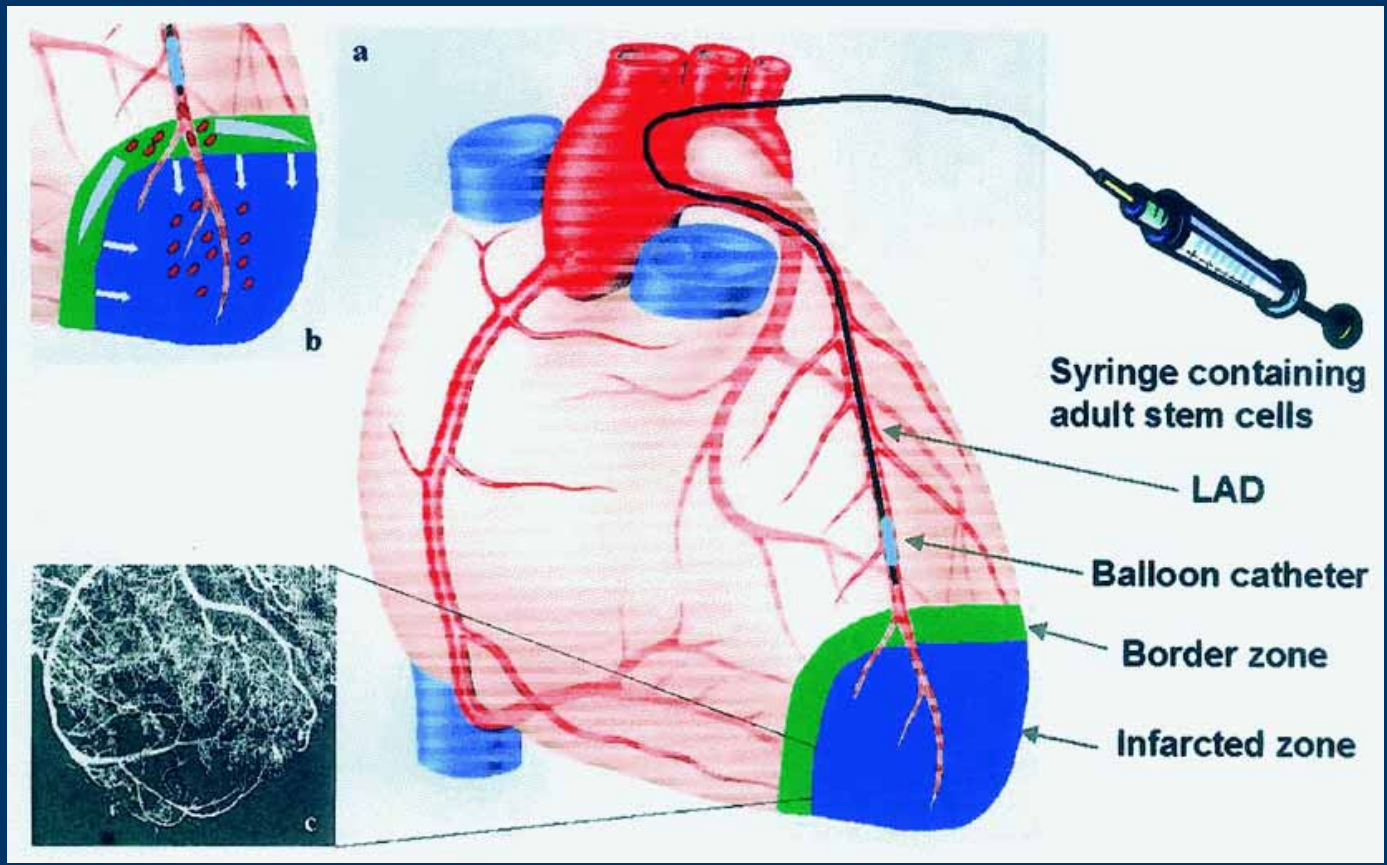


Male recipient cells in female cardiac allografts

(Schwartz and Curfman NEJM 2002; 346: 2 – 4)

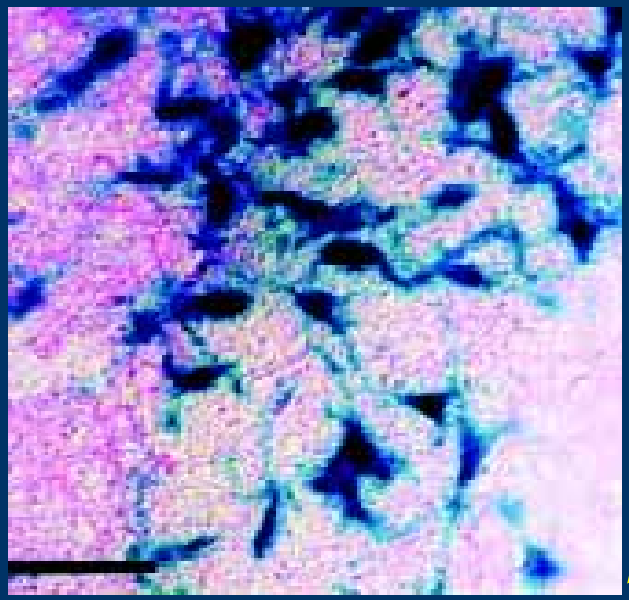
Intracoronary Mononuclear Marrow Cell Transplantation

Strauer BE et al Circulation 106: 1913 – 1918, 2002

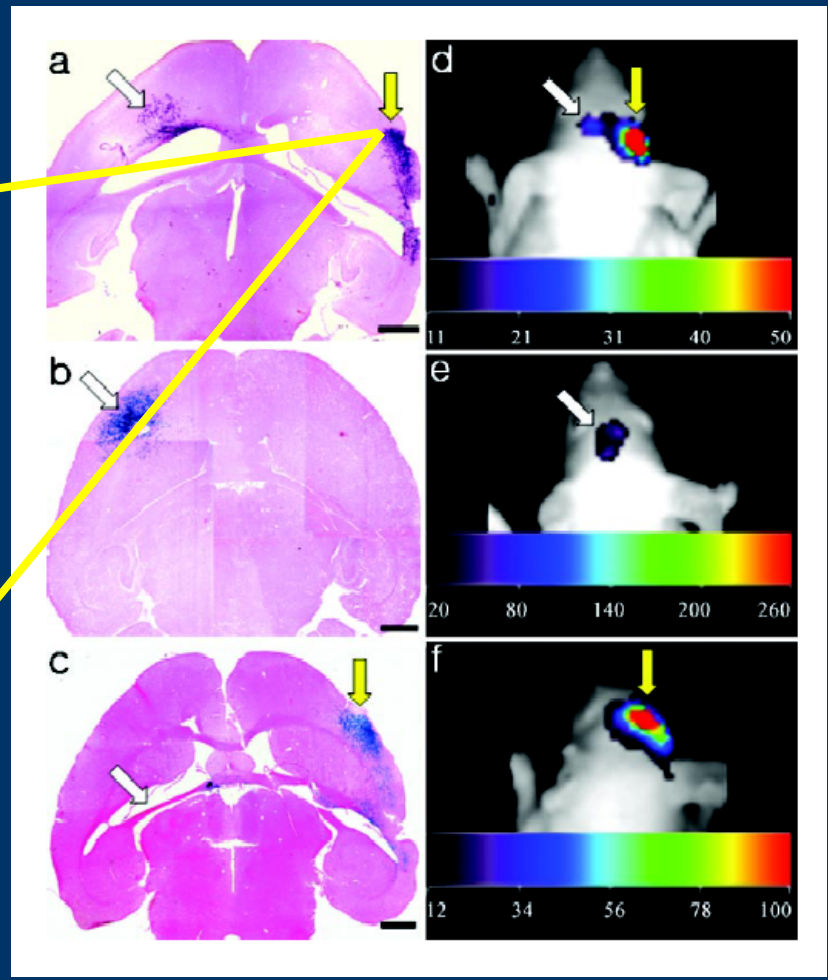


Stem cell recruitment to ischemic infarcts

(Kim DE et al Stroke 2004; 35: 952 – 957)

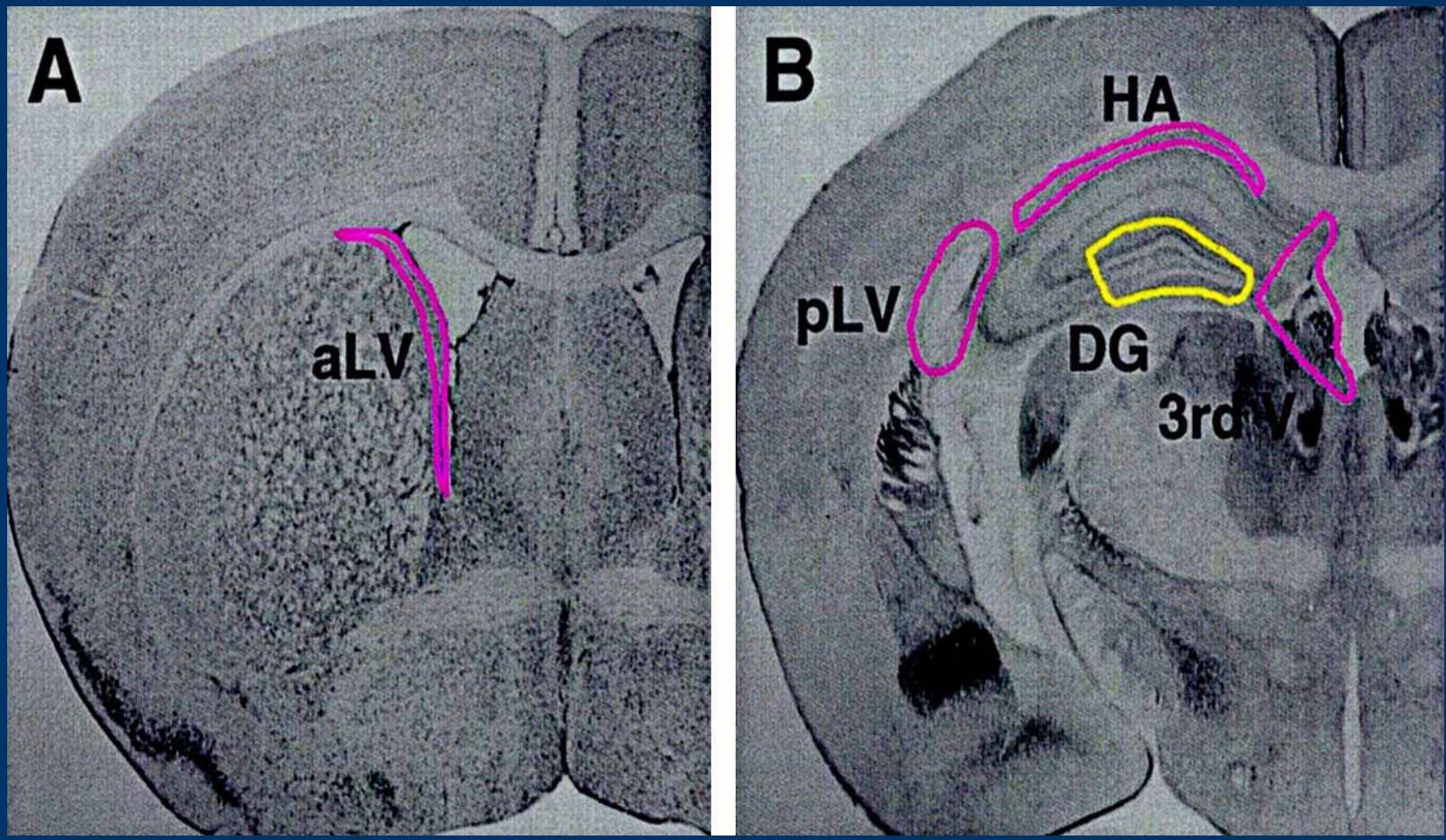


Cells positive for neuronal marker NeuN



Neurogenic Regions in the Mouse

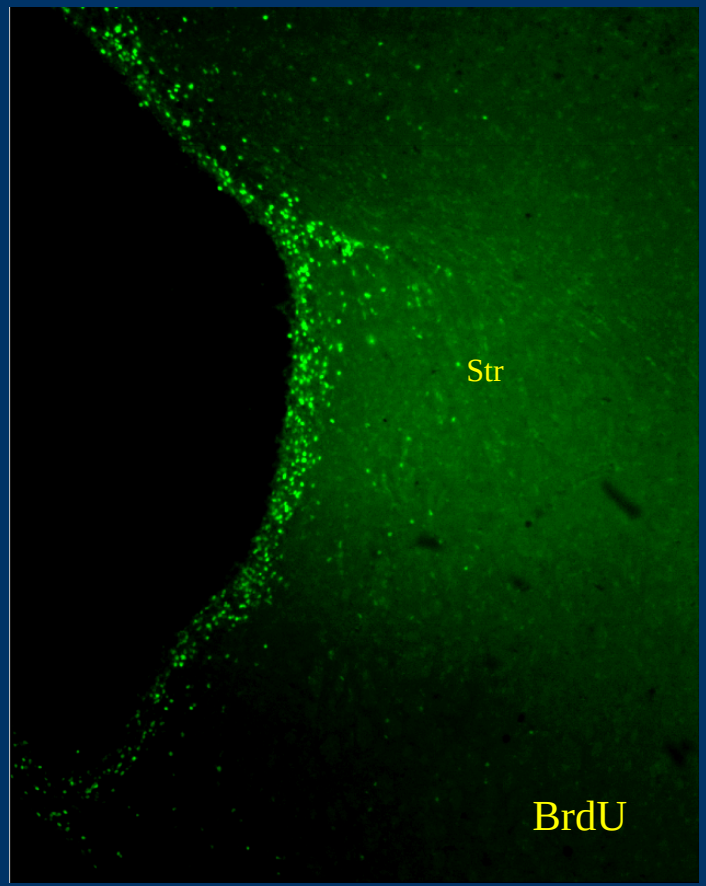
(Seaberg R, van der Kooy D J.Neurosci 2002; 22: 1784 – 1793)



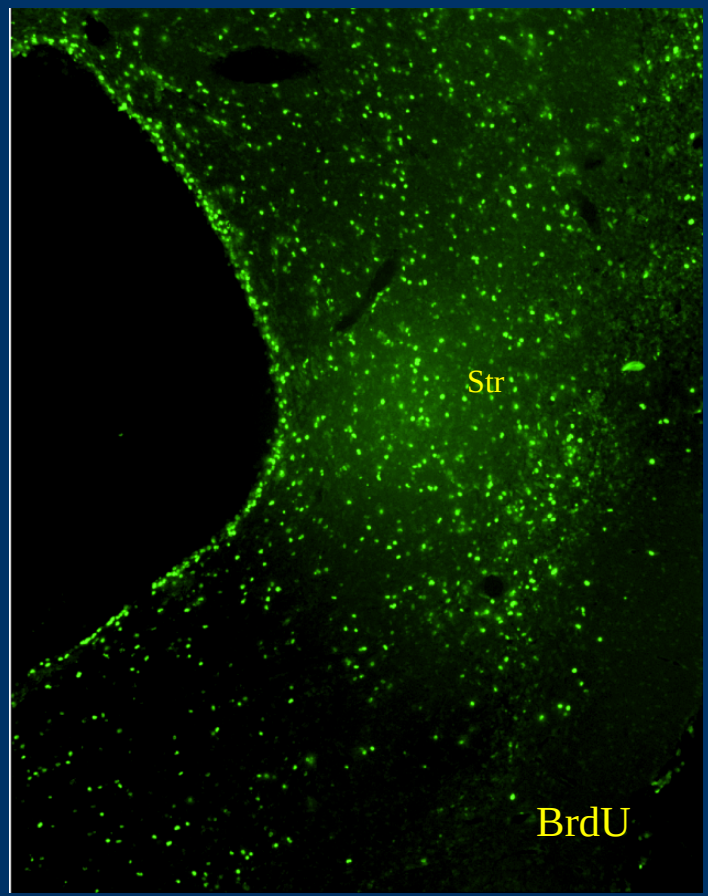
Subventricular zone **Dentate gyrus (DG)**

Newly generated cells in the subventricular zone with EGF or EGF plus EPO

EGF

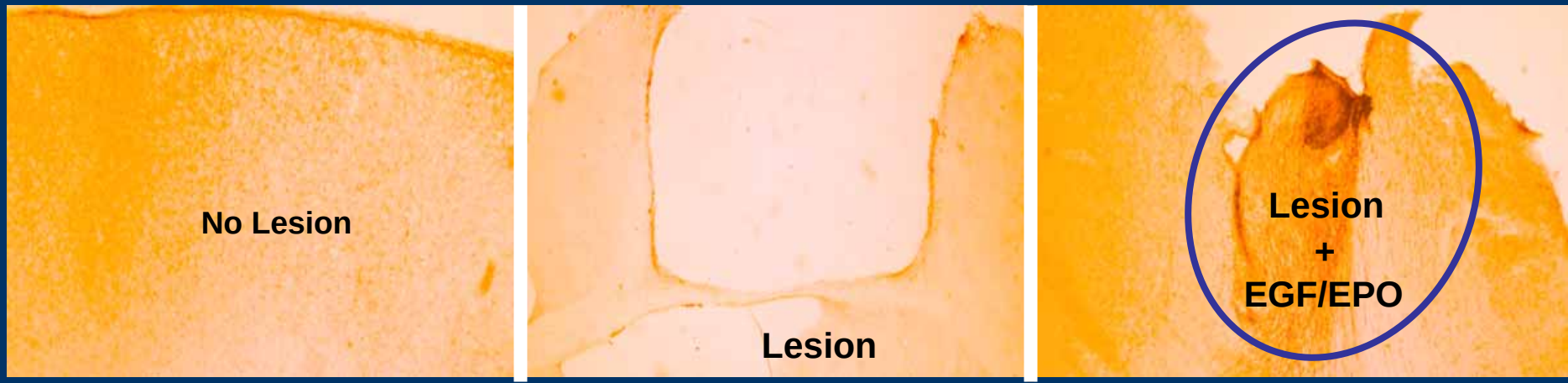


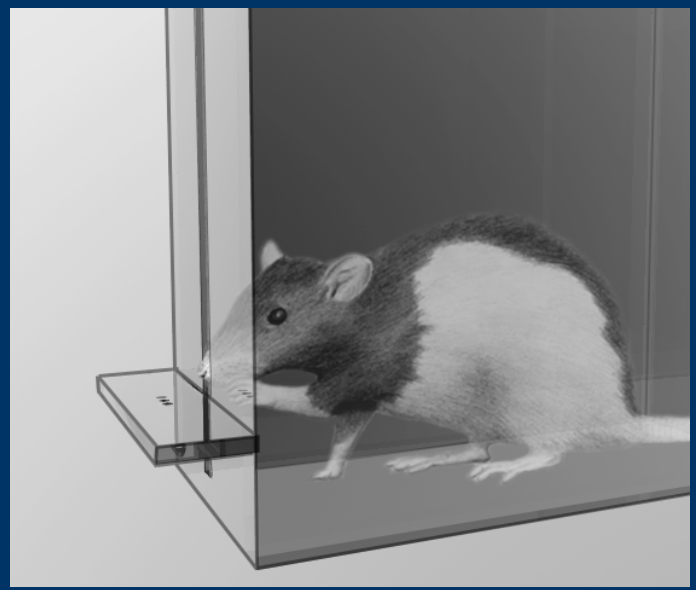
EGF + EPO

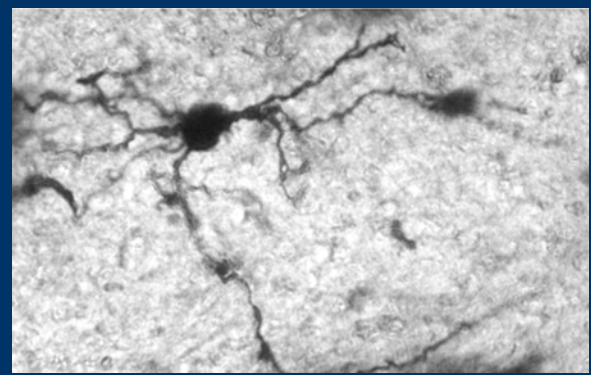


Courtesy Sam Weiss, Calgary

Histological analyses reveal new tissue in the lesion cavity of rats that received EGF+EPO infusions

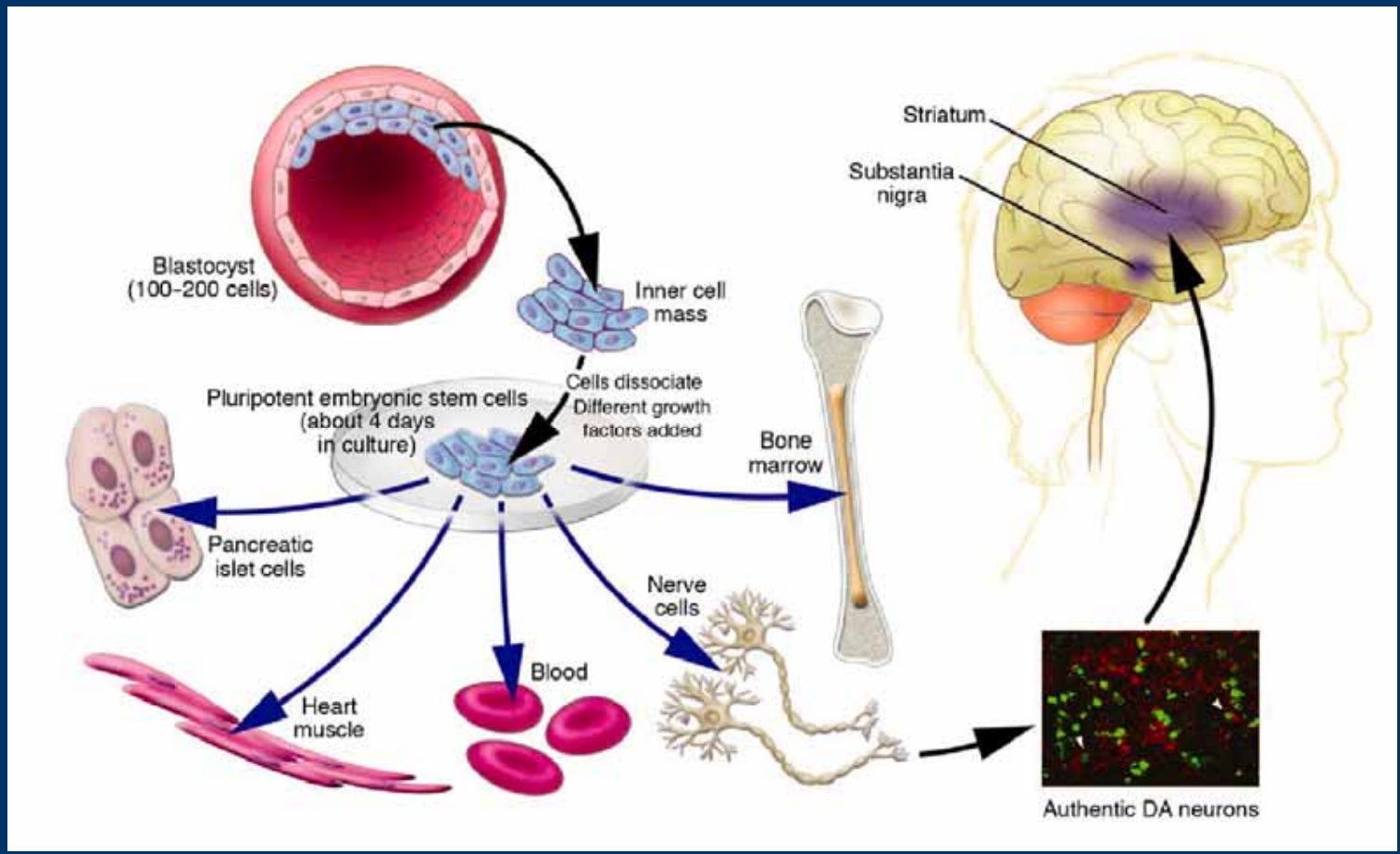






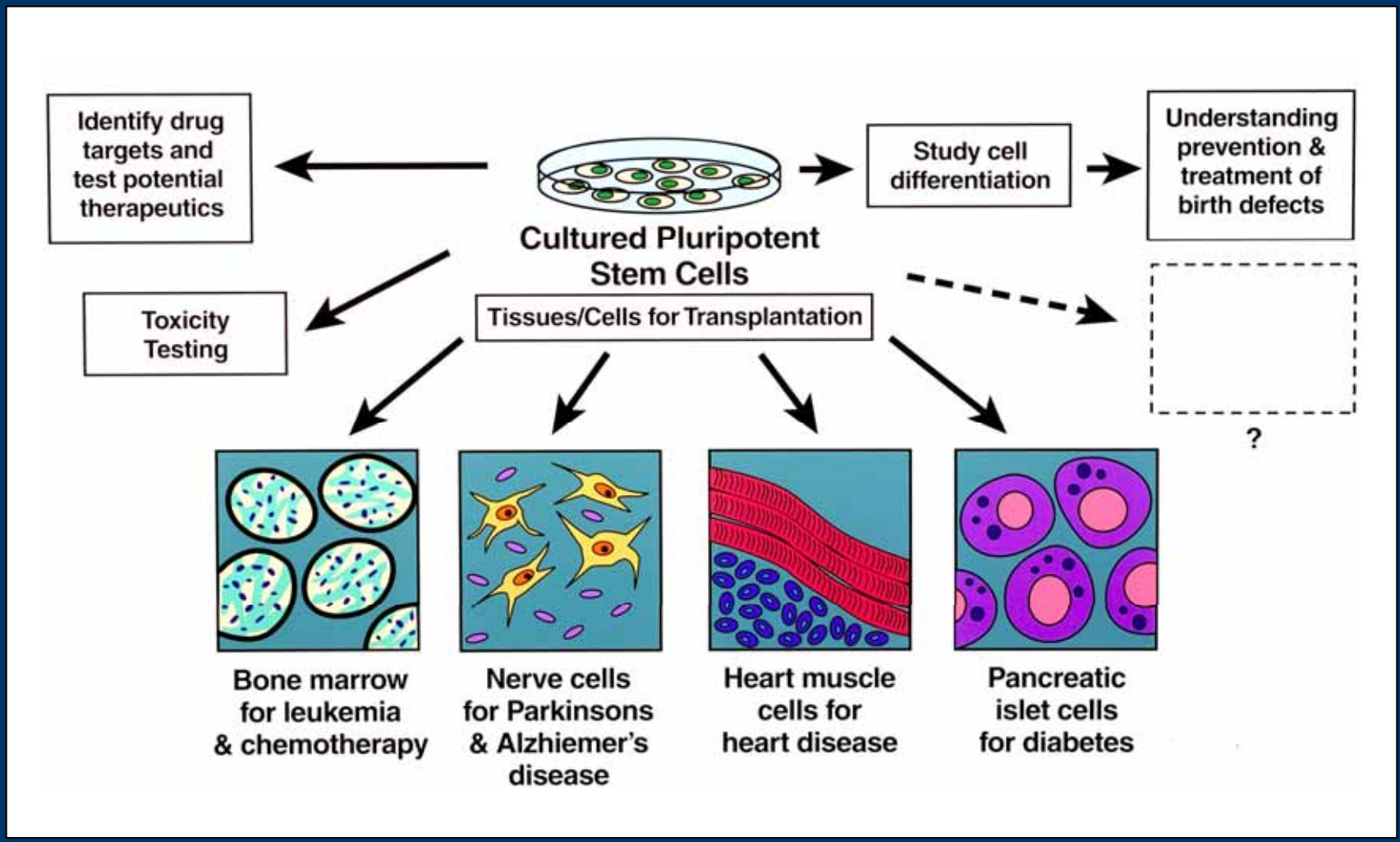
Courtesy Sam Weiss, Calgary

Embryonal Stem Cells



(Langston JW J Clin Invest 2005; 115: 23 – 25)

The promise of stem cell research



Conclusions (I)

- Stem cell transplants are a major treatment modality for patients with marrow failure, hemopoietic malignancies and diseases with immune dysfunction
- Stem cell sources include marrow, peripheral blood and cord blood
- Stem cells can be derived from autologous and allogeneic sources
- Currently available strategies facilitate their use for patients with more advanced age

Conclusions (II)

- Advances are being made to test whether or not stem cells may facilitate repair of defective organs in general