Shahid Beheshti University of Medical Sciences

HSCRC Hematopoietic stem cell research center

Graft Manipulation in Haploidentical Hematopoietic Stem Cell Transplantation

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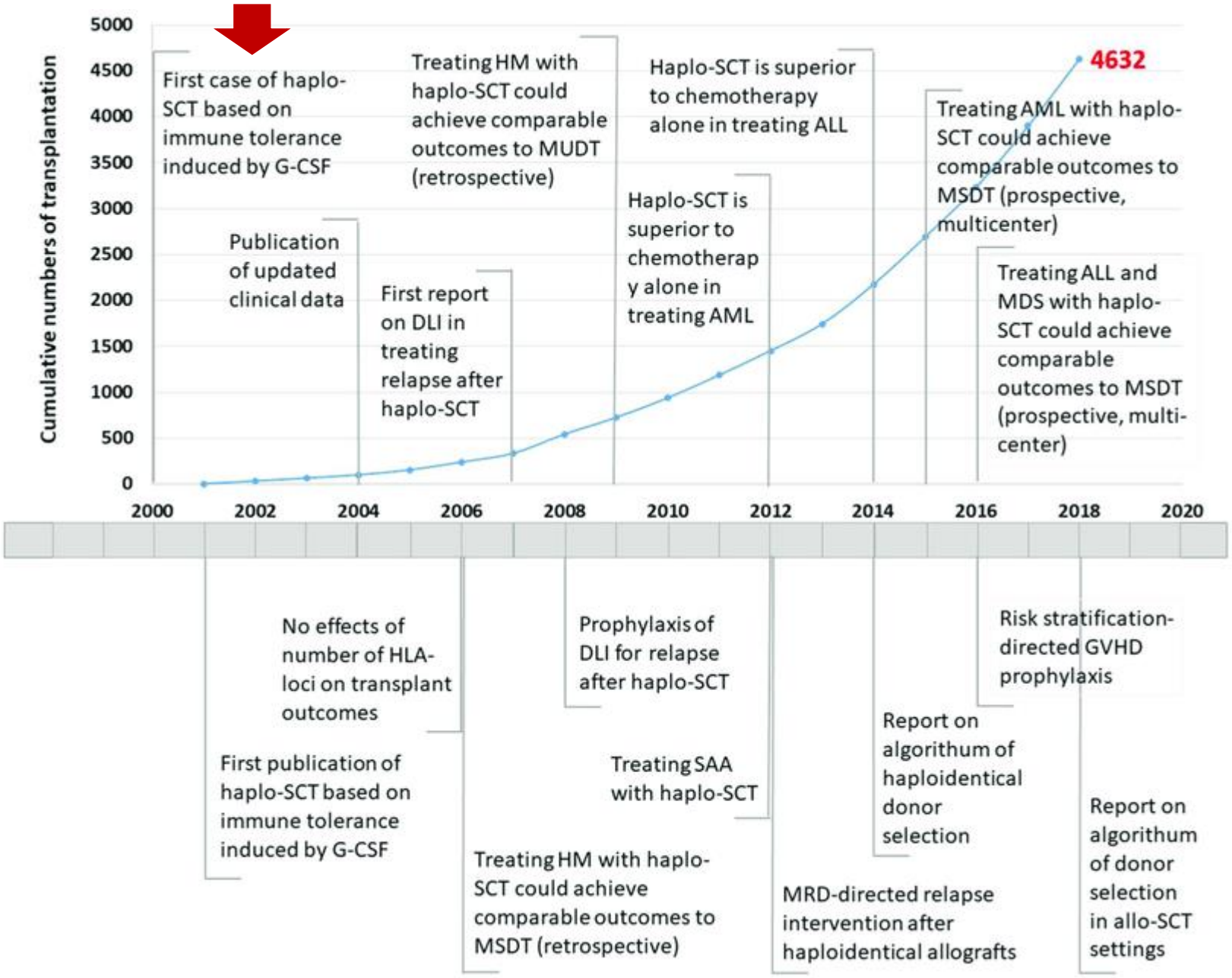
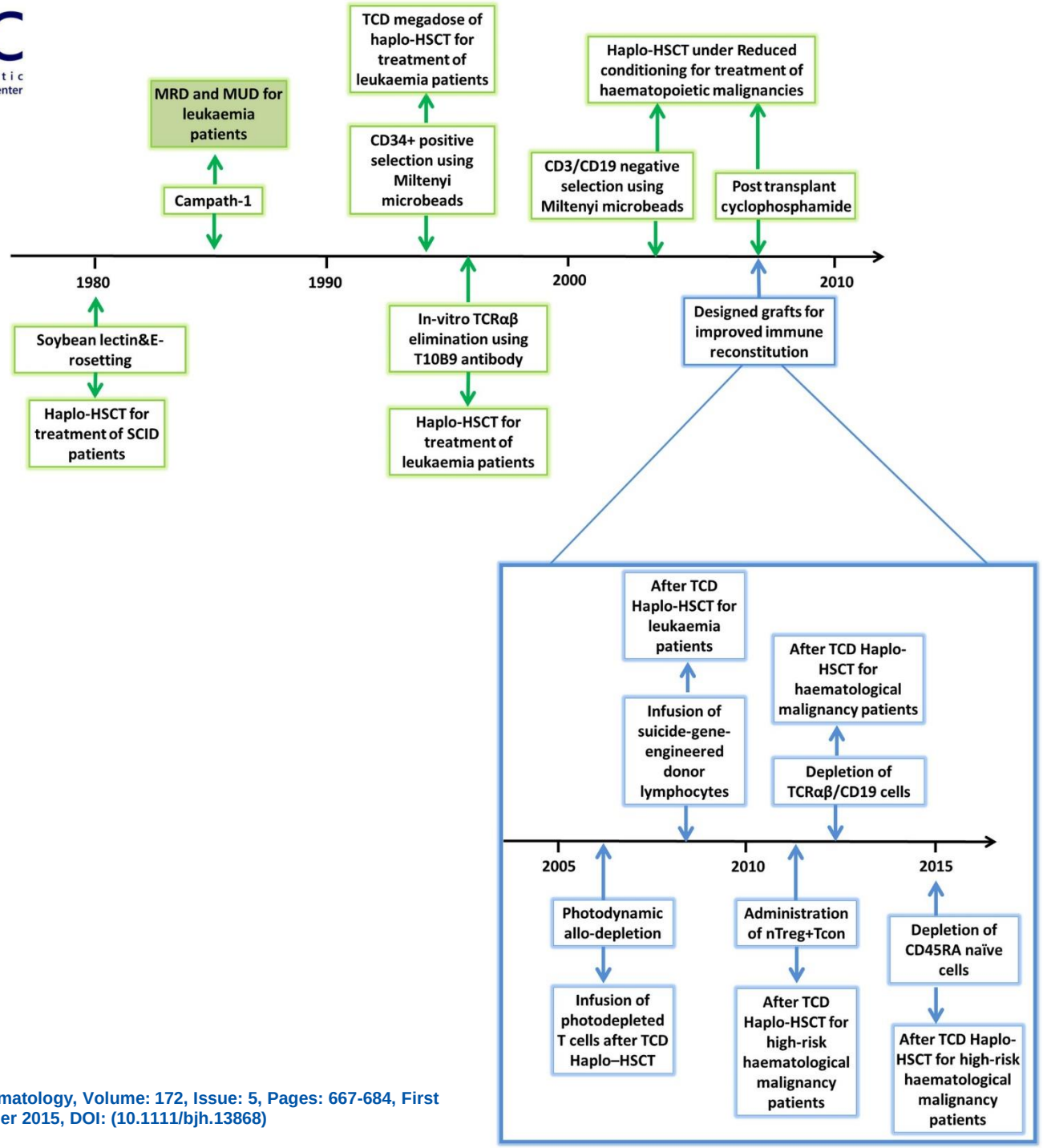
Timeline showing the number of haploidentical stem cell transplantation

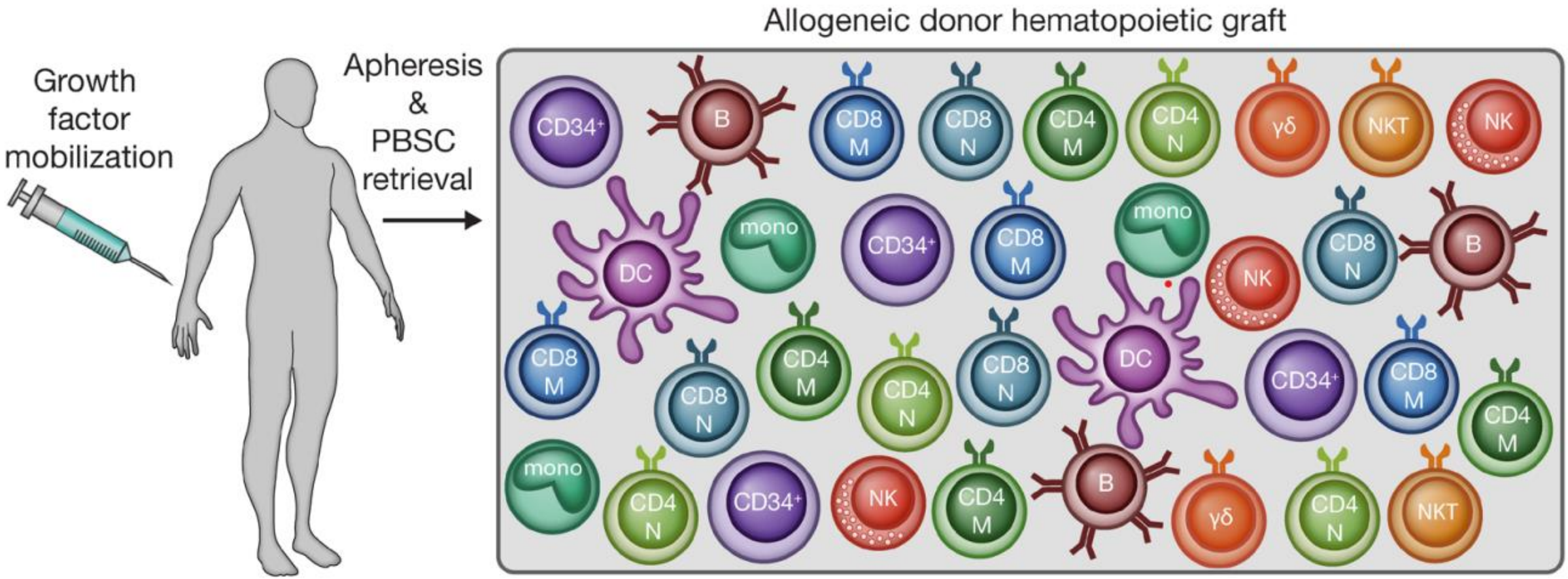


Chang(2019). Granulocyte Colony-Stimulating Factor-Primed Unmanipulated Haploidentical Blood and Marrow Transplantation. Frontiers in Immunology. 10. 2516. 10.3389/fimmu.2019.02516.

The evolution of graft manipulation in haploidentical stem-cell transplantation



British Journal of Haematology, Volume: 172, Issue: 5, Pages: 667-684, First published: 18 December 2015, DOI: (10.1111/bjh.13868)

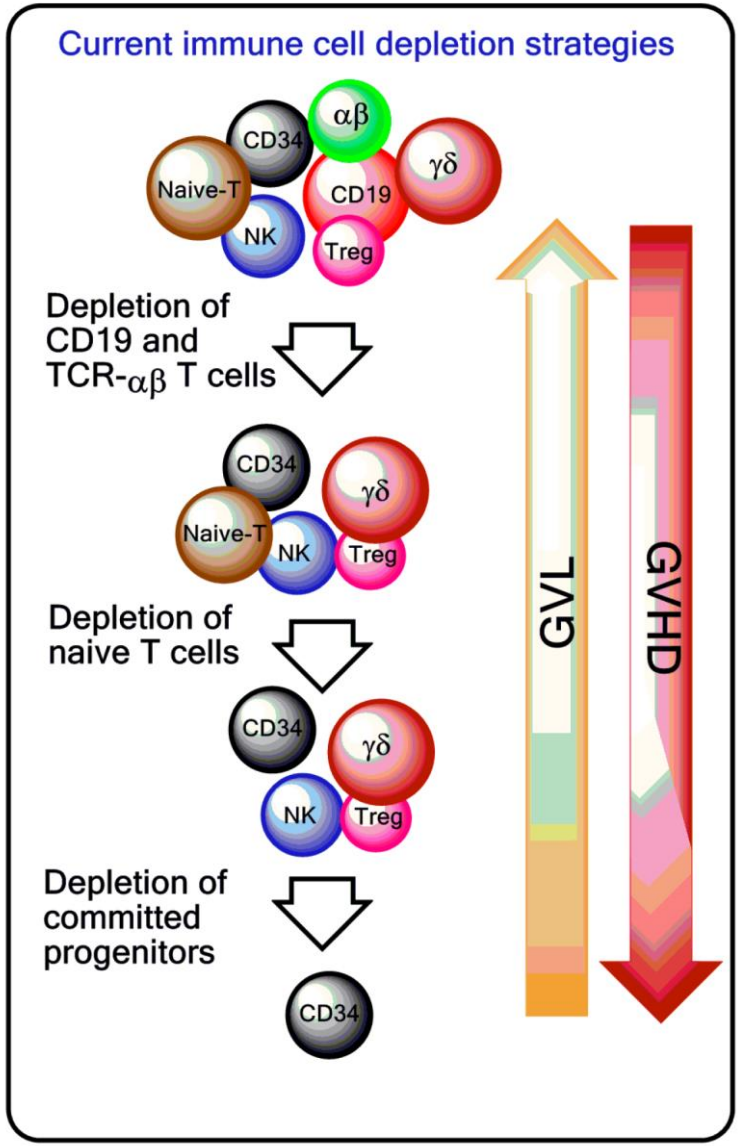

Growth
factor
mobilization
Apheresis
&
PBSC
retrieval
Allogeneic donor hematopoietic graft
CD34+
B
CD8
M
CD8
N
CD4
M
CD4
N
γδ
NKT
NK
DC
mono
CD34+
CD8
M
mono
NK
CD8
N
B
CD8
M
CD4
M
CD8
N
CD4
N
CD8
N
DC
CD34+
CD8
M
CD4
M
mono
CD4
N
CD34+
NK
CD4
M
B
γδ
CD4
N
NKT

Methods of T-cell depletion

Ex vivo methods	In vivo methods
Negative selection of T cells • Soybean lectin agglutination with E-rosette depletion. • Antibody-mediated – Monoclonal antibody with complement or immunotoxin. – Monoclonal antibody with immunomagnetic beads. Positive selection of CD34+ cells • Monoclonal antibody with immunomagnetic beads	Polyclonal ATG • Atgam (horse) • Thymoglobulin (rabbit) • ATG-Fresenius (rabbit) Monoclonal antibody • Alemtuzumab (anti-CD52) post-transplant cyclophosphamide (PTCy)

- Recently, the use of high-dose post-transplant cyclophosphamide following infusion of a T-cell replete graft is revolutionizing haplo HSCT.

- However, there remain several unmet needs to improve haplo HSCT outcome such as improving post-transplant immune reconstitution, which may also decrease relapse rate (in particular with the use of reduced intensity conditioning regimens).



1995

1. CD34+ Selection „pure stem cells“

2. CD3/19 Depletion
Stem cells + effectors (NK cells)

3. TCRαβ/CD19 Depletion
Stem cells + effectors (NK cells + γδT cells)

\+ 4. Antigen-specific T cells

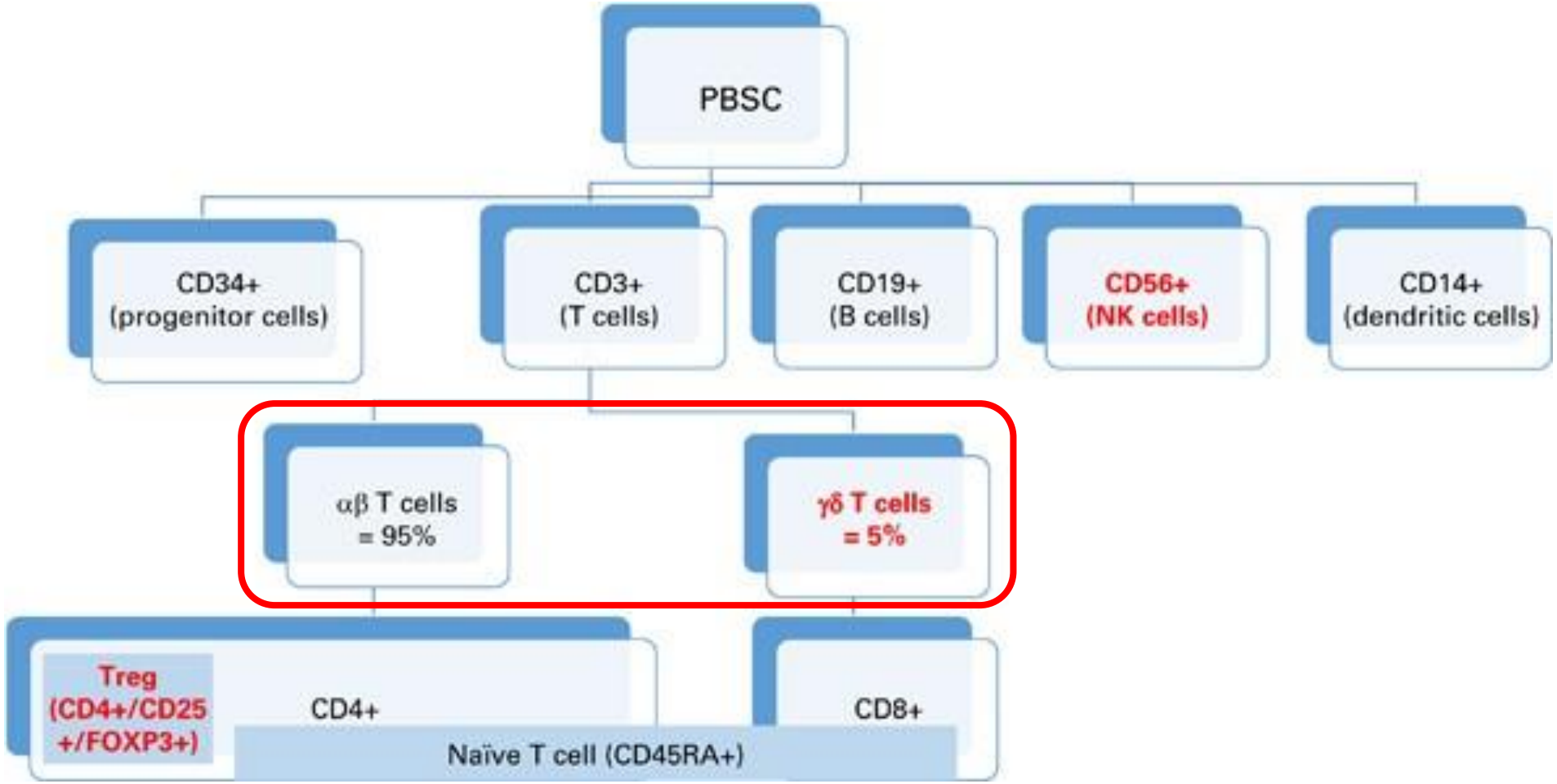
2011

The rationale of the initial combined depletion of donor CD3+ T-cell and CD19+ B cells is to eliminate the T cells that mediate GVHD, and B cells that are implicated in EBV-driven post-transplantation lymphoproliferative disorders and possibly decreasing risk of cGVHD as well.

Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: a phase II study

Birgit Federmann,[1] Martin Bornhauser,[2] Christoph Meisner,[3] Lambros Kordelas,[4] Dietrich W. Beelen,[4] Gernot Stuhler,[5] Matthias Stelljes,[6] Rainer Schwerdtfeger,[7] Maximilian Christopeit,[8] Gerhard Behre,[8]* Christoph Faul,[1] Wichard Vogel,[1] Michael Schumm,[9] Rupert Handgretinger,[9] Lothar Kanz,[1] and Wolfgang A. Bethge[1]

[1]Medical Center, Department of Hematology & Oncology, University of Tuebingen; [2]Medical Center, University of Dresden; [3]Department of Medical Biometrics, University of Tuebingen; [4]Department of Bone Marrow Transplantation, West German Cancer Centre, University Hospital Essen, University of Duisburg-Essen; [5]Medical Center, University of Wuerzburg; [6]Medical Center, University of Muenster; [7]Medical Center, Deutsche Klinik für Diagnostik, Wiesbaden; [8]Medical Center, University of Halle; and [9]Children's Hospital, University of Tuebingen, Germany


PBSC
CD34+
(progenitor cells)
CD3+
(T cells)
CD19+
(B cells)
CD56+
(NK cells)
CD14+
(dendritic cells)
αβ T cells
= 95%
γδ T cells
= 5%
Treg
(CD4+/CD25
+/FOXP3+)
CD4+
CD8+
Naïve T cell (CD45RA+)

- Immune reconstitution studies revealed that NK cell recovery was significantly greater in patients that received αβ TCD grafts than those who received unmanipulated grafts through the first year post transplant.

- Sparing of γδ T cells allowed transplantation of a partially T-cell depleted marrow graft, which resulted in favorable homeostatic reconstitution of γδ T cells in a significant subset of patients compared with that observed with patients receiving OKT3-depleted grafts.

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Influence of T cell depletion method on circulating γδ T cell reconstitution and potential role in the graft-versus-leukemia effect

LS Lamb Jr[1], AP Gee[1,2], LJ Hazlett[1,3], P Musk[1], RS Parrish[1,3], TP O'Hanlon[4], SS Geier[1], RS Folk[1], WG Harris[1], K McPherson[1], C Lee[1] and PJ Henslee-Downey[1]

[1]*Division of Transplantation Medicine, Palmetto Richland Memorial Hospital, Center for Cancer Treatment and Research, University of South Carolina School of Medicine, Columbia, South Carolina, USA*

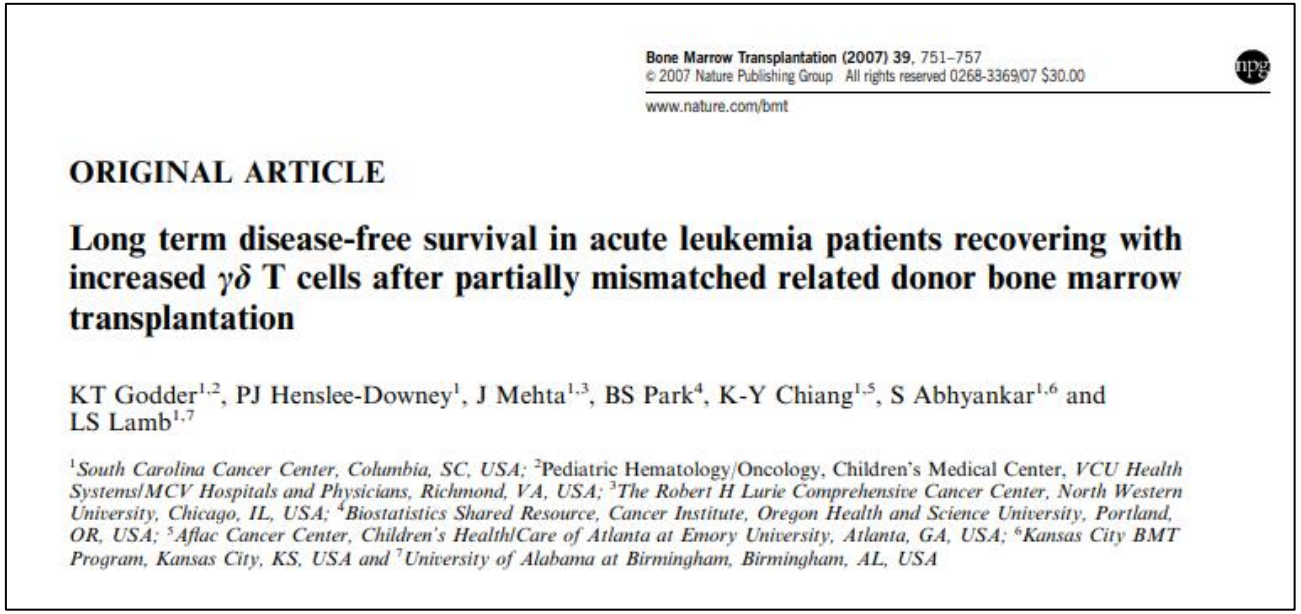
[2]*Center for Gene Therapy, Baylor College of Medicine, Houston, Texas, USA*

[3]*South Carolina Cancer Center, Division of Biometry and Research Computing, 15 Richland Medical Park, Columbia, South Carolina, USA*

[4]*United States Food and Drug Administration, Bethesda, Maryland, USA*

- Decreased relapse rate was noted among haplo HSCT using αß TCD compared with haplo CD3+ pan TCD.

- A subset of patients that received haplo αßTCD transplant showed homeostatic reconstitution of increased peripheral blood γδ T-cell counts that correlated with showed a significant improvement in relapse-free survival.



Bone Marrow Transplantation (2007) 39, 751–757

www.nature.com/bmt

ORIGINAL ARTICLE

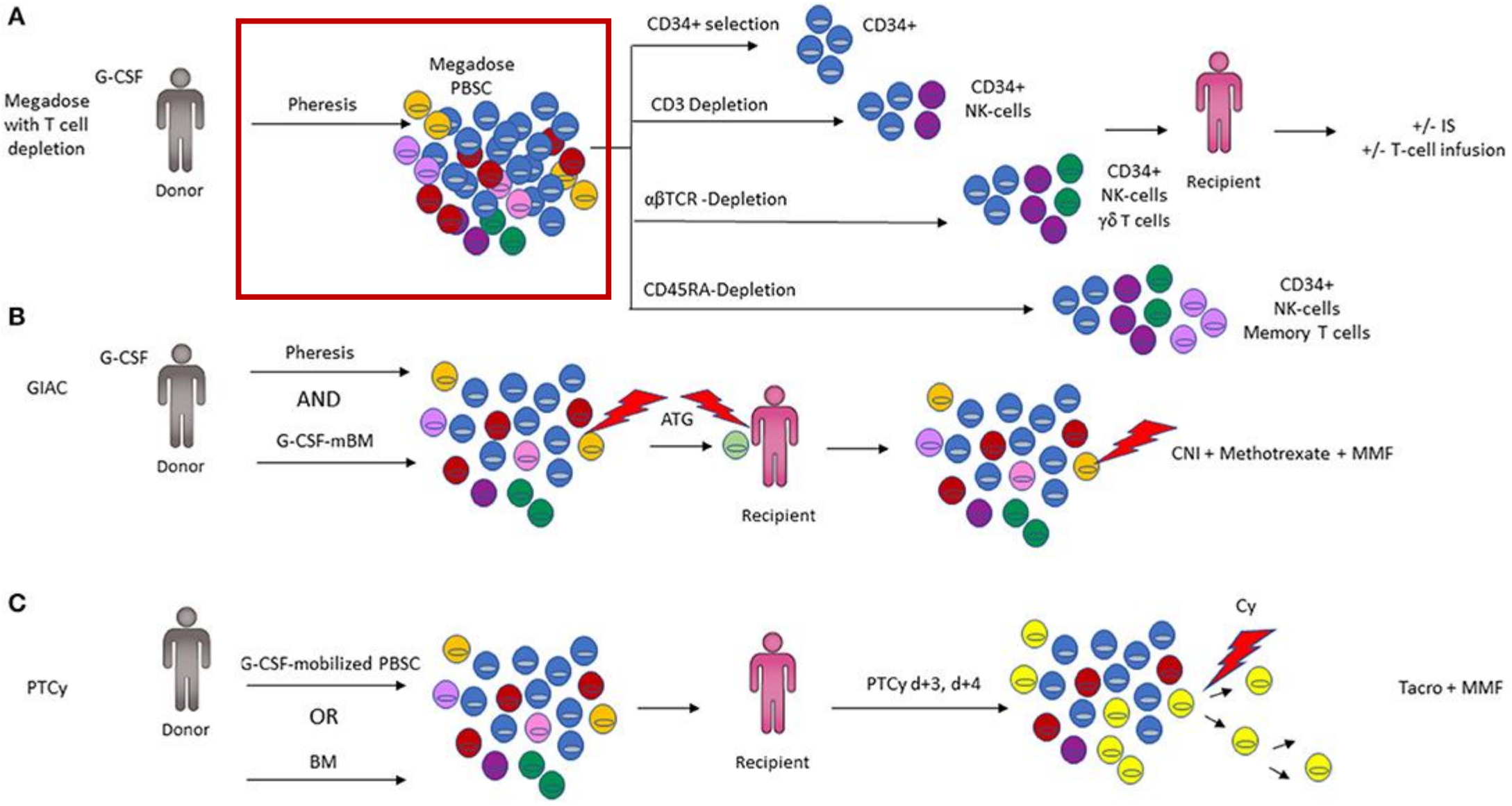
Long term disease-free survival in acute leukemia patients recovering with increased γδ T cells after partially mismatched related donor bone marrow transplantation

KT Godder[1,2], PJ Henslee-Downey[1], J Mehta[1,3], BS Park[4], K-Y Chiang[1,5], S Abhyankar[1,6] and LS Lamb[1,7]

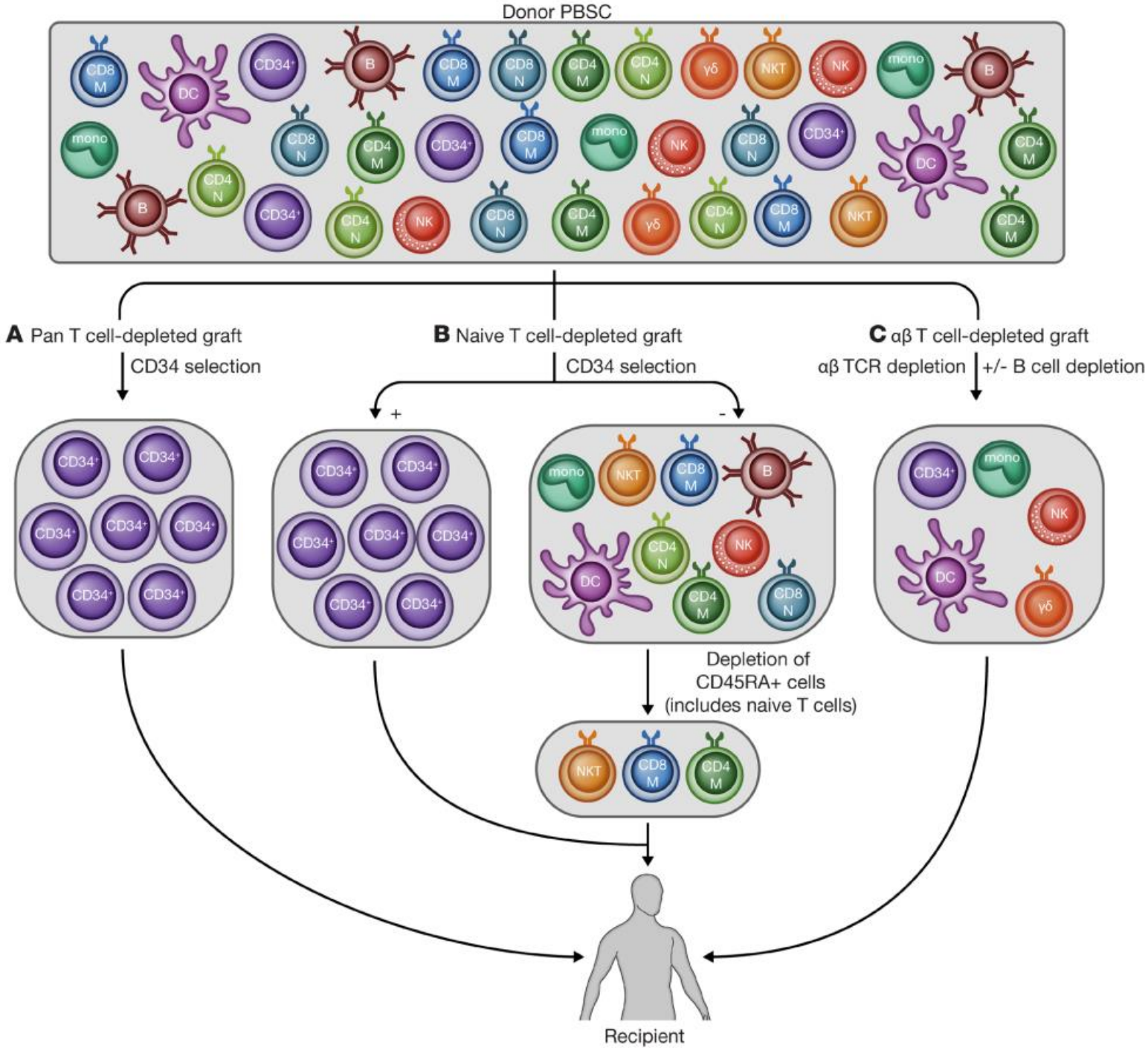
[1]*South Carolina Cancer Center, Columbia, SC, USA;* [2]Pediatric Hematology/Oncology, Children's Medical Center, *VCU Health Systems/MCV Hospitals and Physicians, Richmond, VA, USA;* [3]*The Robert H Lurie Comprehensive Cancer Center, North Western University, Chicago, IL, USA;* [4]*Biostatistics Shared Resource, Cancer Institute, Oregon Health and Science University, Portland, OR, USA;* [5]*Aflac Cancer Center, Children's Health/Care of Atlanta at Emory University, Atlanta, GA, USA;* [6]*Kansas City BMT Program, Kansas City, KS, USA and* [7]*University of Alabama at Birmingham, Birmingham, AL, USA*

- The survival advantage associated with high circulating numbers of γδ T cells was found to be durable over seven years following HSCT.

- Preservation of γδ T cells can also potentially protect against infections



Baumeister SHC, Rambaldi B, Shapiro RM and Romee R (2020) Key Aspects of the Immunobiology of Haploidentical Hematopoietic Cell Transplantation. *Front. Immunol.* 11:191. doi: 10.3389/fimmu.2020.00191


Donor PBSC
A Pan T cell-depleted graft
CD34 selection
B Naive T cell-depleted graft
CD34 selection
+
-
C αβ T cell-depleted graft
αβ TCR depletion
+/- B cell depletion
Depletion of
CD45RA+ cells
(includes naive T cells)
Recipient