Bio 447
December 5th 2025

" Clinical Impact of Stem Cells "
Hematopoietic Stem Cell Transplantation

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UNIL | Université de Lausanne
Faculté de biologie et de médecine

Learning objectives

Hematopoietic stem cell transplants

1. What is a hematopoietic stem cell transplantation (HSCT)?
2. How is it done?
3. What is the difference between autologous and allogeneic transplantation?
4. What is the toxicity and challenges associated to HSCT?
5. Where are hematopoietic stem cells collected from?
6. Why combining gene therapy and HSCT?
7. Examples of other advances being explored in HSCT

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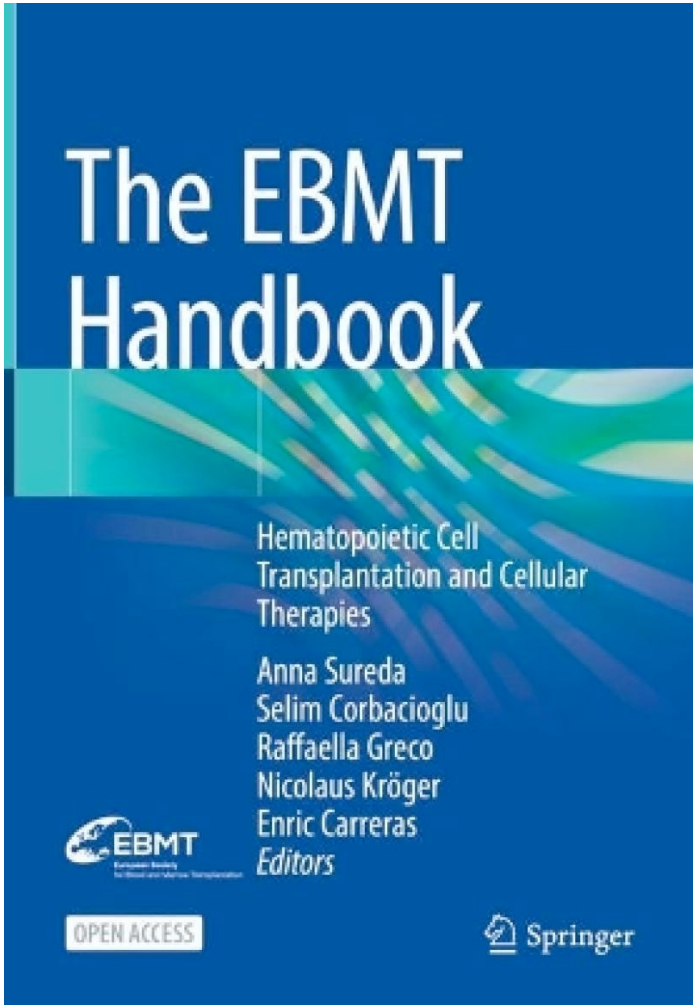
The Bible for further information…



Open Access
2024 edition

(very clinical, though)

What is a HSC transplant ?

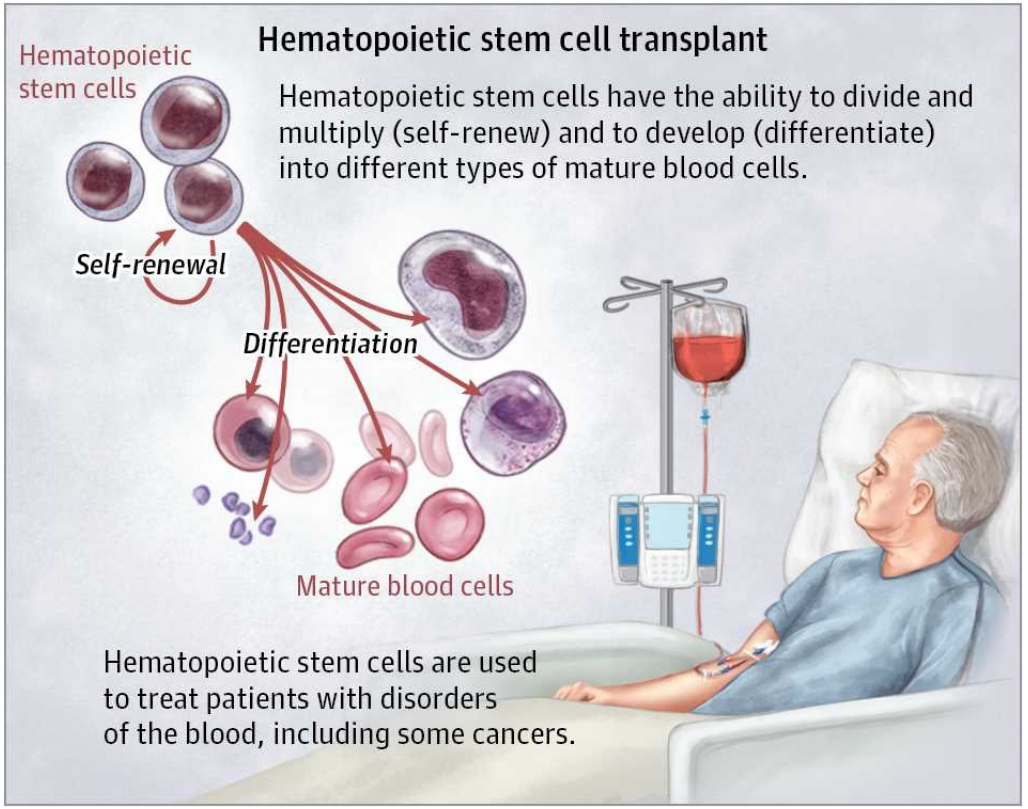
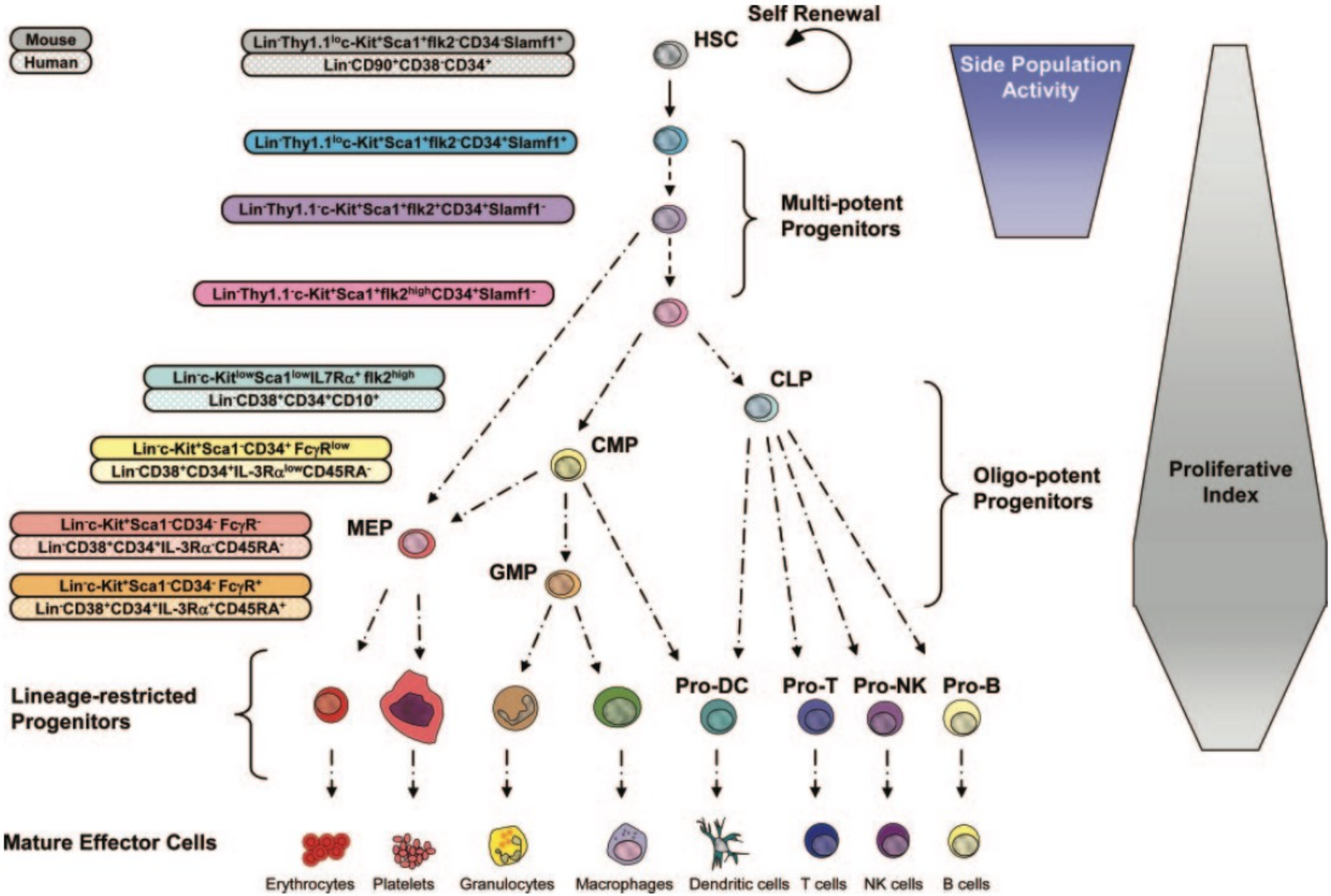
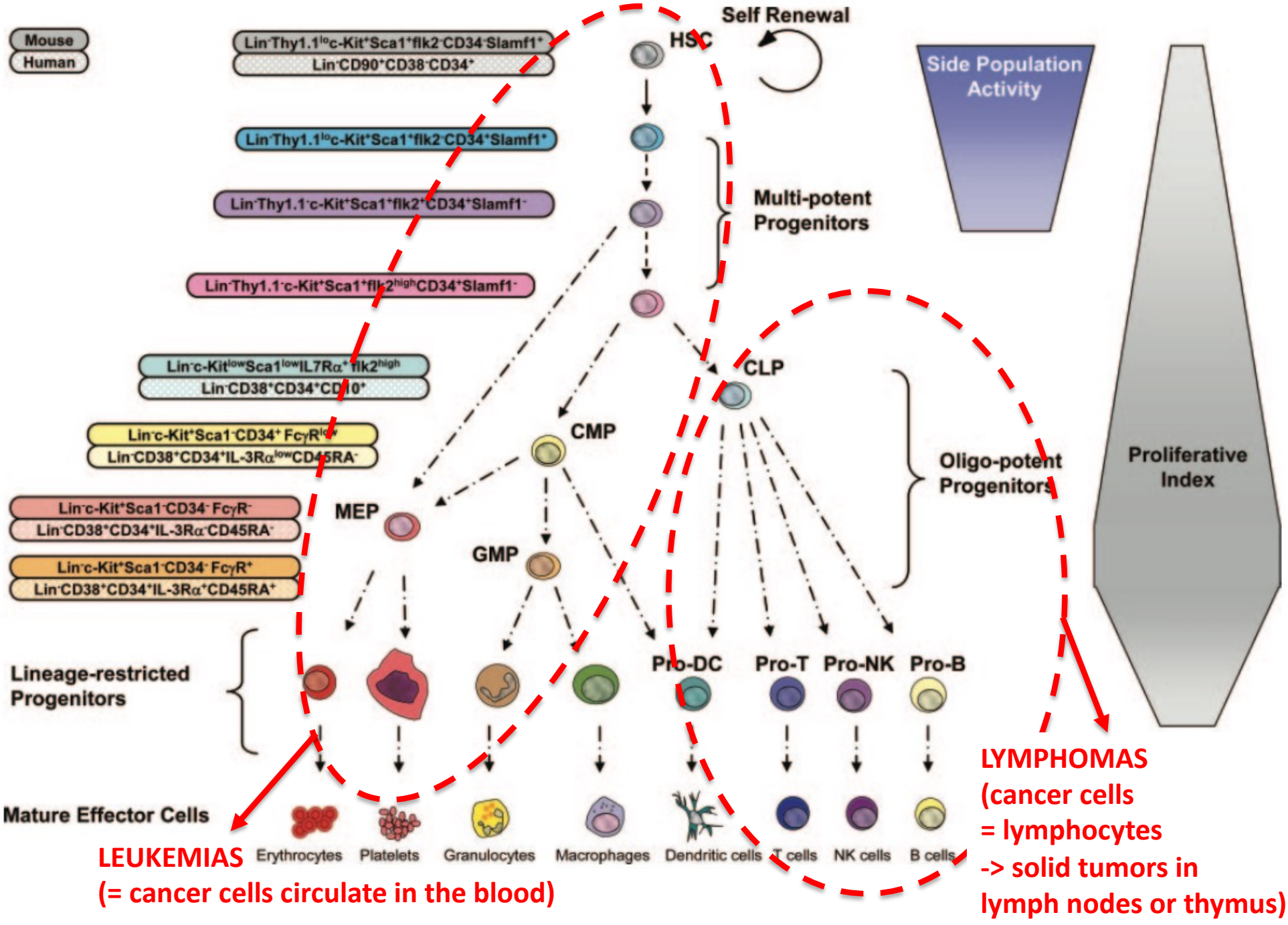


Image credit: https://www.creative-biolabs.com/vaccine/hematopoietic-stem-cell-transplantation-platform.htm

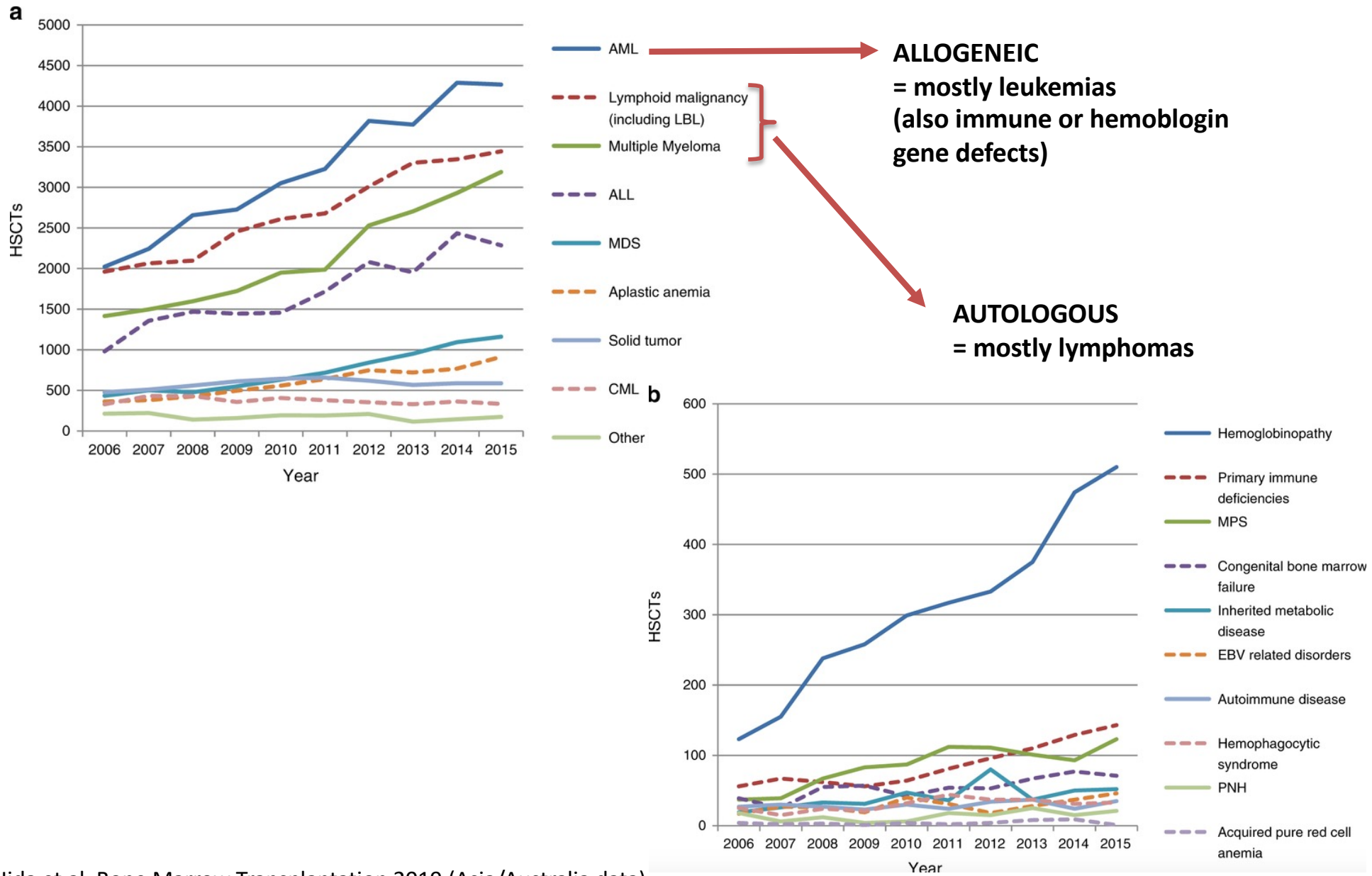
The HSC hierarchy :



When hematopoietic cells become cancerous:

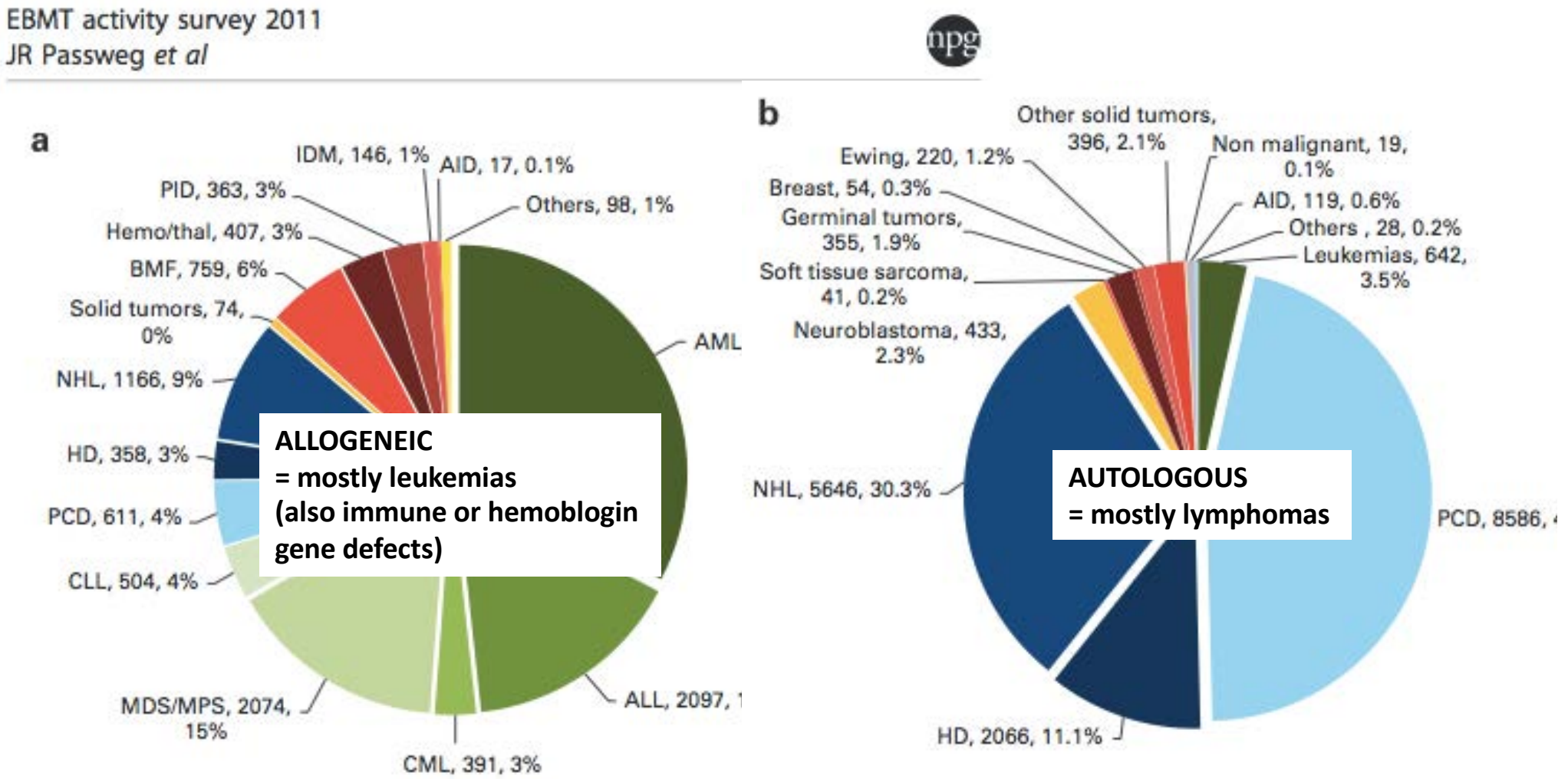


Who needs a HSC transplant?

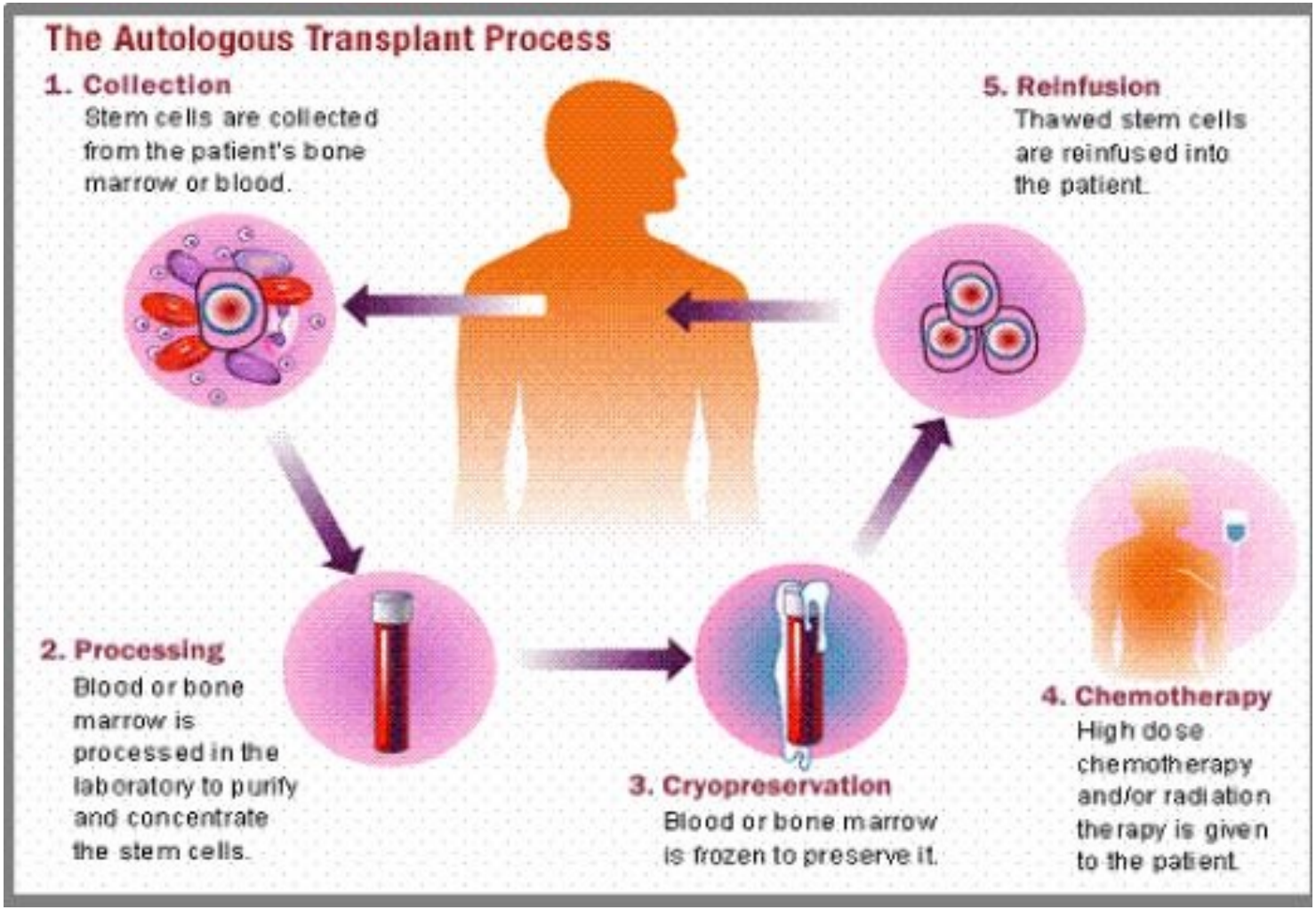


Iida et al. Bone Marrow Transplantation 2019 (Asia/Australia data)

Who needs a HSC transplant?

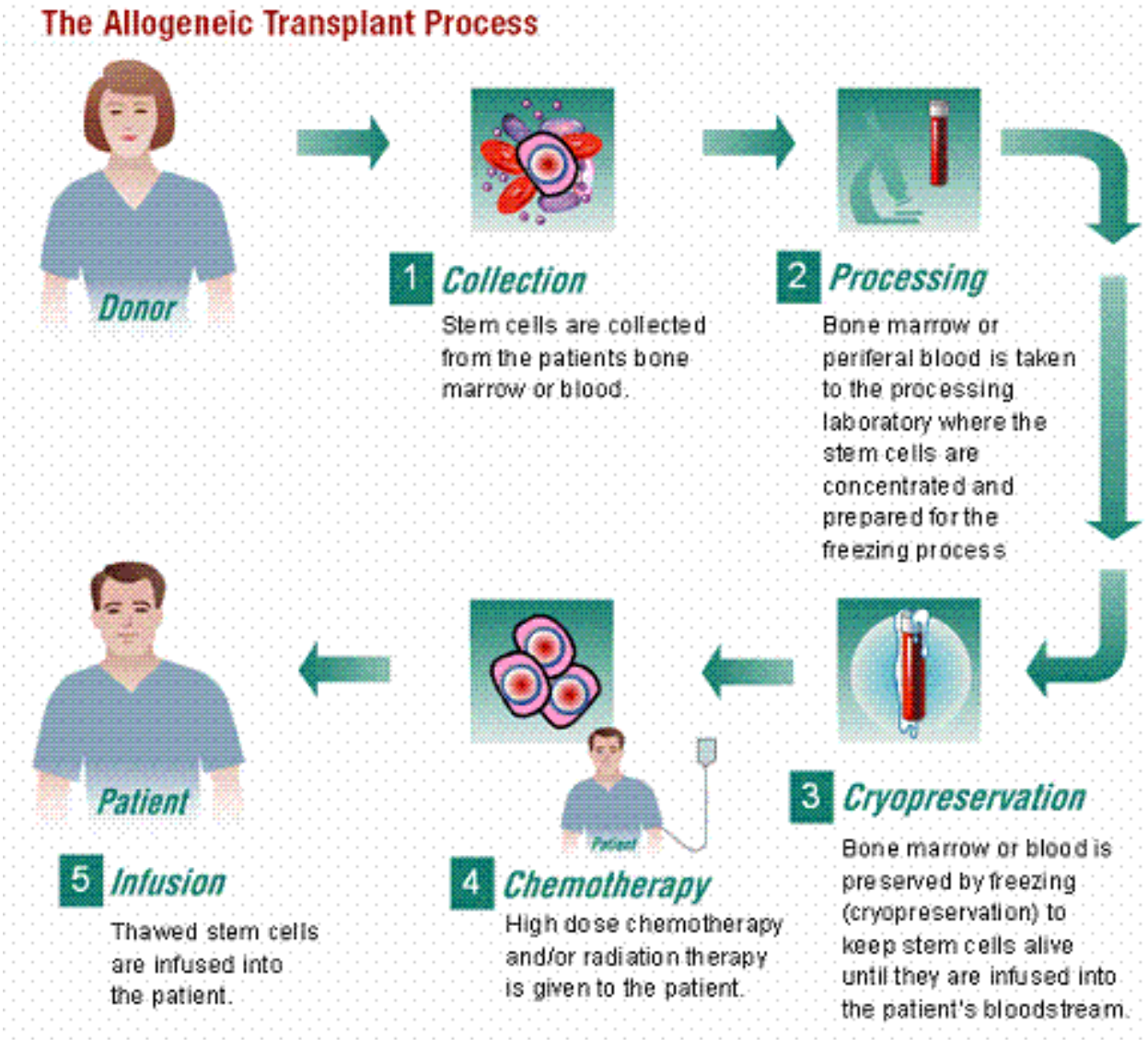


What is an **autologous** HSC Transplantation?



Autologous HSC transplantation is a way to administer a very high dose of chemotherapy to a blood cancer, as the transplanted HSCs will rescue the normal hematopoietic system killed by the chemotherapy.

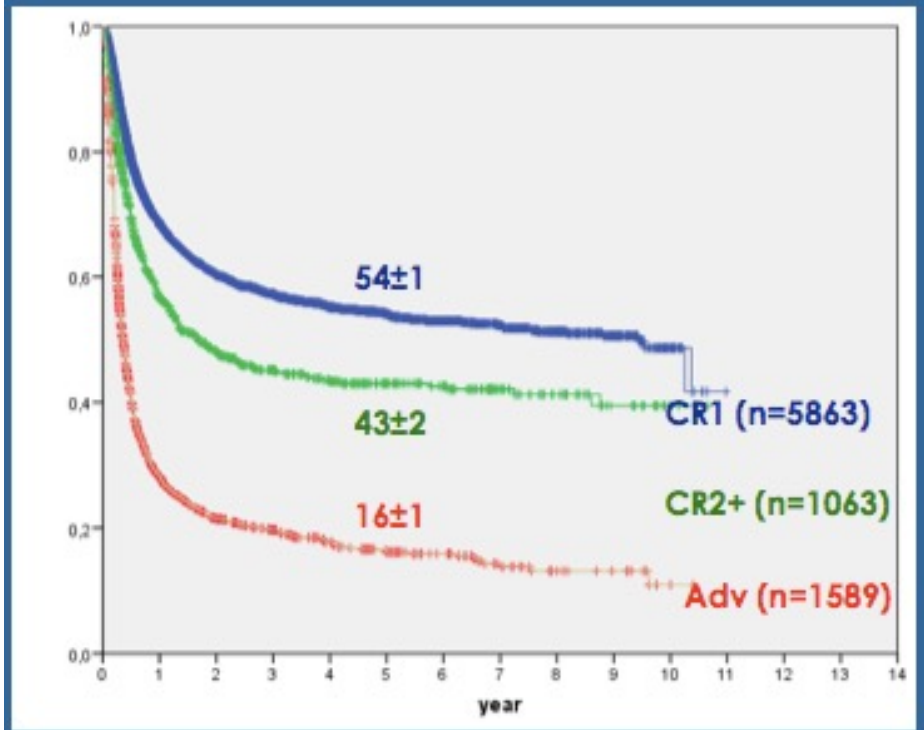
What is an **allogeneic** HSC Transplantation?



Allogeneic HSC transplantation substitutes the patient's blood system by a different one, either to repair it (genetic defects) or to allow for a constant immune-surveillance against the underlying blood cancer (called Graft versus Leukemia effect =GvL)

Early mortality in ablative HSCT -> not the holy grail!

AML (n=8534)



SURVIVAL RESULTS ARE FOR ALLOGENEIC HLA IDENTICAL SIBLING (= best possible match)

CR1 = Complete Remission 1
CR2 = Complete Remission 2
Adv = Advanced leukemia (no remission)

-> Half the mortality in the very best scenario (CR1 and identical sibling donor = blue line) is due to the toxicity of HSCT -> risk of infection and of GvHD.
So aprox. 25% mortality due to the toxicity of HSCT!!

Source: EMBT database

Where do donor Hematopoietic Stem Cells come from?

1. **Adult:**
   Site:
   - From blood : "Mobilized" progenitors (G-CSF = filgrastim)
   - From bone marrow collection (rarely, for autoimmune diseases)

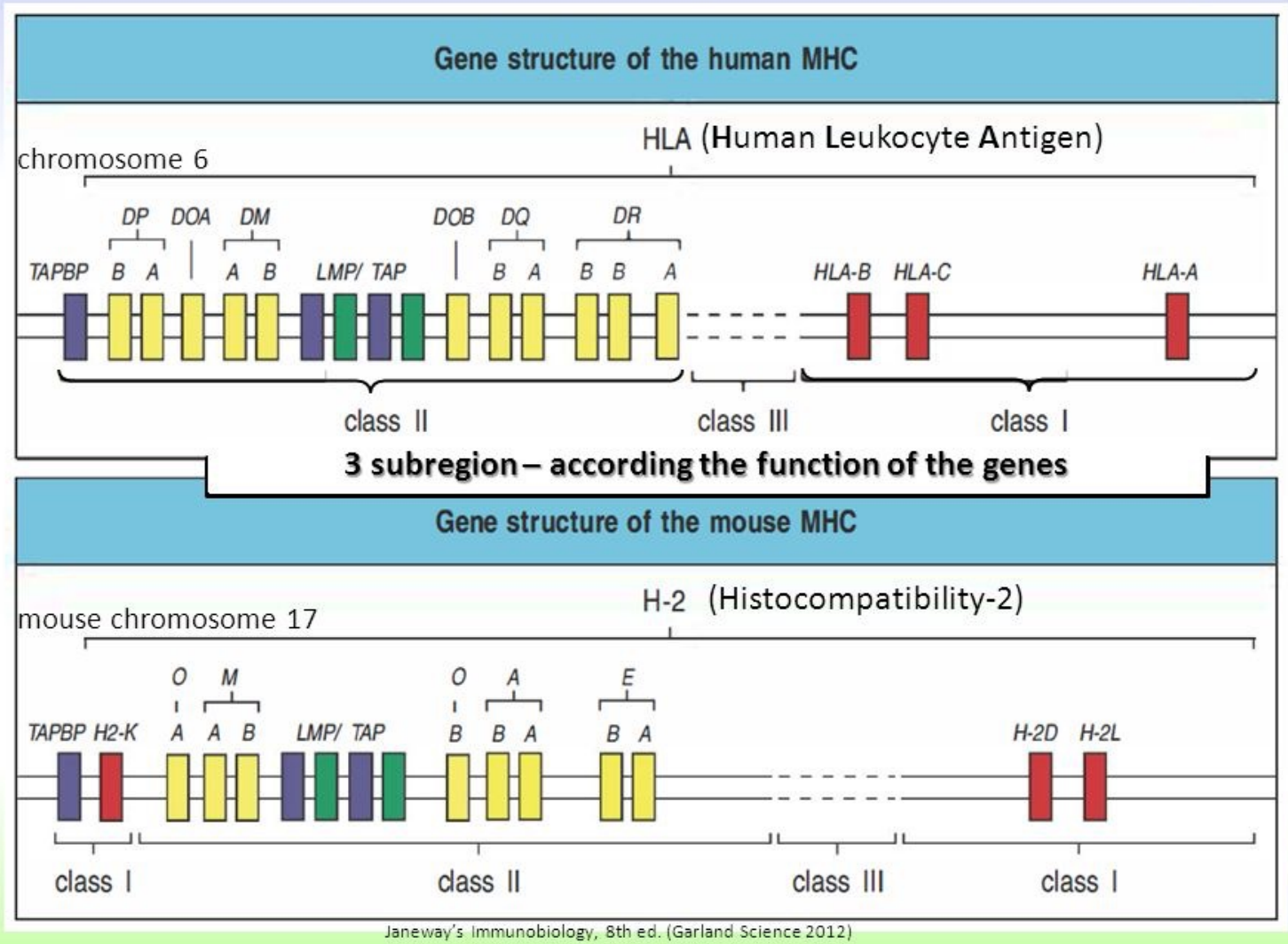
   Donor type:
   - Allogeneic vs autologous
   - Related vs unrelated donor
   - Identical HLA-match vs. Haploidentical (father/mother)

2. **Newborn:**
   - Cord blood banking (almost always unrelated, allogeneic)

3. **Pluripotent stem cells** (not in clinical hematology yet!)
   - iPS, embryonic stem cells

What is the Major Histocompatibility Complex (MHC or HLA)?

Leukocytes were used for the identification of the proteins → Human Leukocyte Antigen (HLA)



Janeway's Immunobiology, 8th ed. (Garland Science 2012)

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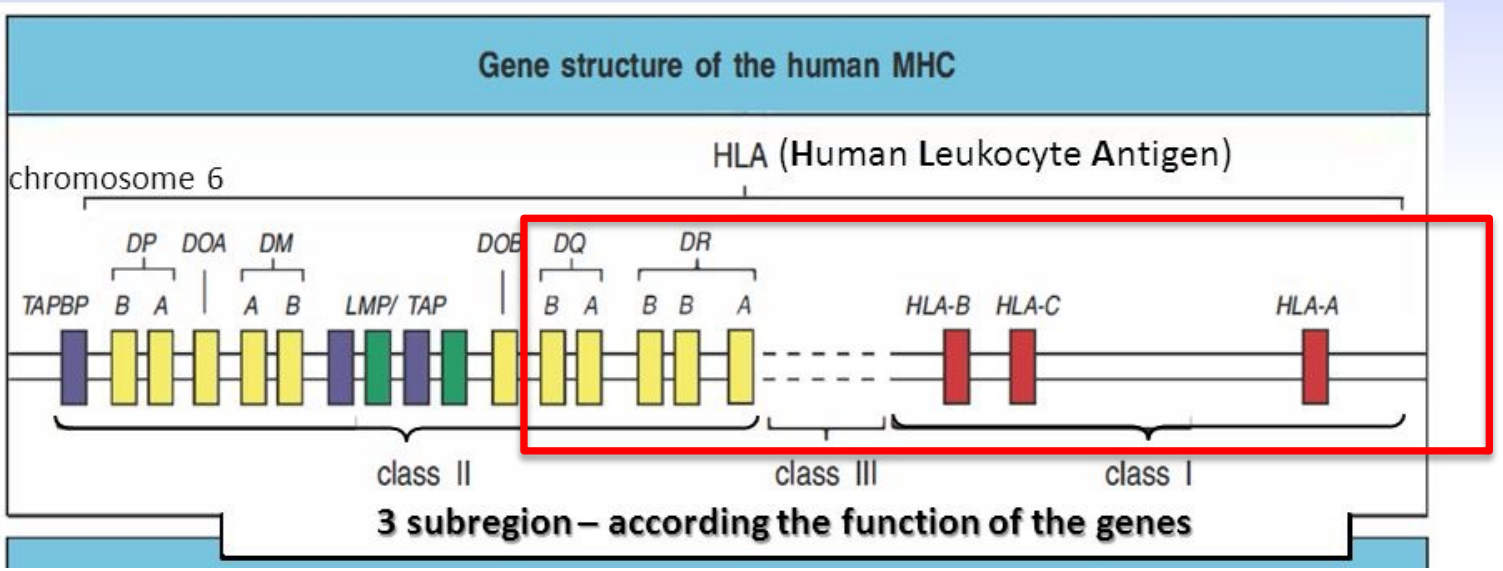
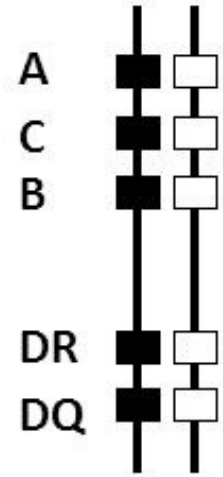
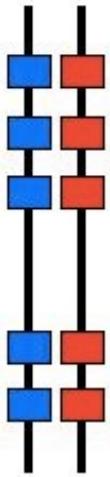


HLA inheritance

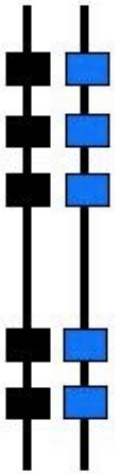


Mother

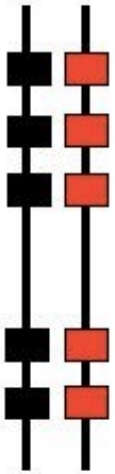


Father

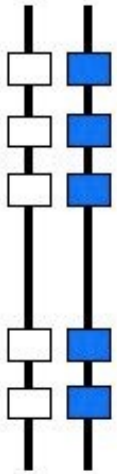
Patient



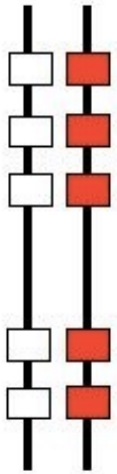
Sib 1



Sib 2



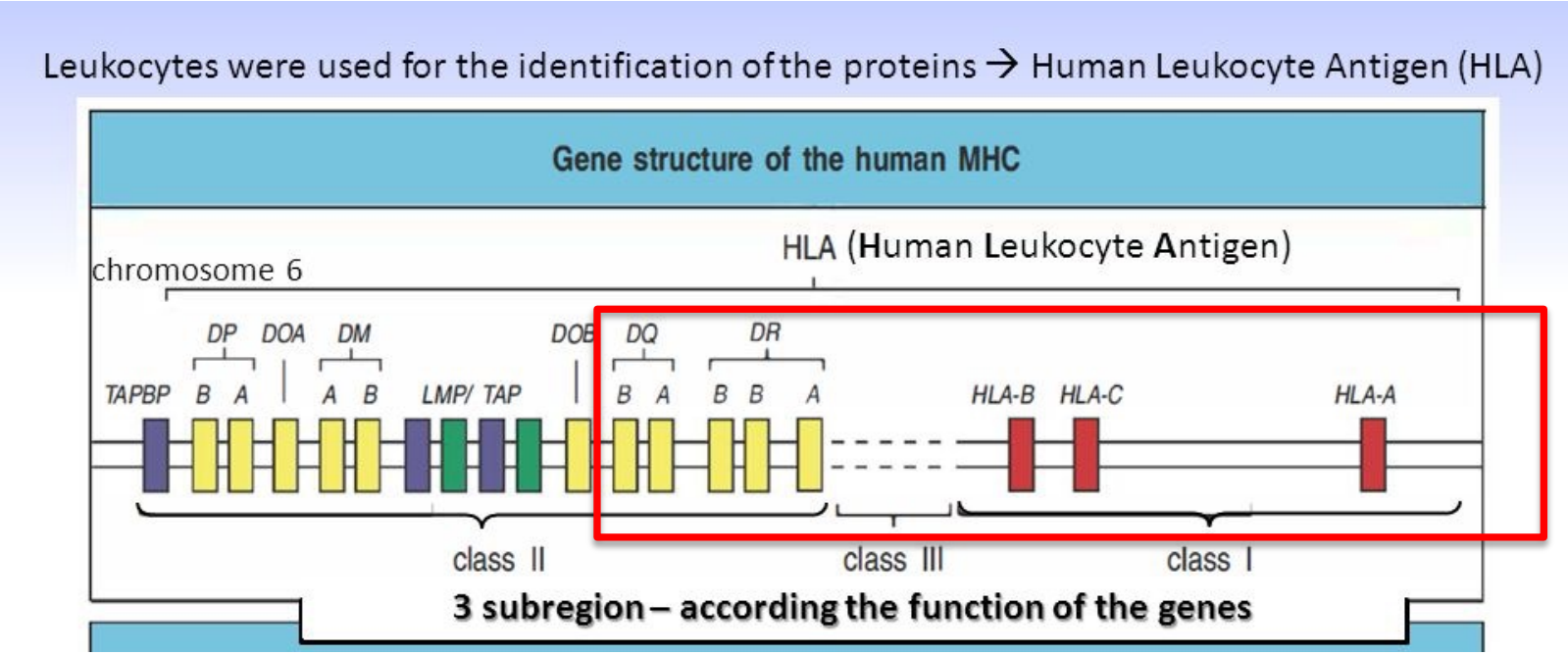
Sib 3



Sib 4

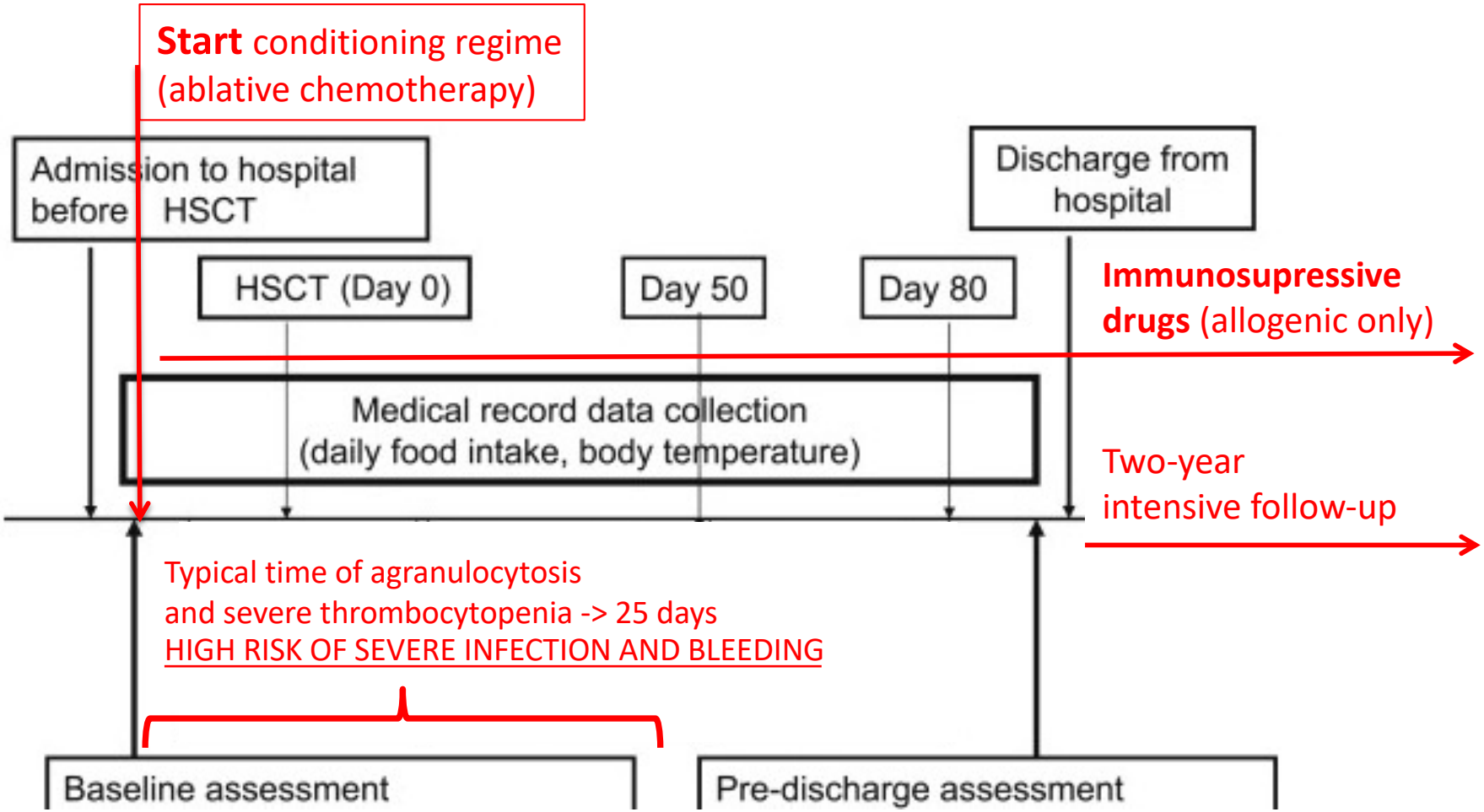
25% chance of having an HLA matched sibling
50% chance of having a haploidentical sibling

What is the Major Histocompatibility Complex (MHC or HLA)?



- These 5 HLA-A,B,C, DQ and DR alleles (5 paternal + 5 maternal = 10) need to be matched between donor and recipient for the donor not produce a severe immune reaction against the recipient at the time of the transplant, named “Graft versus Host Disease” (GvHD).
- Probability to find a 10/10 donor within the siblings : 25% (Mendelian)
- Probability to find a 9-10/10 donor in the Bone Marrow Worldwide Donor registry:
  - 60-80% for Caucasians
  - 16% for Indians
  - 11% for Asians

How HSCT transplantation works for the patient…



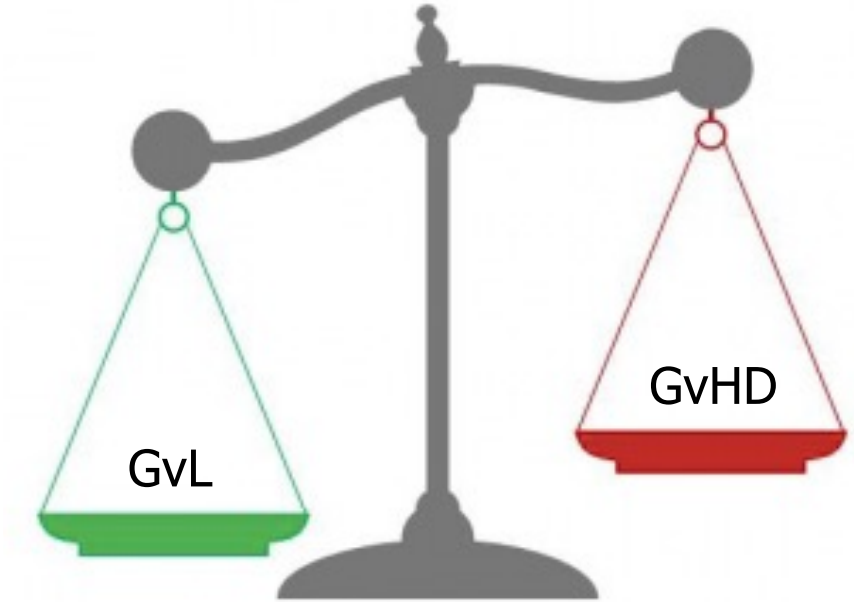
* Agranulocytosis = almost no circulating white blood cells -> high risk of infection

** Thrombocytopenia = almost no circulating platelets -> high risk of bleeding

The hard balance between GvL and GvHD

GvL = Graft versus Leukemia effect -> maintains the long-term immune-surveillance against the blood cancer

GvHD = Graft versus Host Disease -> immune reaction of the donor lymphocytes against the recipient's body (typically against the intestine, the liver and the skin)



Immune suppressive Drugs

Risk of complications after allogeneic HSCT increases with:

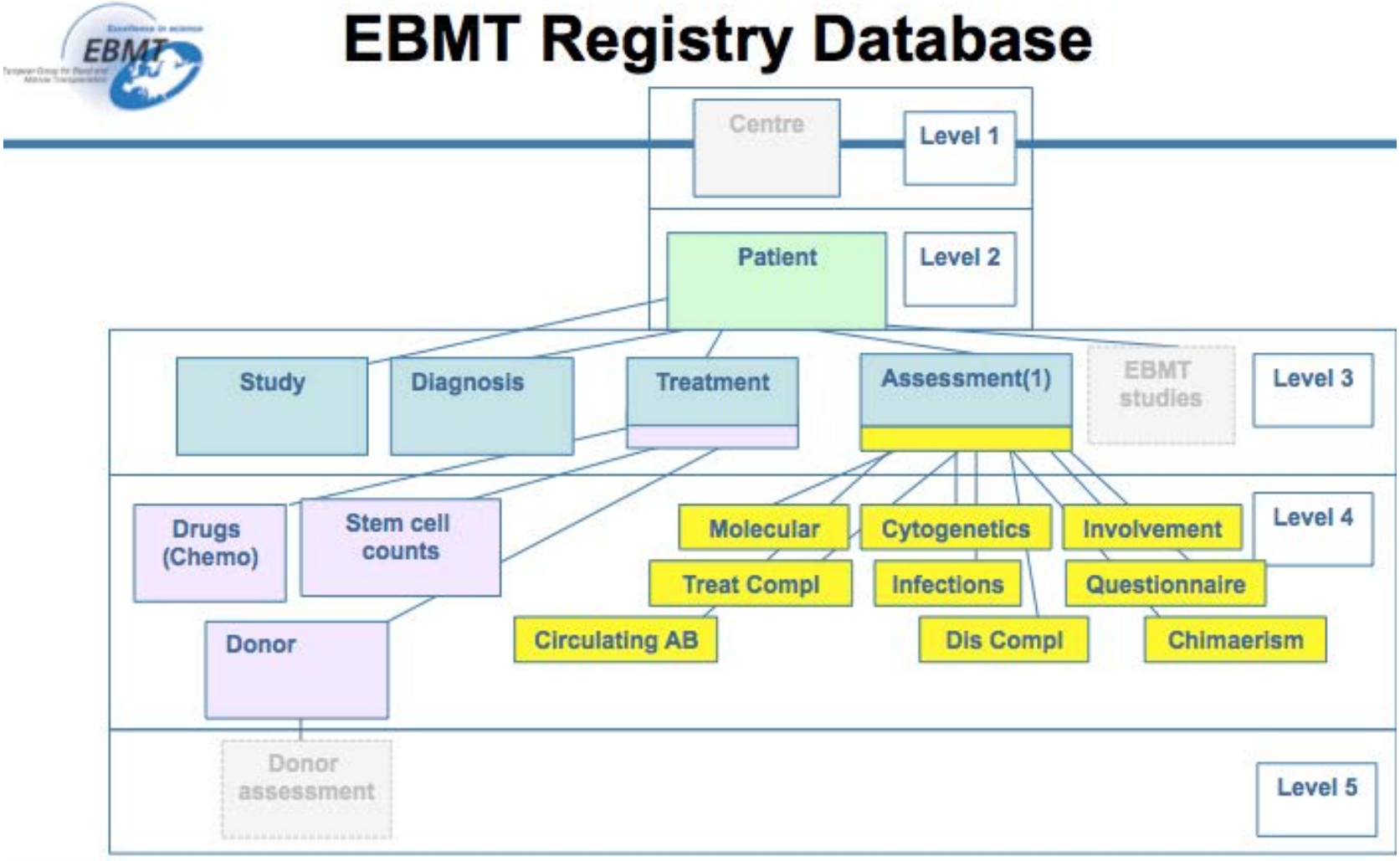
- Number of HLA mismatches
  (ideally at least 10 matches for the 12 HLA loci)
- Unrelated donor from International Registry (instead of compatible sibling)
- Age of recipient

-> Translates into:

- Increased time of hematopoietic reconstitution
  (agranulocytosis, lymphopenia, transfussion-dependency)
- Increased Degree of Graft vs. Host Disease (GvDH)

Reminder:
Complete compatibility (as between identical twins) is not desirable for the treatment of blood cancers because loss of the Graft vs. Leukemia effect (GvL)

HSCT transplantation requires significant infrastructure



-> Many highly-qualified players required to perform a HSCT, so only specialized centers can do it (with certification by "JACIE standards")

Current advances/research in HSCT:

1. Reduced conditioning regimes for non-oncological indications of HSCT -> sickle cell anemia

2. Niche : intra-bone marrow injection for cord blood HSCT or co-delivery of mesenchymal stromal cells

3. Combined gene therapy and HSCT for the cure of severe combined immunodeficiency (SCID or “bubble boy”)

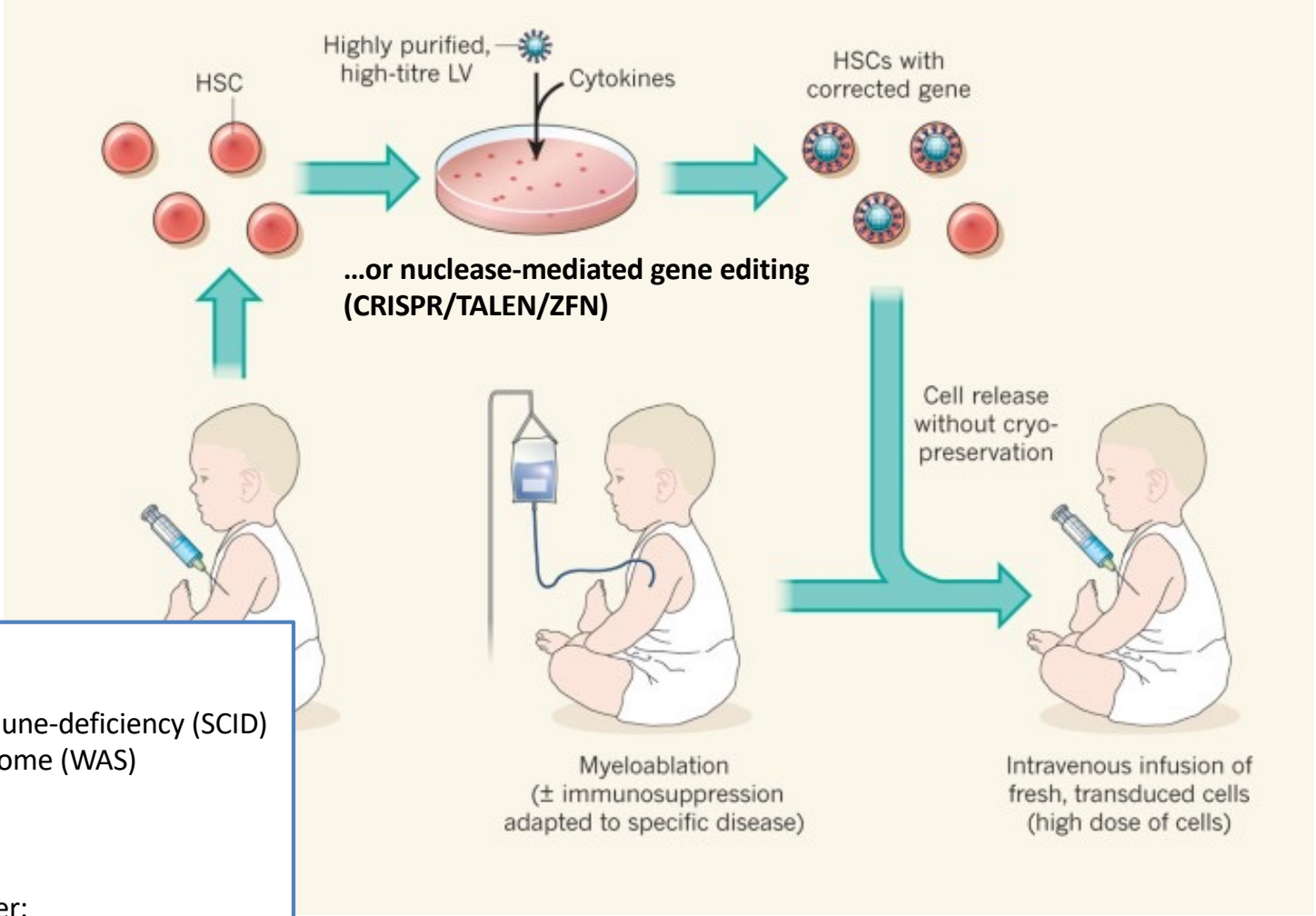
4. Solid organ tolerance induction through highly purified HSCT (myeloma, then polycystic kidney disease)

5. Curing HIV with HSCT (CCR5-/- donor)

6. T-cell adoptive transfer to improve anti-leukemia effect, including T cells (DLI), in vitro expanded NK cells, and CAR-T cells

Why useful to combine HSCT and gene therapy ?

Gene addition through retroviral/lentiviral vectors

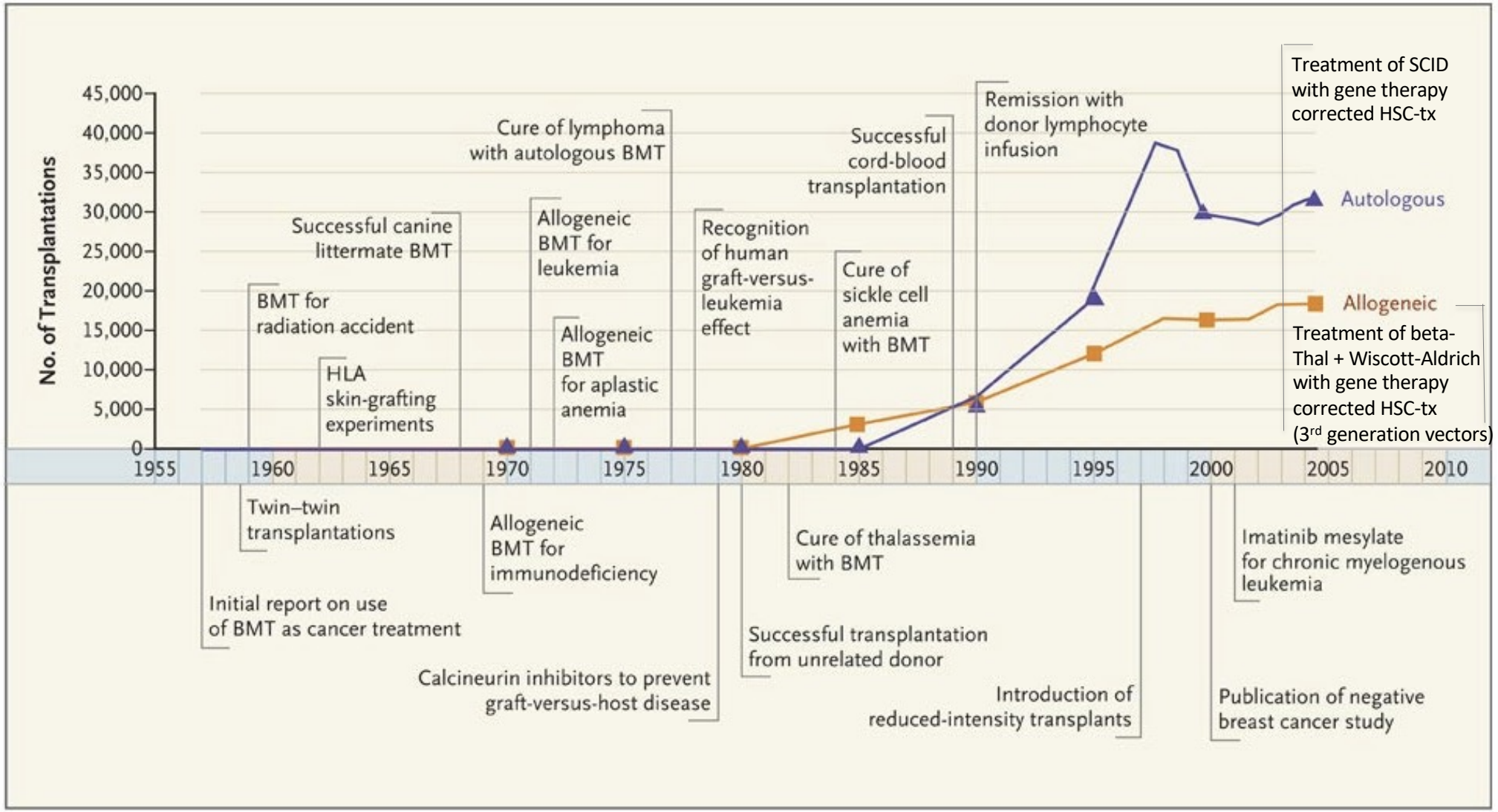


Patient with :

- genetic immune deficiency
  - Severe combined immune-deficiency (SCID)
  - Wiskott–Aldrich syndrome (WAS)
- hemoglobin defect :
  - Thalassemia
  - Sickle cell anemia
- or inherited metabolic disorder:
  - Adrenoleukodystrophy (ALD)
  - Metachromatic leukodystrophy (MLD)

Modified from Leboulch P., Nature 500; 280 (2013)

A “little” history of HSC transplantation…



Updated from FR. Appelbaum, N Engl J Med 2007; 357:1472-1475

The landmark study combining HSCT and gene therapy:

Gene Therapy of Human Severe Combined Immunodeficiency (SCID)–X1 Disease

Marina Cavazzana-Calvo,*[1,2,3] Salima Hacein-Bey,*[1,2,3] Geneviève de Saint Basile,[1] Fabian Gross,[2] Eric Yvon,[3] Patrick Nusbaum,[2] Françoise Selz,[1] Christophe Hue,[1,2] Stéphanie Certain,[1] Jean-Laurent Casanova,[1,4] Philippe Bousso,[5] Françoise Le Deist,[1] Alain Fischer[1,2,4]†

Severe combined immunodeficiency–X1 (SCID-X1) is an X-linked inherited disorder characterized by an early block in T and natural killer (NK) lymphocyte differentiation. This block is caused by mutations of the gene encoding the γc cytokine receptor subunit of interleukin-2, -4, -7, -9, and -15 receptors, which participates in the delivery of growth, survival, and differentiation signals to early lymphoid progenitors. After preclinical studies, a gene therapy trial for SCID-X1 was initiated, based on the use of complementary DNA containing a defective γc Moloney retrovirus–derived vector and ex vivo infection of $CD34^+$ cells. After a 10-month follow-up period, γc transgene–expressing T and NK cells were detected in two patients. T, B, and NK cell counts and function, including antigen-specific responses, were comparable to those of age-matched controls. Thus, gene therapy was able to provide full correction of disease phenotype and, hence, clinical benefit.

The landmark study showing the first HIV patient cured by HSCT :

ORIGINAL ARTICLE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

N Engl J Med 2009; 360:692-698 | February 12, 2009 | DOI: 10.1056/NEJMoa0802905

- Frequency of the CCR5 Delta32/32 mut : 3-15%
- Given the low probability of finding a compatible donor in the worldwide registry who on top of being 10/10 immune- compatible happens to be a CCR5 D32/D32 mutant, what are other possibilities to give a curative HSCTs to an HIV+ patient to obtain long-term control of the HIV?
- - > add gene therapy to the patients' own cells to substitute the native wildtype CCR5 receptor by a mutated one (via gene editing)

The landmark study showing the first HIV patient cured
by autologous HSCT after receiving their own gene-edited cells :

ORIGINAL ARTICLE

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.
N Engl J Med 2014; 370:901-910 | March 6, 2014 | DOI: 10.1056/NEJMoa1300662

- Infusion of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN).
- The median concentration of *CCR5*-modified CD4 T cells at 1 week was 250 cells/uL
- HIV RNA became undetectable in one of four patients who could be evaluated.

A “little” history of HSC transplantation…

HSCT + gene therapy -> first 2017 sickle cell anemia patient transplanted!

Bluebird Bio

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Magnani, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

A “little” history of HSC transplantation…

HSCT + gene therapy -> 2018 commercial product!

LentiGlobin BB305 (clinicalTrials.gov for updates)

The NEW ENGLAND JOURNAL of MEDICINE

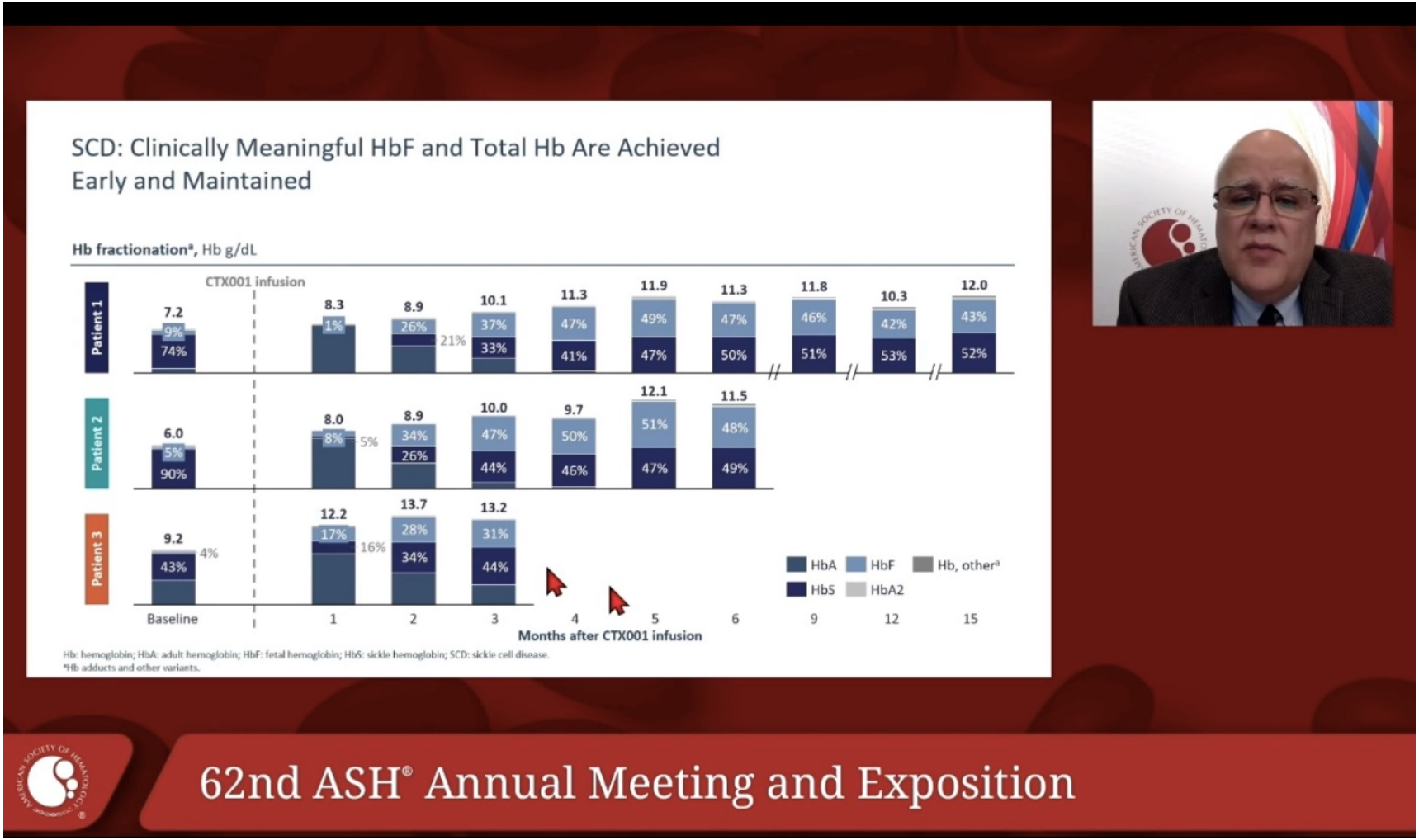
ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

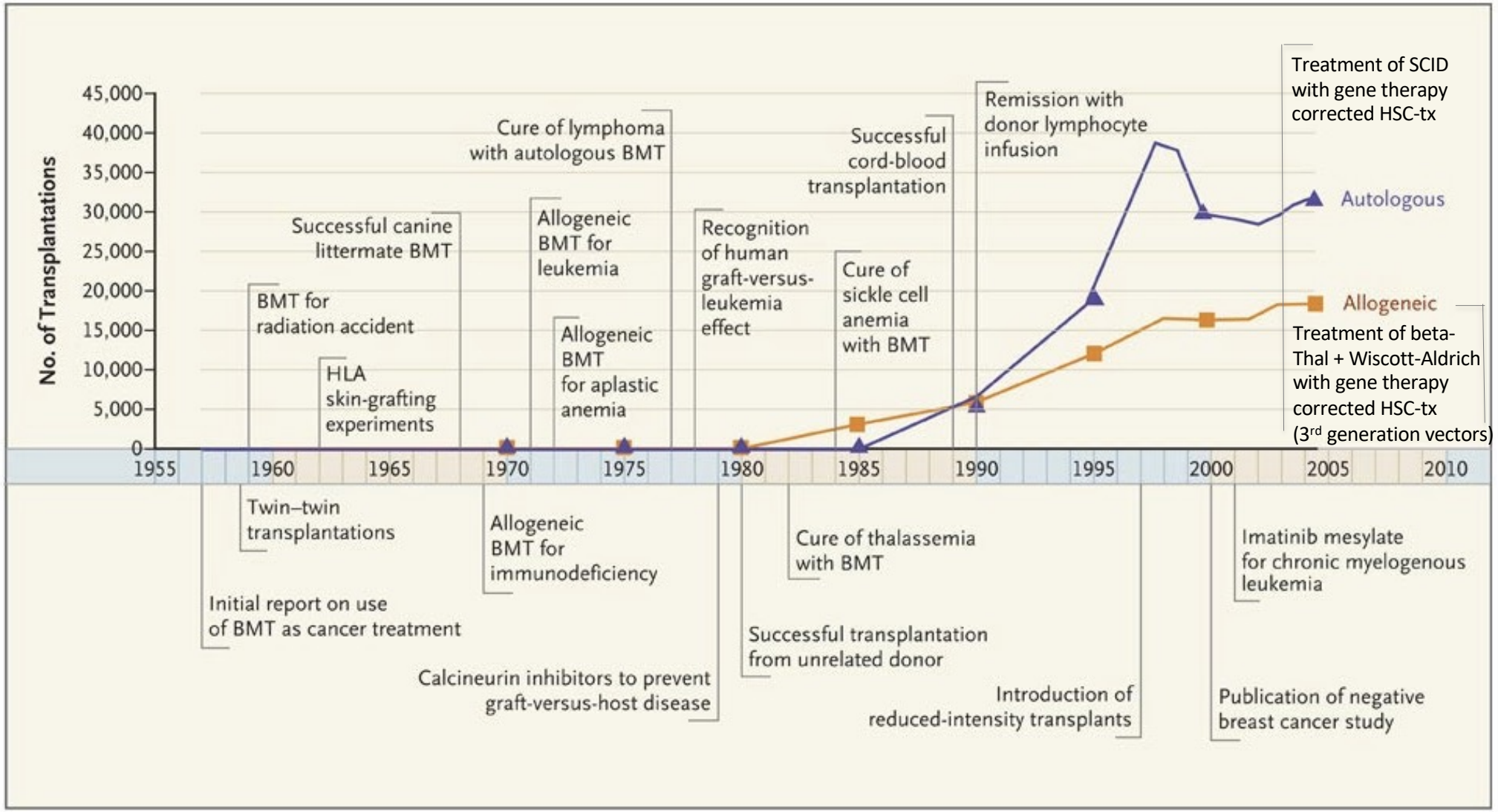
A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller, E. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, L. Caccavelli, J.-S. Diana, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarré, Y. Beuzard, S. Chrétien, T. Lefebvre, D.T. Teachey, U. Anurathapan, P.J. Ho, C. von Kalle, M. Kletzel, E. Vichinsky, S. Soni, G. Veres, O. Negre, R.W. Ross, D. Davidson, A. Petrusich, L. Sandler, M. Asmal, O. Hermine, M. De Montalembert, S. Hacein-Bey-Abina, S. Blanche, P. Leboulch, and M. Cavazzana

A “little” history of HSC transplantation…

HSCT + CRISPR-Cas9 gene editing -> first gene-edited HSCs transplanted to a patient (2019 sickle cell anemia)

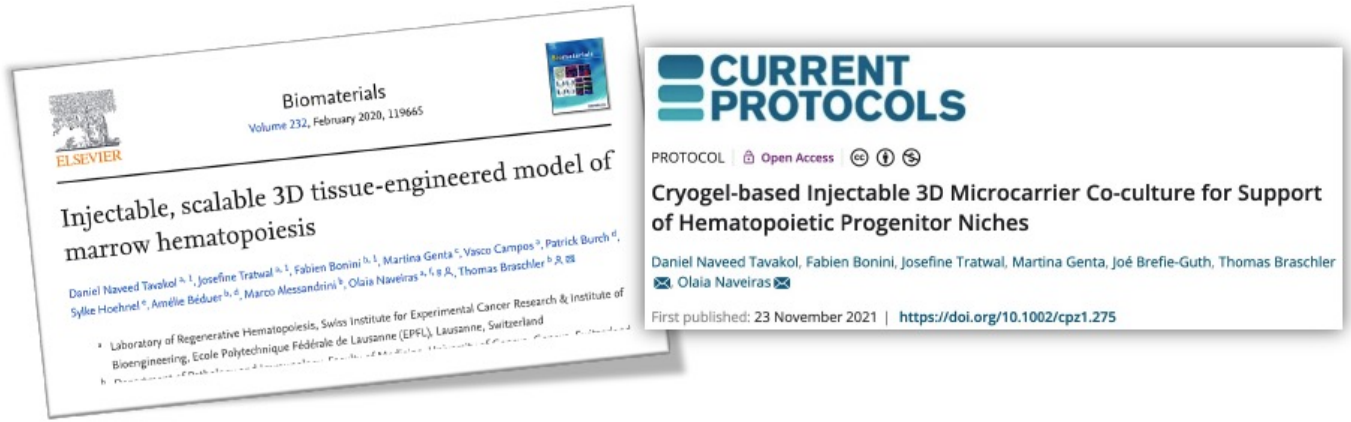


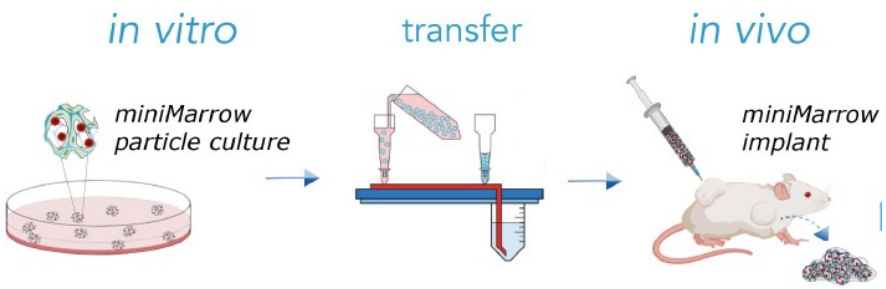
A “little” history of HSC transplantation…

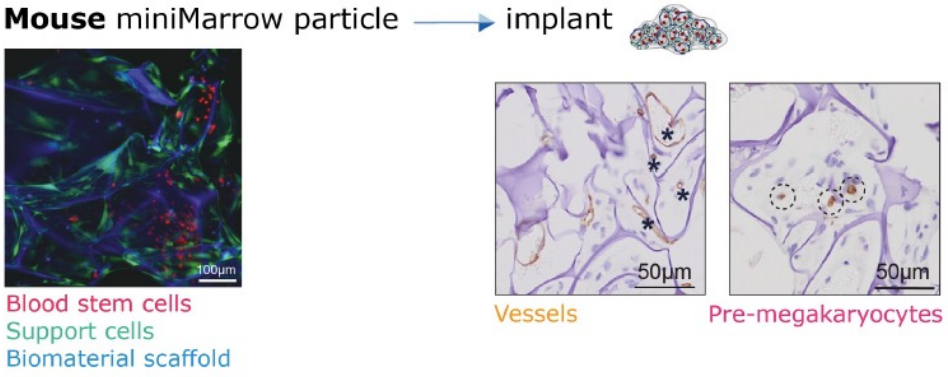


Updated from FR. Appelbaum, N Engl J Med 2007; 357:1472-1475

RECONSTRUCTING THE BM NICHE: boneless injectable niches inspired by myelolipomas





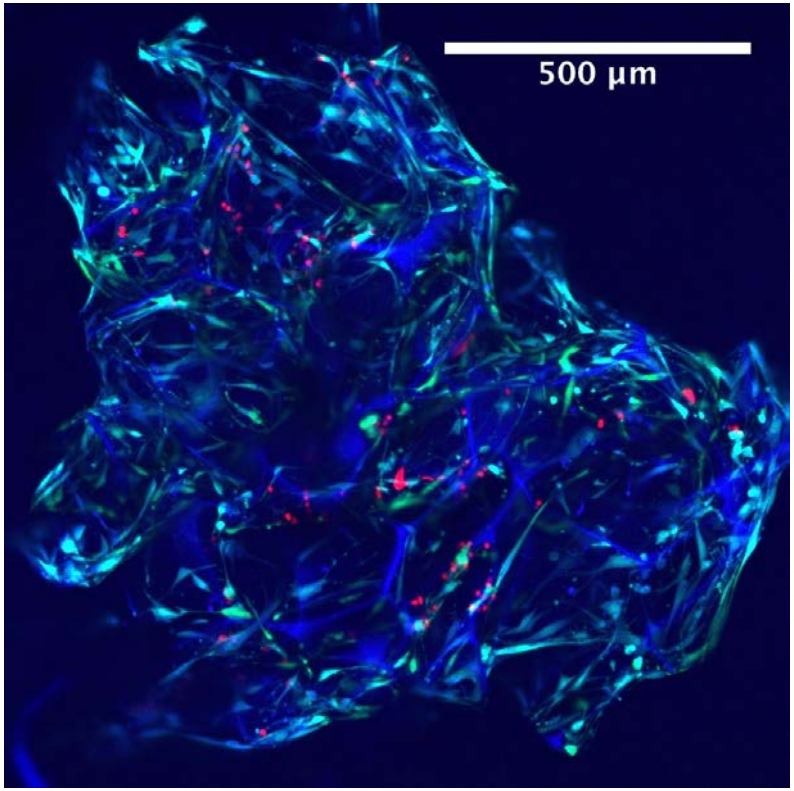


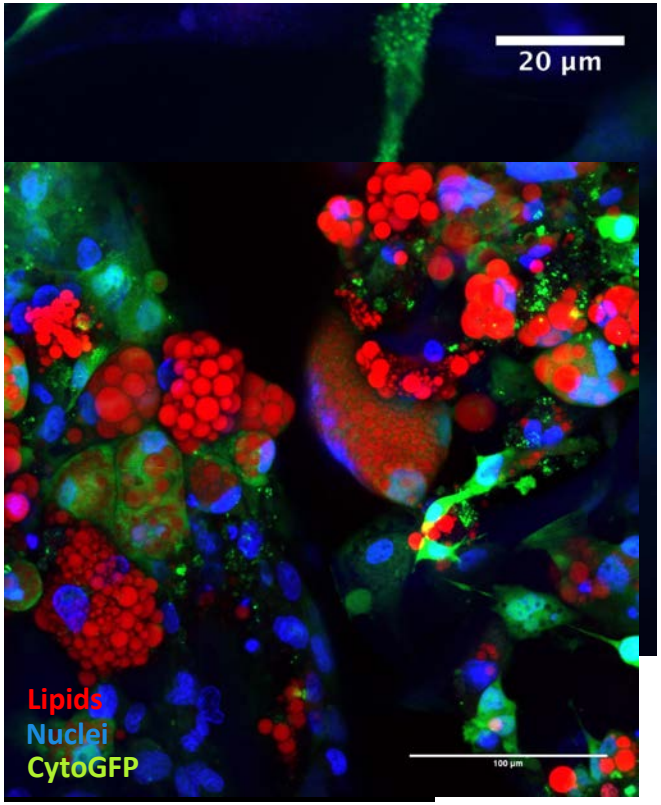
LABORATORY OF REGENERATIVE HEMATOPOIESIS

N. Tavakol, F. Bonnini*, J. Tratwal*, J. Brefie et al. 2020 and 2021*

CHUV Unil.

RECONSTRUCTING THE BM NICHE: boneless injectable niches inspired by myelolipomas

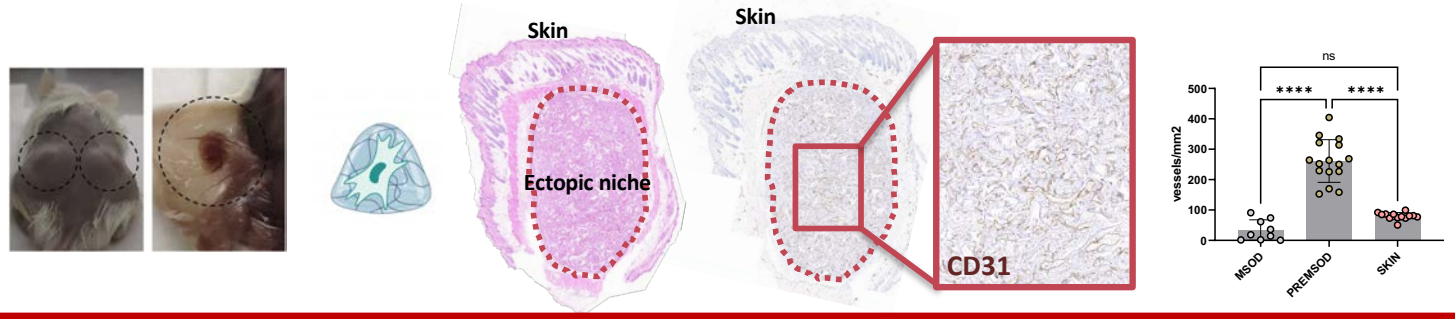




N. Tavakol, F. Bonnini*, J. Tratwal*,*
J. Brefie et al. 2020 and 2021

Can we reconstruct subcutaneous hematopoietic niches for clinical applications?

High vascular density and hematopoiesis in the MarrowPatch after 4 weeks in vivo (human into mouse)



F. Bonnini et al. in preparation

Questions ?

Olaia.Naveiras@unil.ch

LABORATORY OF
REGENERATIVE
HEMATOPOIESIS

MARROW
be a match

Don de cellules souches

Devenir donneur !

Insta : @Marrow_Lausanne


LABORATORY OF
REGENERATIVE
HEMATOPOIESIS


CHUV


Unil
UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Clinical applications of stem cells

Other key articles for reference

HSCT + gene therapy + IPS?

Cell, Vol. 109, 17–27, April 5, 2002, Copyright ©200

Correction of a Gen by Nuclear Transpla Combined Cell and

William M. Rideout III,[1,6] Konrad Hochedl
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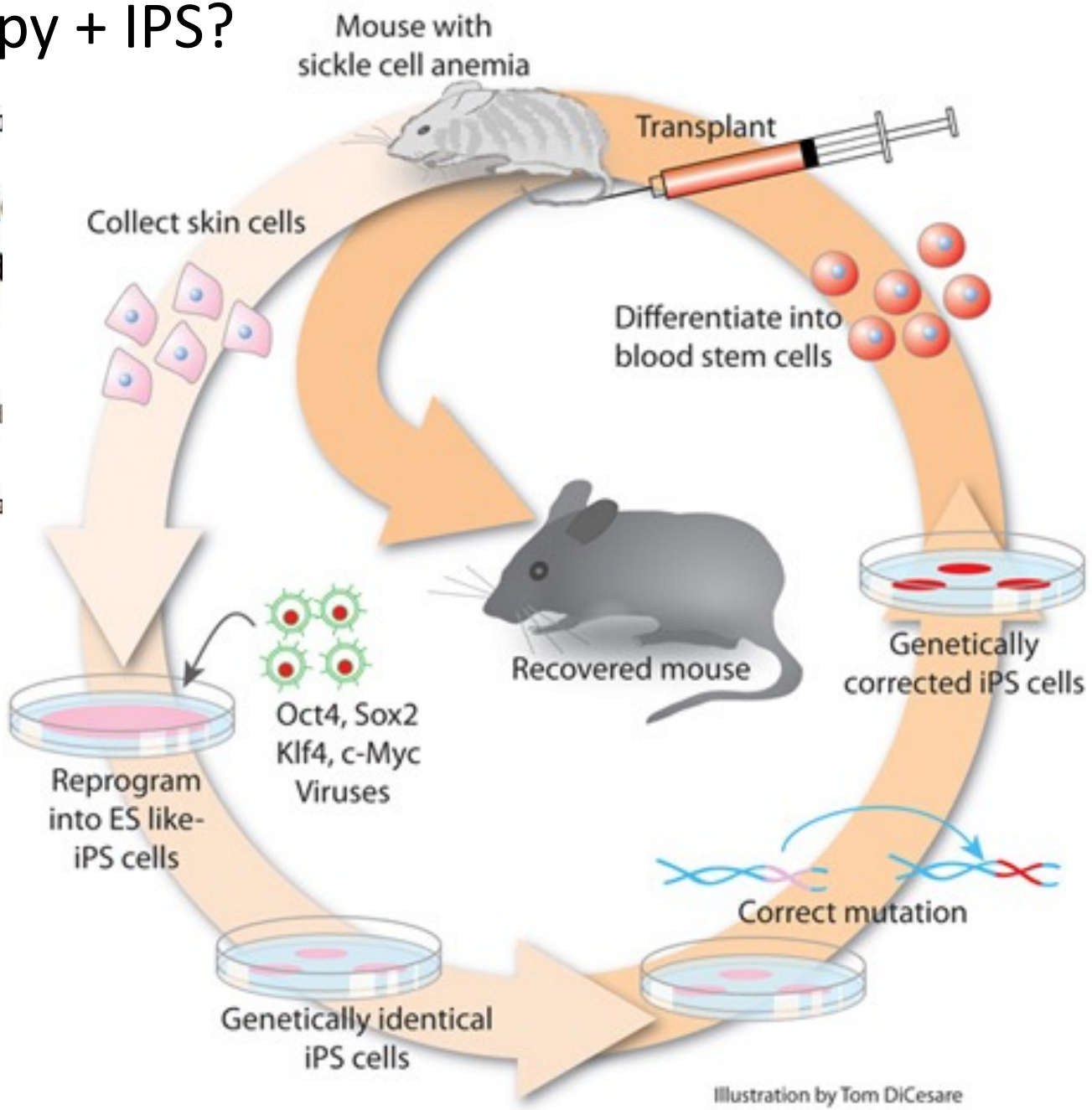

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HSCT + gene therapy + IPS?

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Correction of a Genetic Defect by Nuclear Transplantation and Combined Cell and Gene Therapy

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Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin

Jacob Hanna,[1] Marius Wernig,[1] Styliani Markoulaki,[1] Chiao-Wang Sun,[2]
Alexander Meissner,[1] John P. Cassady,[1,3] Caroline Beard,[1] Tobias Brambrink,[1]
Li-Chen Wu,[2] Tim M. Townes,[2]* Rudolf Jaenisch[1,3]*

New clinical landmark:
Inducing solid organ tolerance through HSCT

Transplantation. 2002 Nov 27;74(10):1405-9.

Induction of kidney allograft tolerance after transient lymphohematopoietic chimerism in patients with multiple myeloma and end-stage renal disease.

Bühler LH, Spitzer TR, Sykes M, Sachs DH, Delmonico FL, Tolkoff-Rubin N, Saidman SL, Sackstein R, McAfee S, Dey B, Colby C, Cosimi AB.

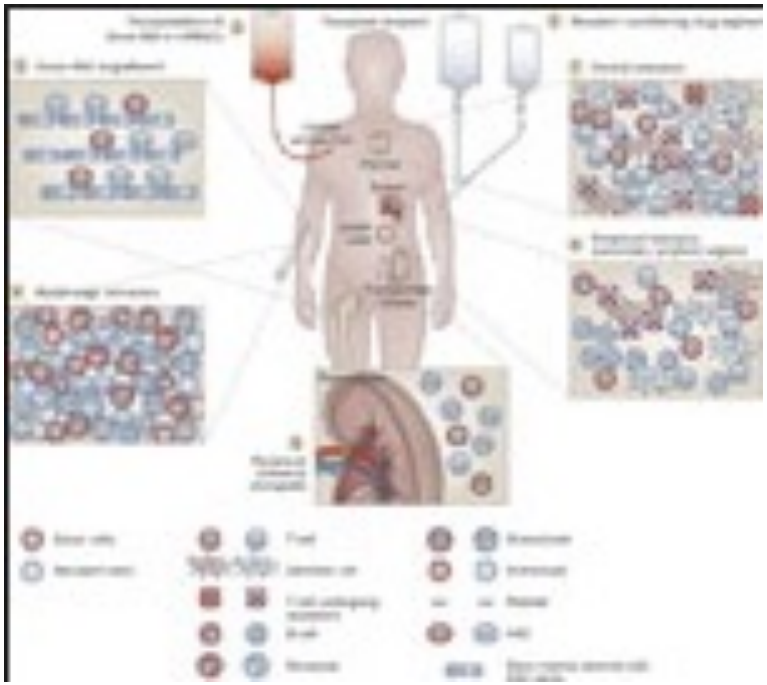
Department of Surgery, Massachusetts General Hospital, Boston, MA 02114, USA. leo.buhler@hcuge.ch

Transplantation. 2011 Mar 27;91(6):672-6. doi: 10.1097/TP.0b013e31820a3068.

Long-term follow-up of recipients of combined human leukocyte antigen-matched bone marrow and kidney transplantation for multiple myeloma with end-stage renal disease.

Spitzer TR, Sykes M, Tolkoff-Rubin N, Kawai T, McAfee SL, Dey BR, Ballen K, Delmonico F, Saidman S, Sachs DH, Cosimi AB.

Department of Medicine, Bone Marrow Transpl *Nature Reviews Nephrology* **6**, 594-605 (October 2010) @partners.org



Nature Reviews Nephrology **6**, 594-605 (October 2010)

Inducing solid organ tolerance through mixed chimerism
Patient testimonial (HSC + kidney transplant)

http://www.nationalstemcellfoundation.org/blog/patient_highlights/rob-waddell/

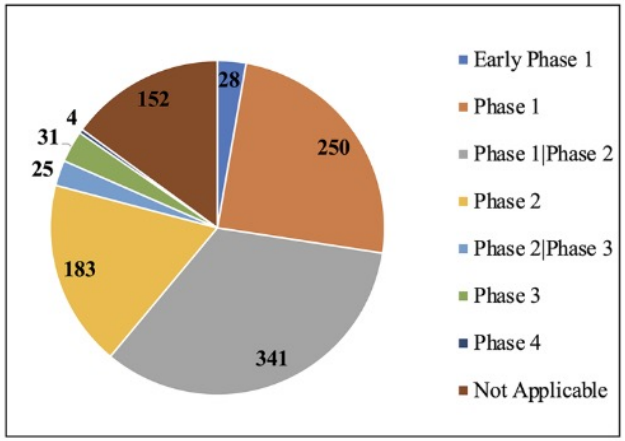
The importance of the niche / microenvironment
Clinical trials with Mesenchymal Stromal/Stem Cells

Stem Cell Reviews and Reports (2022) 18:1525–1545
https://doi.org/10.1007/s12015-022-10369-1

A Brief Overview of Global Trends in MSC-Based Cell Therapy

Dragomirka Jovic[1,2] · Yingjia Yu[1,2] · Dan Wang[3,4] · Kuixing Wang[4] · Hanbo Li[1,2] · Fengping Xu[1,2,4] · Chenglong Liu[4] · Junnian Liu[1,4] · Yonglun Luo[1,2,5,6]

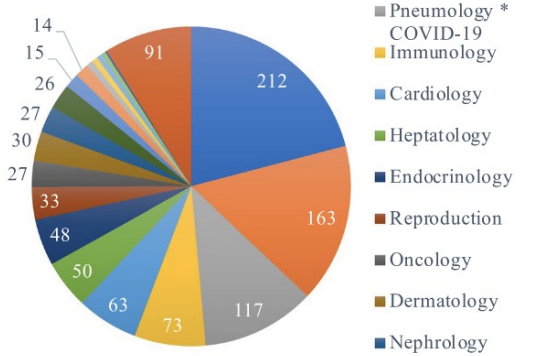
Accepted: 15 March 2022 / Published online: 28 March 2022



MSCs Clinical Trial Phases

B) Clinical trials classified by medical specialty-disease category

Medical specialty	Number of CT
Musculoskeletal	212
Neurology	163
Pneumology *	117
Immunology	73
Cardiology	63
Heptatology	50
Endocrinology	48
Reproduction	33
Oncology	27
Dermatology	30
Nephrology	27
Gastroenterology	26
Opthalmology	15
Anal Disorders	14
Aging	7
Urology	6
Hematology	6
Psychiatry	4
HIV	2
Other	91
Total	1014



*COVID-19 (65)