New Era OF Allo-SCT

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Disclosure statement

CONFLICT OF INTEREST DISCLOSURES

I have no personal or financial interests to declare

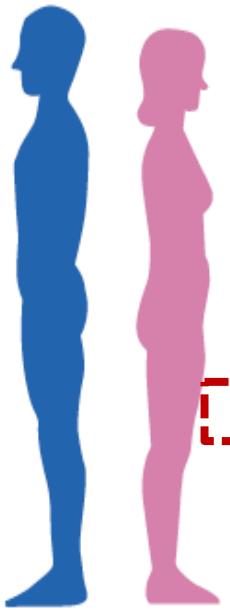
Leukemia: A Life-Threatening Malignancy

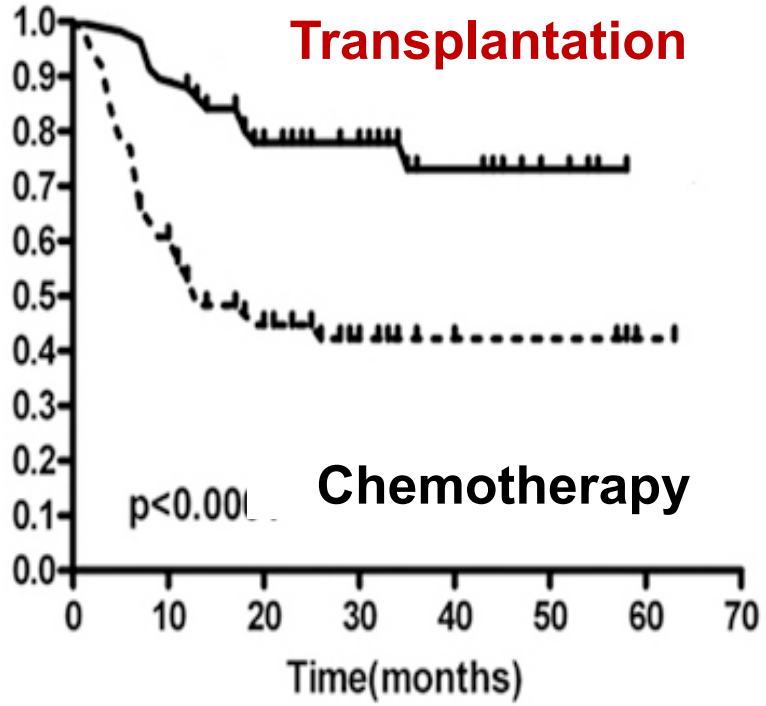
Allo-HSCT remains a curative therapy for leukemia

Mortality of Cancer

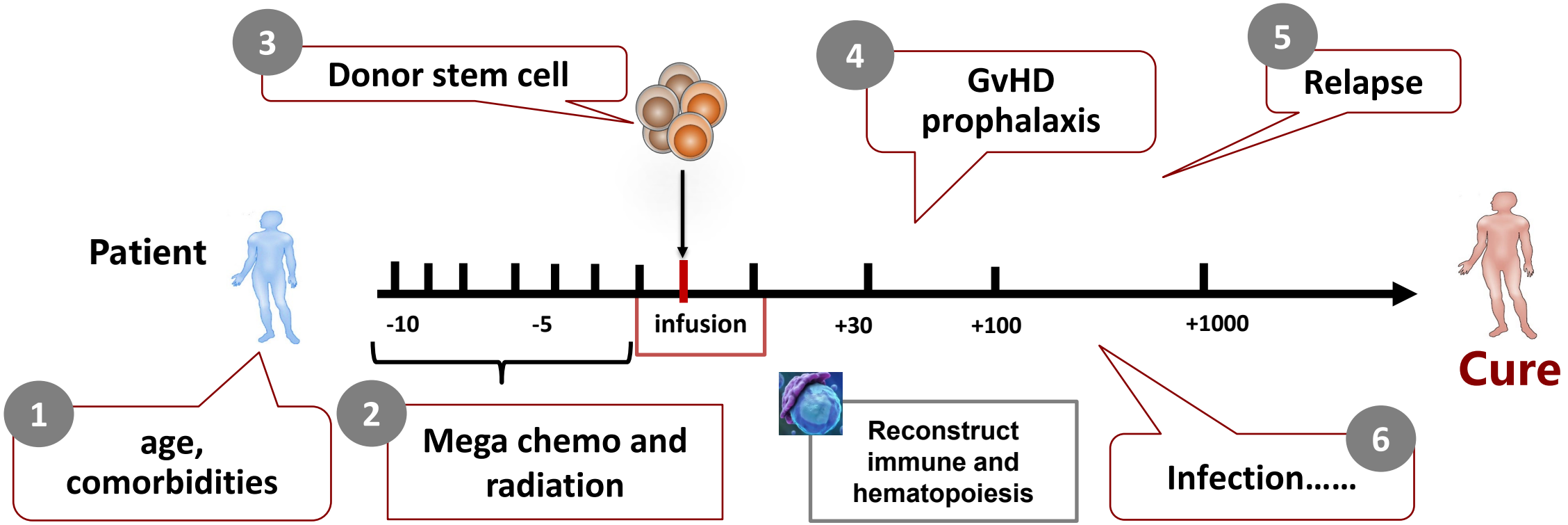
Estimated Deaths

Males			Females		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**	**All Sites**	**285,210**	**100%**





HSCT as Therapeutic Platform



Indications of HSCT

70 Types: **Leukemia,** Inherited Disease, ……

Ciurea SO, et al. Blood Rev. 2015; 29(2): 63-70

Beatty PG, et al. N Eng J Med. 1985; 313(13): 765-71

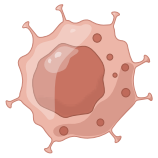
O'Reilly RJ, et al. Bone Marrow Transplant. 1988; (3): 3-6

Szydlo R, et al. J Clin Oncol. 1997; 15(5): 1767-77

Donor T cells play critical role in allo-HSCT

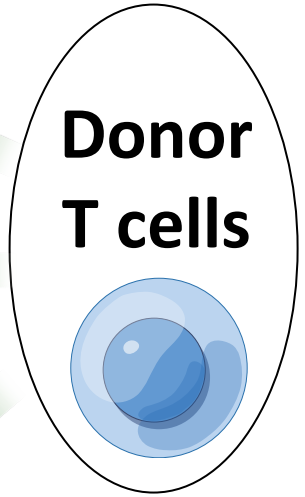
Advantages

Pro- Engraftment



Anti-Leukemia

Anti-infection



Disadvantages

Graft-v-Host

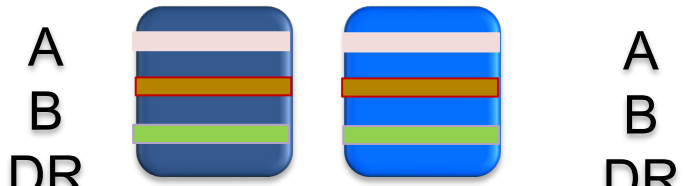
Skin

ileum

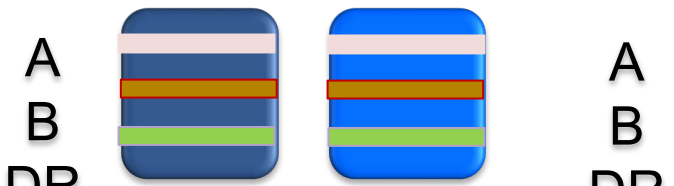
Human HLA Barrier

Haplo-HSCT had been “Forbidden”

	HLA Matched	HLA Haplo-
GvHD	20-30%	70-90% ↑
Engraftment	95-99%	50-81% ↓
Non-Relapse Mortality	10-30%	50-70%
Overall Survival	60-70%	10-20% ↓



Donor

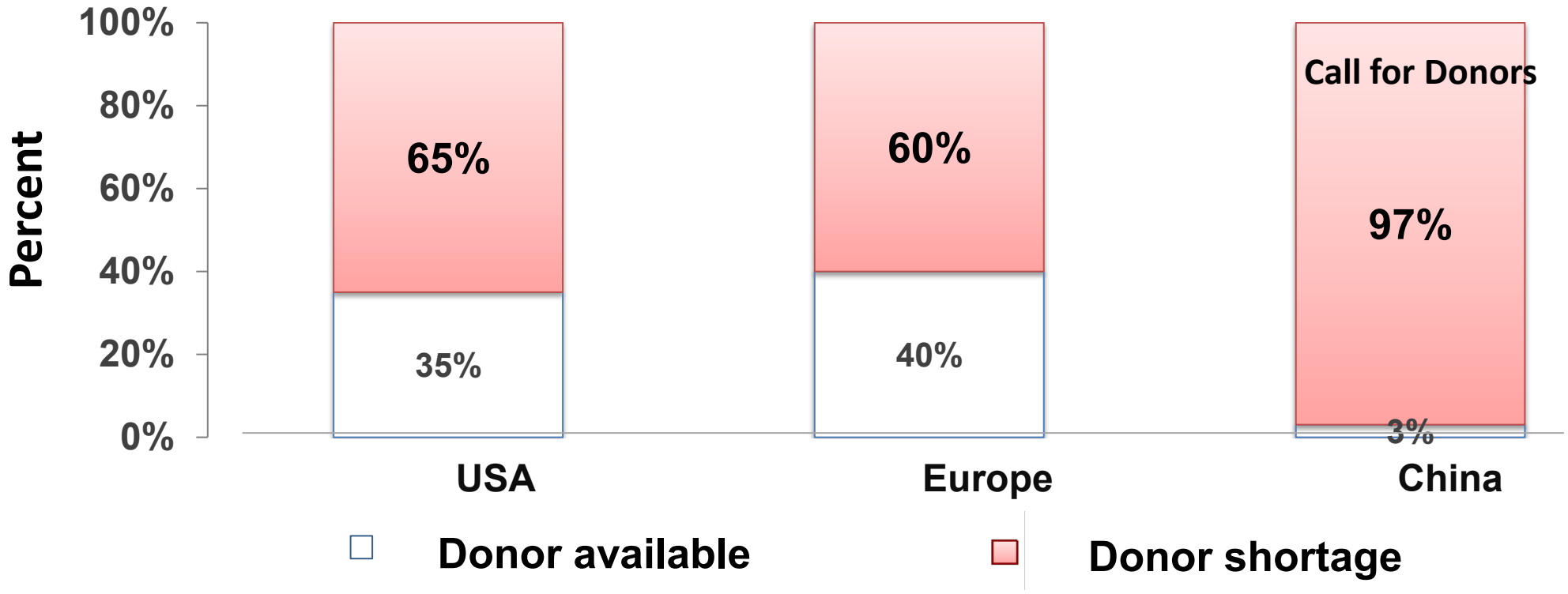


Recipient

Donor had been restricted to HLA-Matched before 2000

Ciurea SO, et al. Blood Rev. 2015; 29(2): 63-70
Beatty PG, et al. N Eng J Med. 1985; 313(13): 765-71
O’Reilly RJ, et al. Bone Marrow Transplant. 1988; (3): 3-6
Szydlo R, et al. J Clin Oncol. 1997; 15(5): 1767-77

Donor shortage had been a challenge over the world



Donor had been restricted to HLA-Matched before 2000

USA 2017 (www.cibmtr.org)、Europe 2017 (Passweg J. R. Bone Marrow Transplant 2019)、Chinese Registry 2018

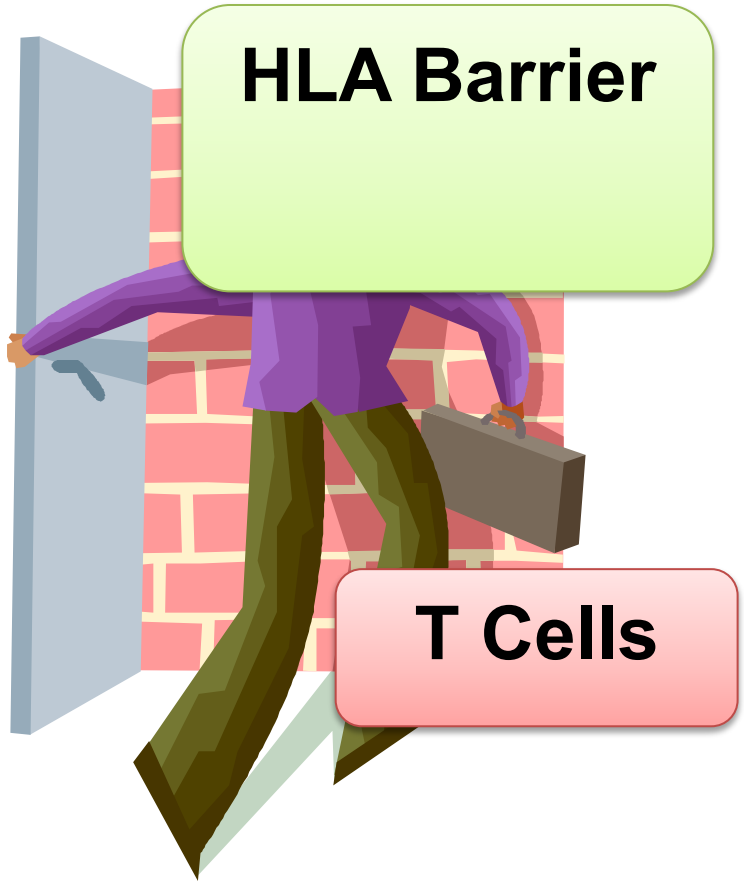
Aljurf M, et al. Bone Marrow Transplant. 2019; 54(8): 1179-1188

Miranda-Filho A, et al. Lancet Haematol. 2018; 5(1): e14-e24

Chen WQ, et al. Chin J Cancer Res. 2018; 30(1): 1-12

Chin Hematology 1999; 20(2).91-93

How to make a breakthrough for haplo-HSCT ?



T cell Suppression

1990s USA

X

Can we decrease GVHD by regulating T Cell function without T cell depletion?

1997-2000s Our team

?

Huang XJ. et al. Journal of Peking University(Health). 2004(36) (Corresponding)
Huang XJ. et al. Biol Blood Marrow Transplant. 2009; 15(2) (Corresponding)
Huang XJ. et al. Front Immunol. 2019. (Corresponding)
Huang XJ. et al. Bone Marrow Transplant. 2006; 38(4) (Corresponding)

How to make a breakthrough for haplo-HSCT ?

Can we decrease GVHD by regulating T Cell function without T cell depletion?

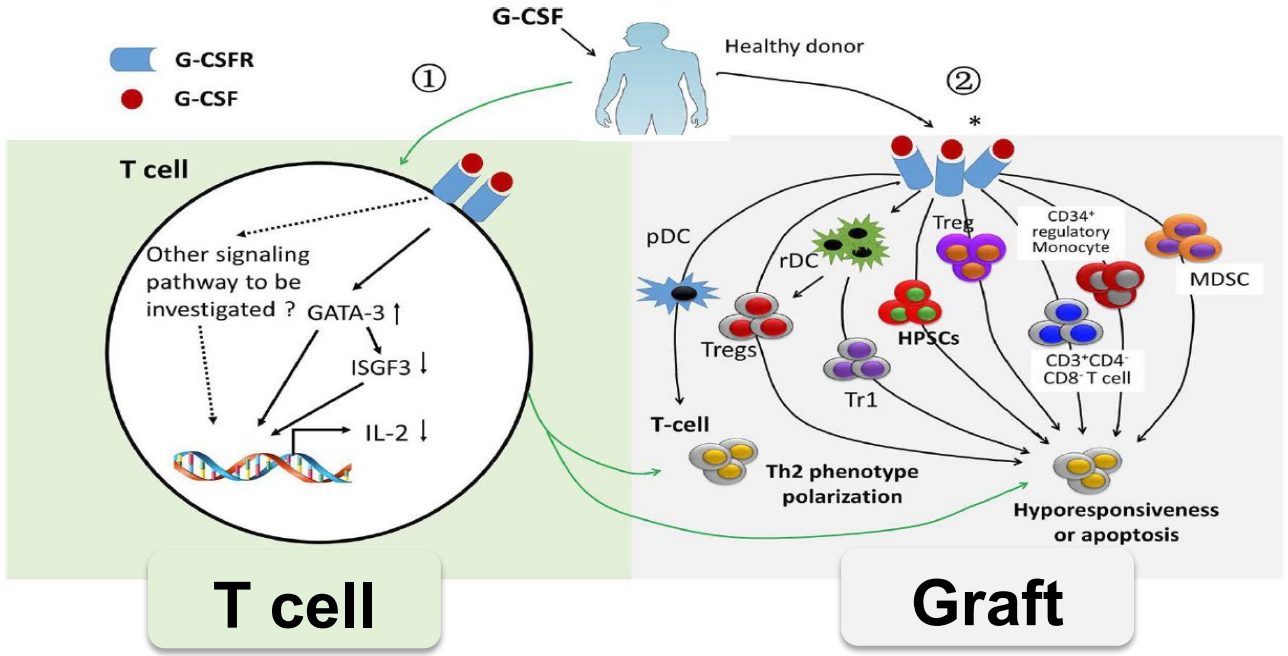
?

1997-2000s Our team

G-CSF

① T cell hypo-responsiveness

② Chang graft composition



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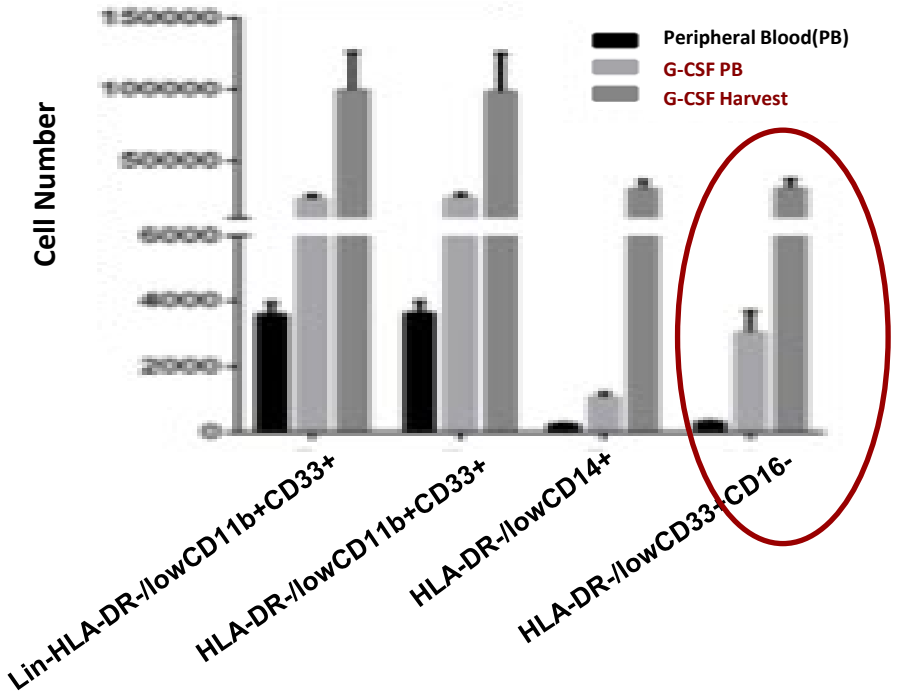
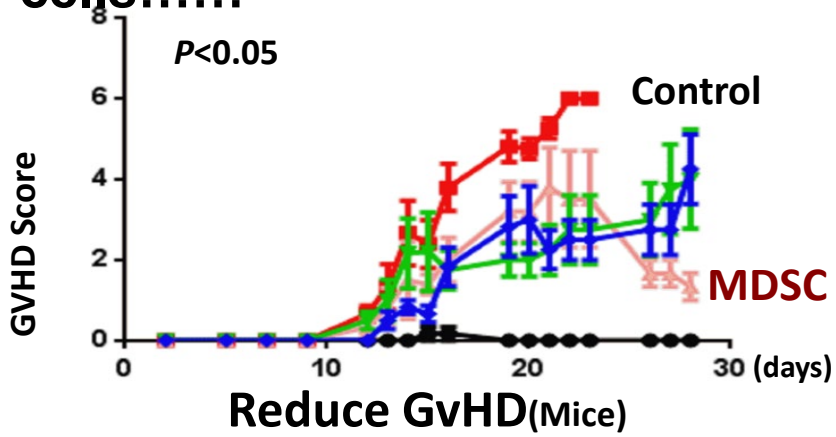
Huang XJ. et al. Front Immunol. 2019. (Corresponding)
Huang XJ. et al. Bone Marrow Transplant. 2006; 38(4) (Corresponding)

In vivo application of G-CSF decreased GVHD

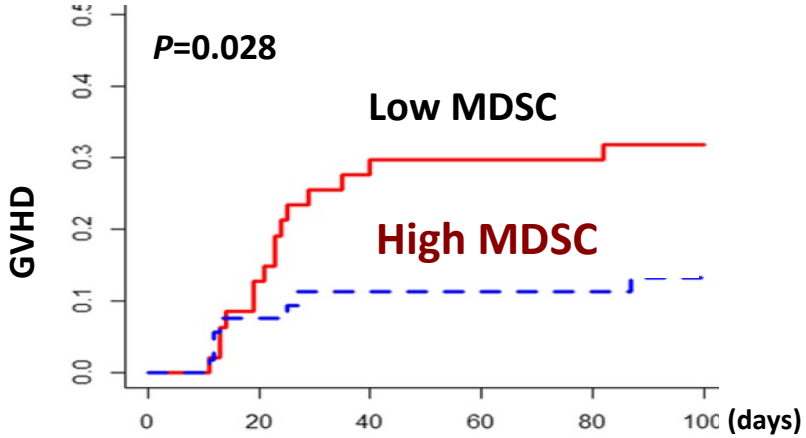
G-CSF → Donor → Expansion → **New MDSCs, Regulatory B cells……**

Ex: Myeloid-derived suppressor cells (MDSCs)





Reduce GvHD(Mice)

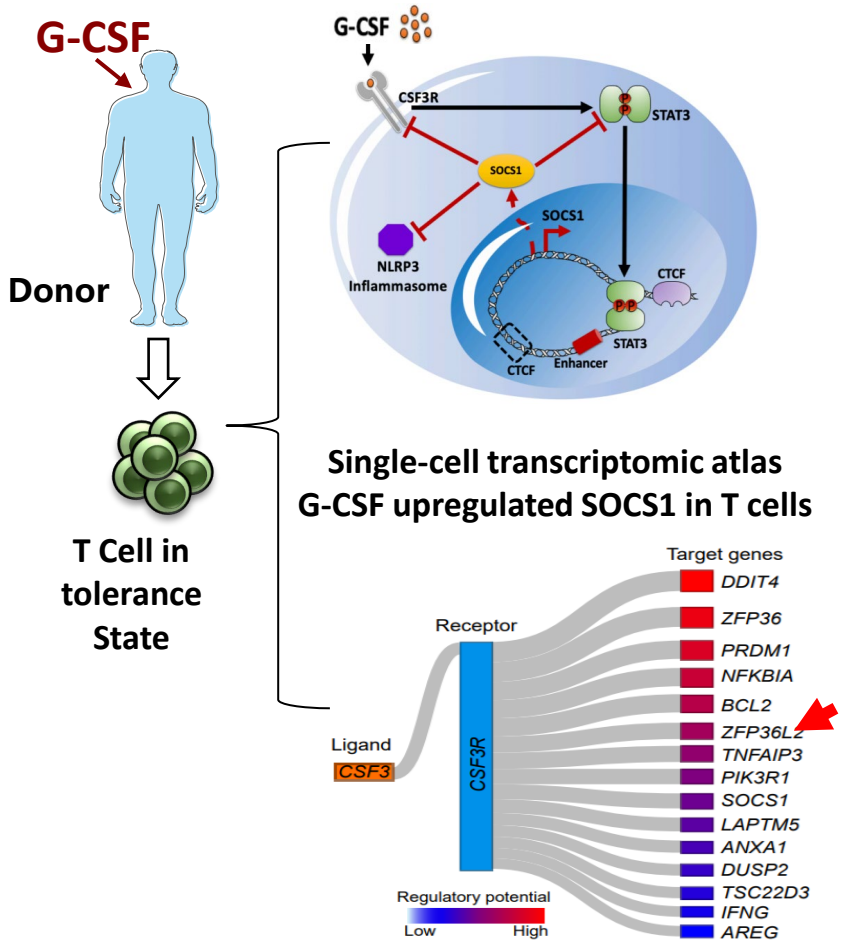


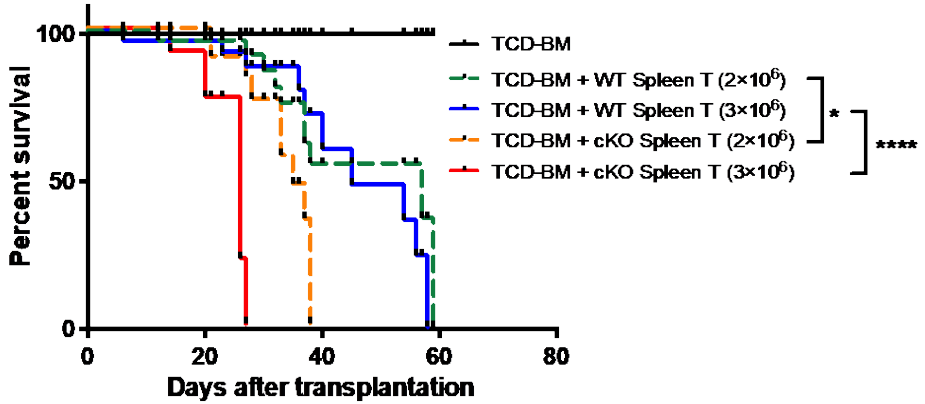
Reduce GvHD(patients)

Huang XJ. et al. J Hematol Oncol. 2019; 12(1) (Corresponding)
Huang XJ. et al. Oncoimmunology. 2017; e1284721 (Corresponding)
Huang XJ. et al. Haematologica. 2004, 2005 (Corresponding)

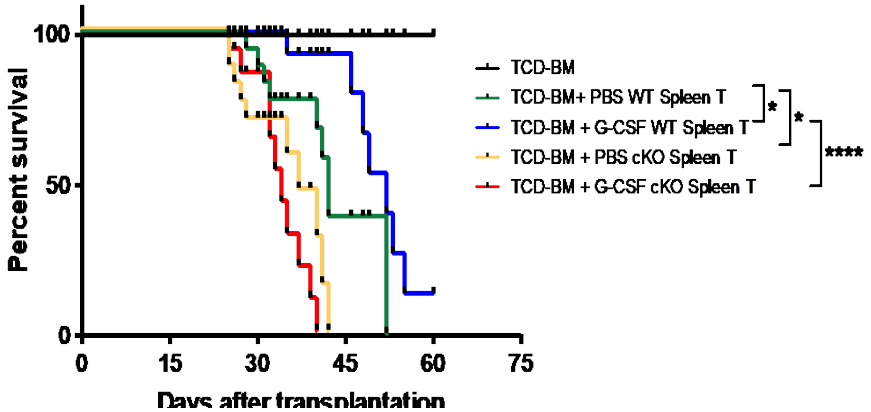
Firstly Identify molecular for G-CSF inducing T cell tolerance

Multiomics Analysis revealed G-CSF upregulated SOCS1





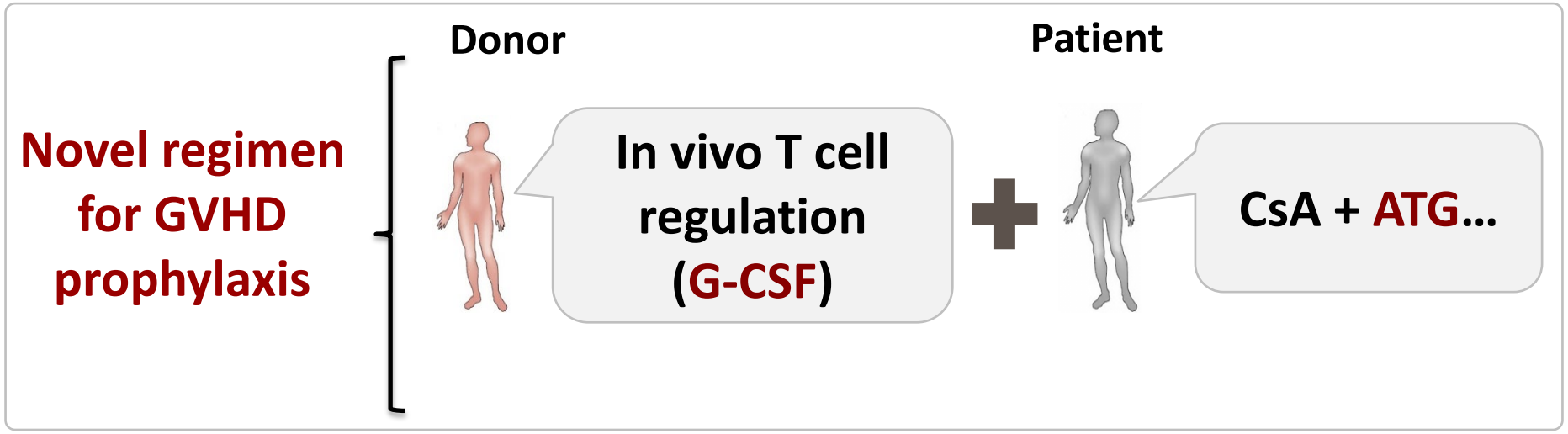
① T cell-specific SOCS1 conditional Knockout aggregates GVHD

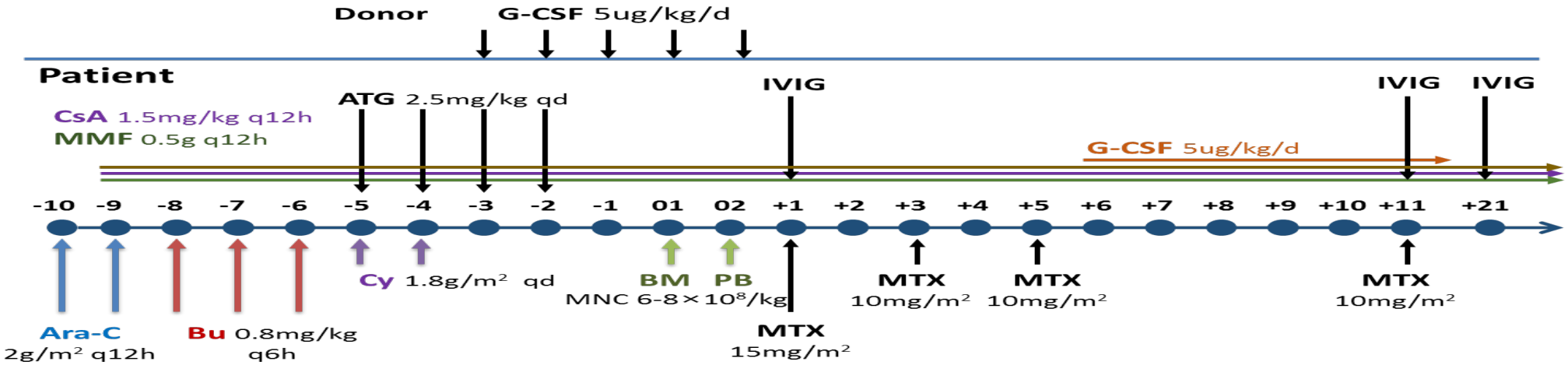


② G-CSF ameliorates GVHD by SOCS1

Huang XJ. et al. Advanced Science. 2022:e2200978 (Corresponding)
Huang XJ. et al. Cell Discov. 2022;8(1) (Corresponding)

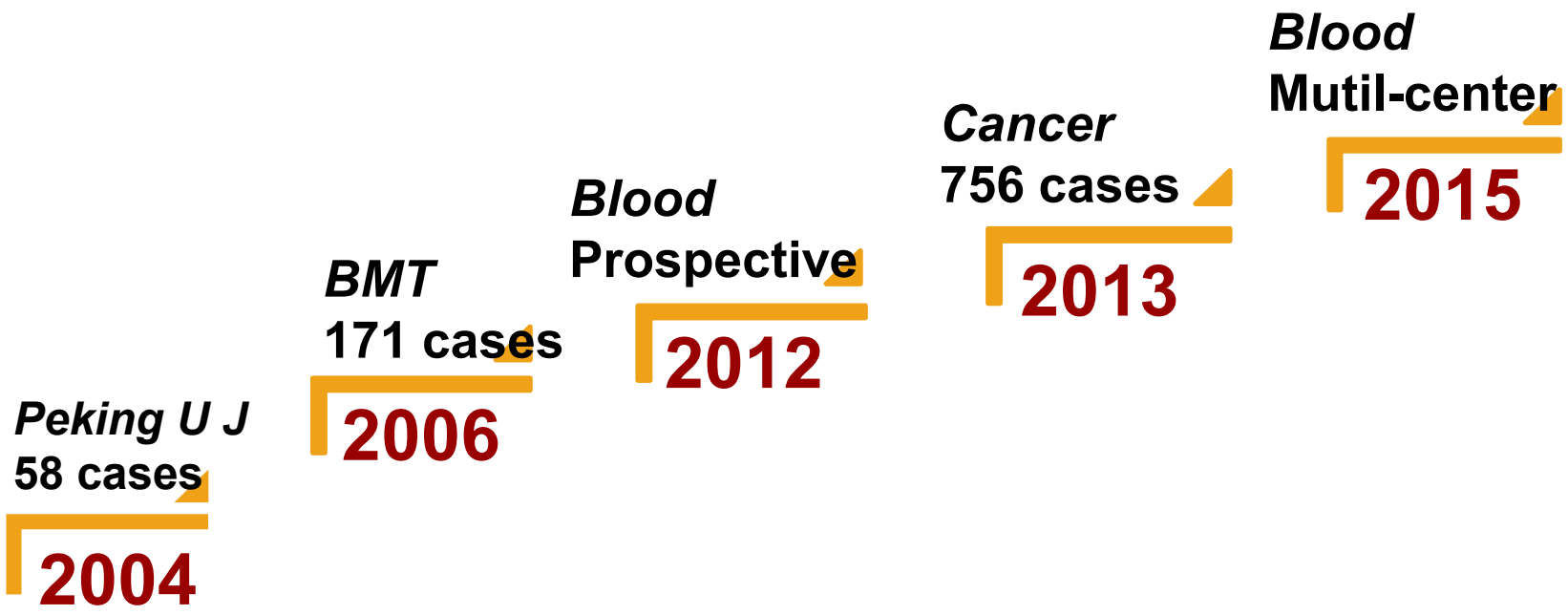
Novel regimen for GVHD prophylaxis of haplo-HSCT





Huang XJ, et al. Bone Marrow Transplant. 2006;38(4) (Corresponding)
Huang XJ, et al. Chin Med J (Engl). 2004;117(12) (Corresponding)

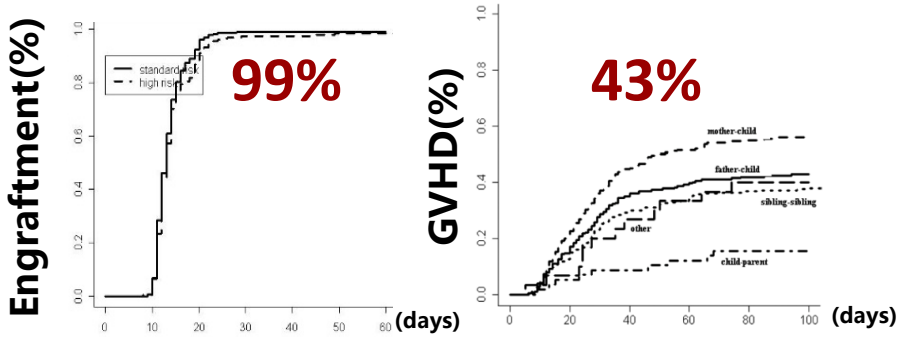
Novel regimen decreasing GVHD of haplo-HSCT



First Haplo-HSCT in 2000……

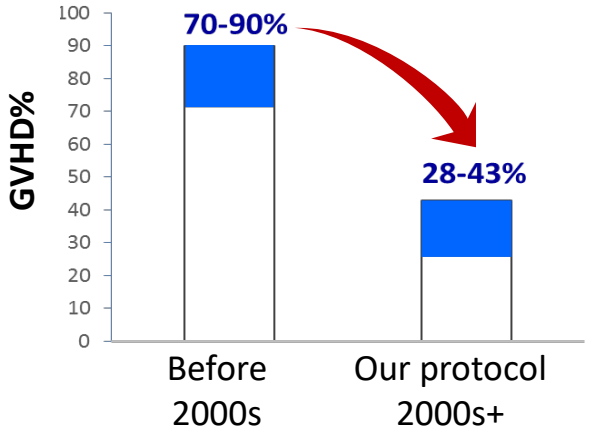
Novel regimen decreasing GVHD of haplo-HSCT

Pro-Engraftment



Cancer **(2013, 756 cases)**

Reduce GvHD



Peking U J
58 cases
2004

BMT
171 cases
2006

Blood
Prospective
2012

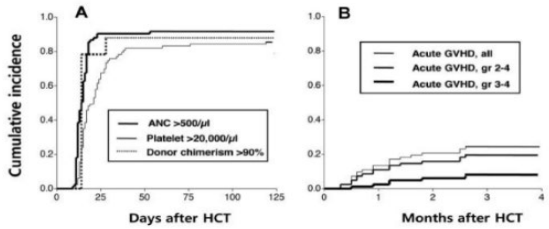
Cancer
756 cases
2013

Blood
Mutil-Center
2015

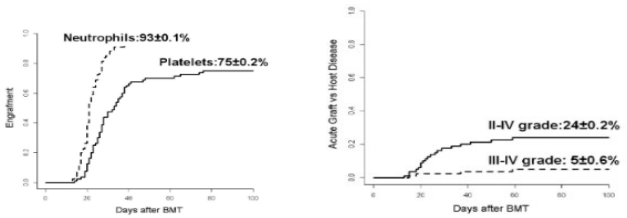
First Haplo-HSCT in 2000

Novel regimen decreasing GVHD of haplo-HSCT

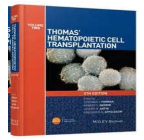
Novel regimen was reproduced



Korea
Blood (2011)



Italy&Israel
Blood (2013)



Thomas' Hematopoietic Cell Transplantation

Stem Cell Transplantation

2015《Thomas' Hematopoietic Cell Transplantation》

Huang and other investigators from Peking University (Beijing, China) utilized rabbit ATG (Thymoglobulin) 10 mg/kg over 4 days,

Whereas the effectiveness of the Beijing regimen was verified by these two external trials, it remains unclear whether each of its

Effectiveness of the Beijing Regimen was verified

Andrea Velardi

the Huang group in Beijing first applied G-CSF–priming of unmanipulated hap-

activity.[8] By applying a modified protocol, Di Bartolomeo et al have achieved promising results in terms of engraftment rate, incidence of GVHD, and survival.[1] Key features of their

***Blood* Commentary*(2013)*:**

Huang group First applied G-CSF priming of unmanipulated..

Achieved promising engraftment rate, GvHD and survival

Lee KH, et al. Blood. 2011; 118(9): 2609-17 *Di Bartolomeo P, et al. Blood. 2013; 121(5): 849-57* *Velardi A, et al. Blood. 2013; 121: 719-20*

Breakthrough of GVHD prophylaxis in haplo-HSCT

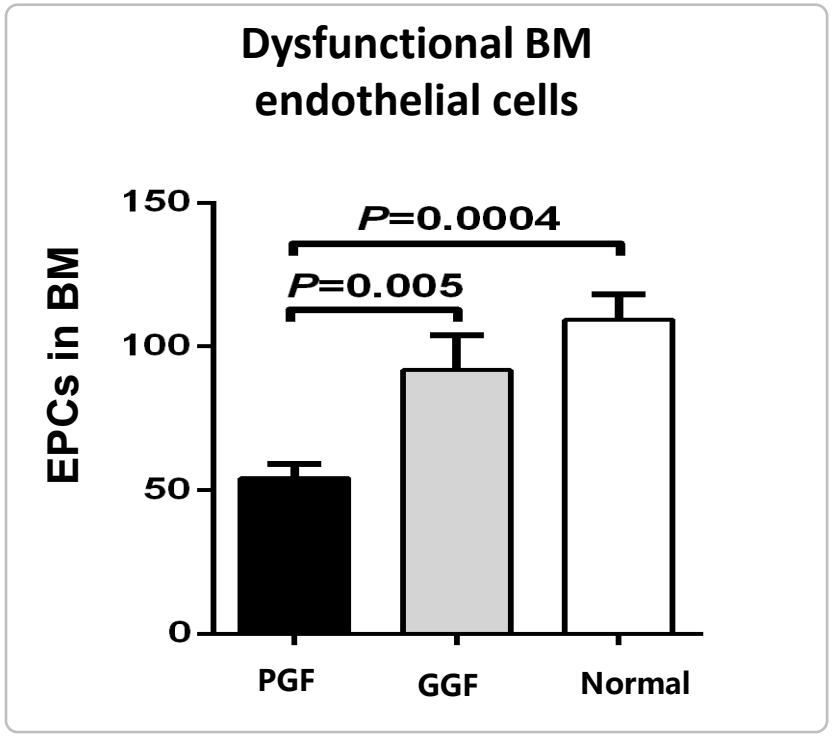
- **Novel Regimen for Immune Tolerance**
- **Reduce Graft-versus-Host Diseases**

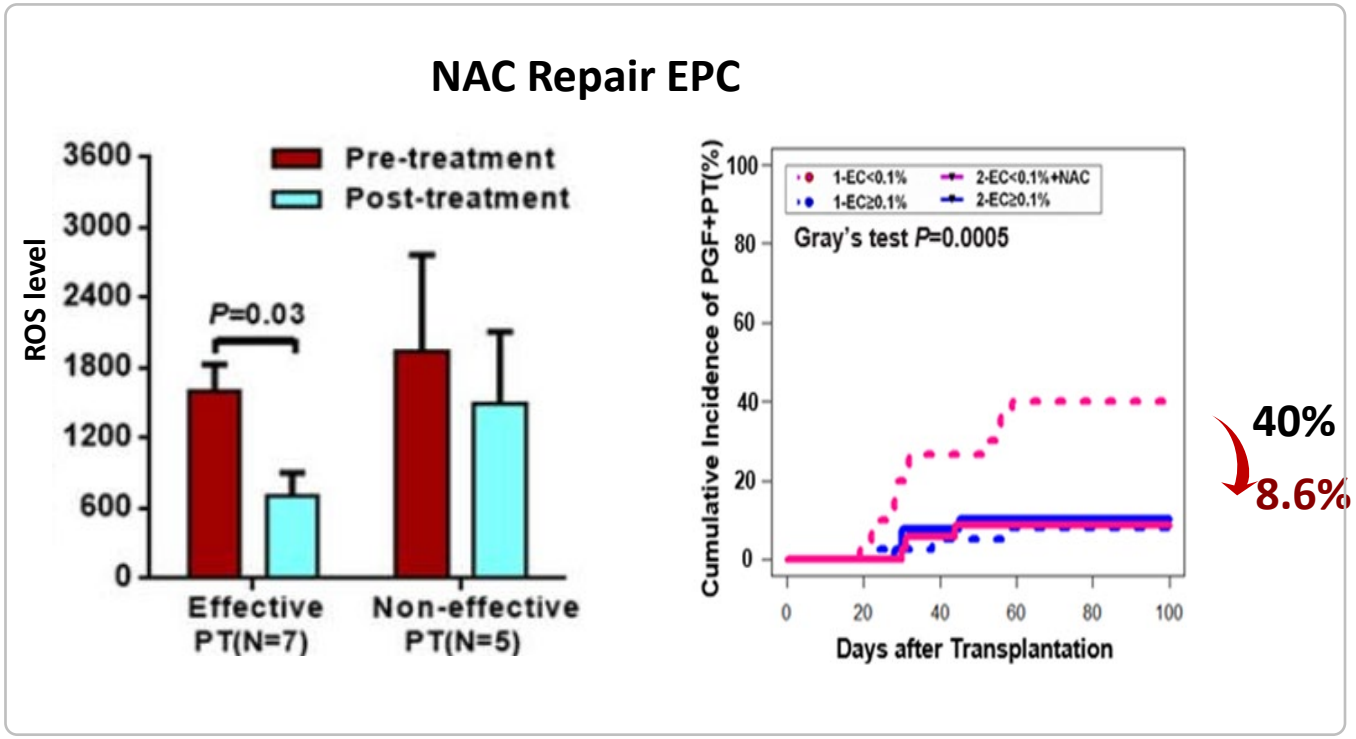
Could haplo-HSCT become the first-line option?

Questions to be addressed

- How to avoid poor engraftment ?
- How to further decrease GvHD ?
- How to deal with relapse?
- How to choose the best donor ?
- ……
- Can Haplo-HSCT be superior to chemotherapy ?
- Can Haplo be comparable to HLA matched donor ?

Finding new mechanism of poor graft function





PGF: poor graft function

GGF: good graft function

NAC: N-acetylcysteine

Bulletin du CANCER

Guideline

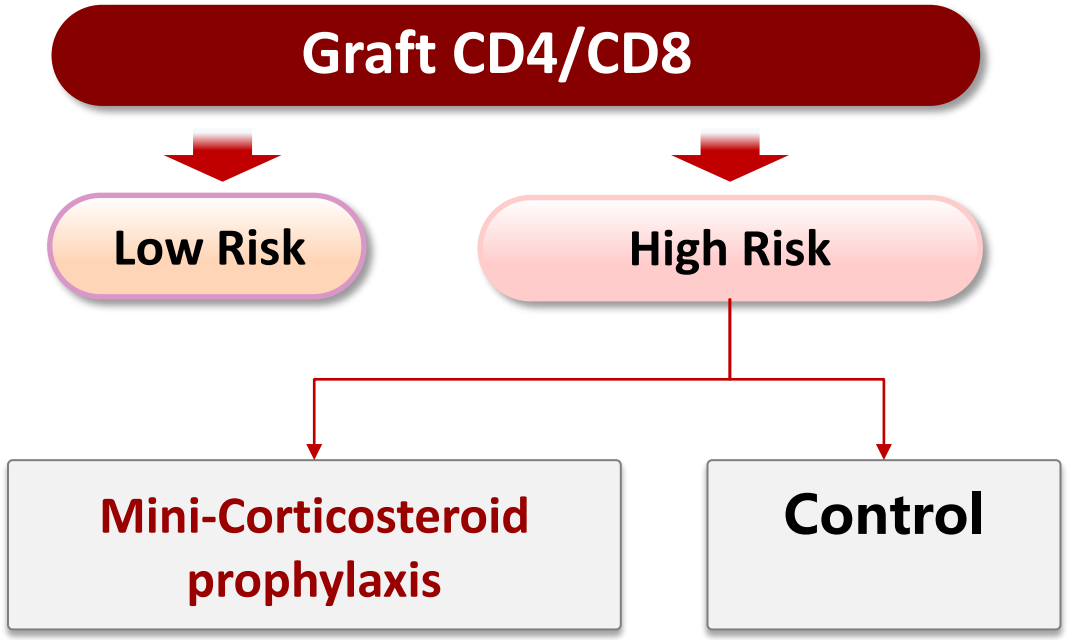
"Management of graft failure--guidelines from the French Society"

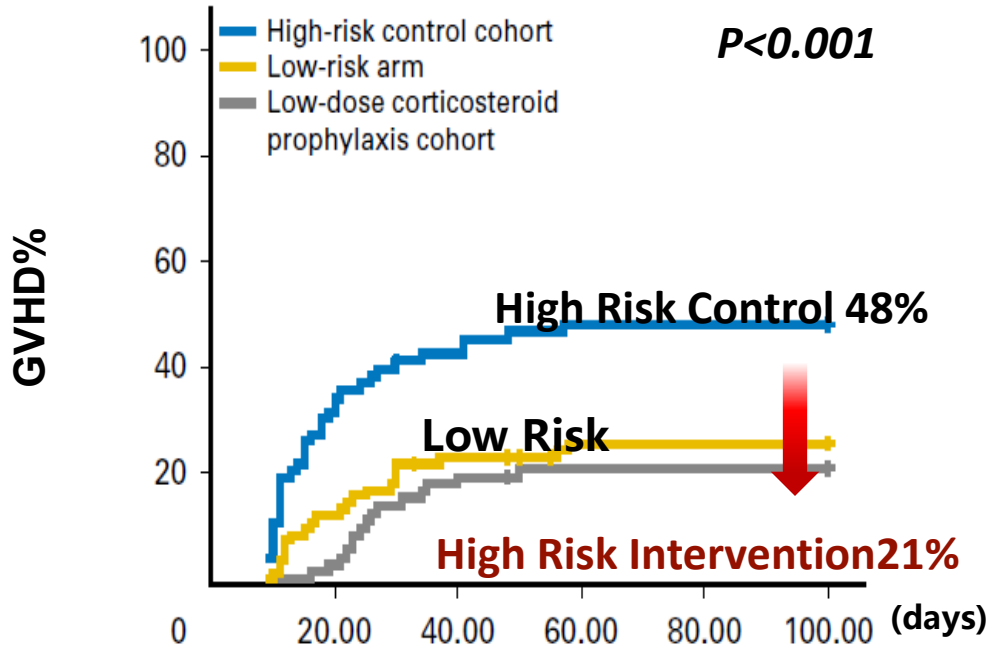
Cornillon J, et al. Bull Cancer. 2016;103(11S): S248-54

Huang XJ. et al. Blood Advances. 2019; 3(8) (Corresponding)
Huang XJ. et al. Am J Hematol. 2018; 93(7) (Corresponding)

Huang XJ. et al. Blood. 2016; 128(25) (Corresponding)

Risk-directed prophylaxis further decreasing GVHD in haplo-SCT





VOLUME 34 · NUMBER 16 · JUNE 1, 2016
JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

Graft-Versus-Host Disease Prevention: Corticosteroids Revisited

Edwin P. Alyea, *Dana-Farber Cancer Institute, Boston, MA*

See accompanying article on page 1855

Harvard.U Prof.Alyea commented in *J Clin Oncol*

undergoing haploidentical transplantation. This trial provides an opportunity to consider both the opportunities and challenges of this type of trial design to identify new regimens to prevent GVHD and the applicability of these results to other transplantation settings.

"Opportunities to prevent GVHD and applicability to other settings"

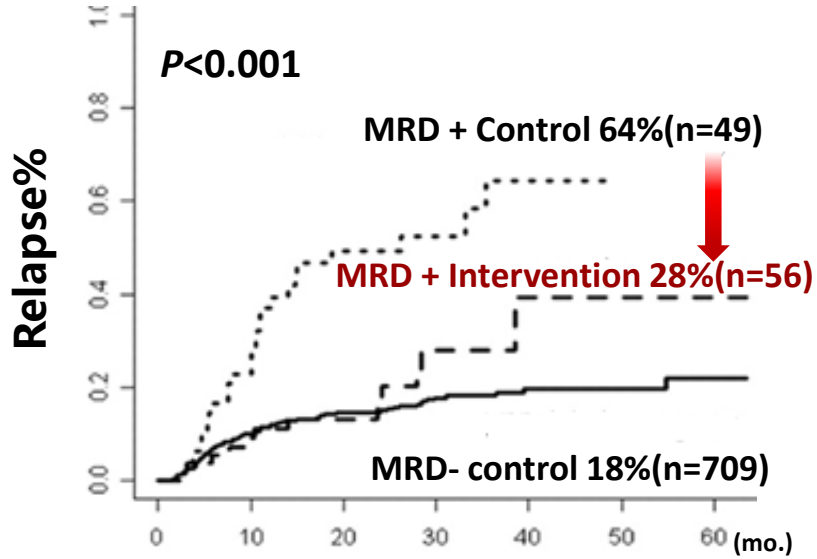
Alyea EP, et al. J Clin Oncol. 2016; 34(16): 1836-7

Huang XJ. et al. J Clin Oncol. 2016; 34(6) (Corresponding)

Novel method for post HSCT Relapse after haplo-HSCT

Novel Method

- G-CSF mobilized cells
- \+
- Short term Immune Suppression



Yair Reisner

According to Huang et al in Beijing, G-CSF–primed donor HSCs and robust posttransplantation GVHD prophylaxis reduced the risk of transplantation-related mortality (TRM) and improved long-term survival.[10] A follow-up study of 250 mis- acute leukemia was higher in haploidentical recipients than in matched sibling recipients (42% vs 20%, $P = .048$), presumably because of a stronger GVL effect.[12]

***Commented in Blood* (2011) :**

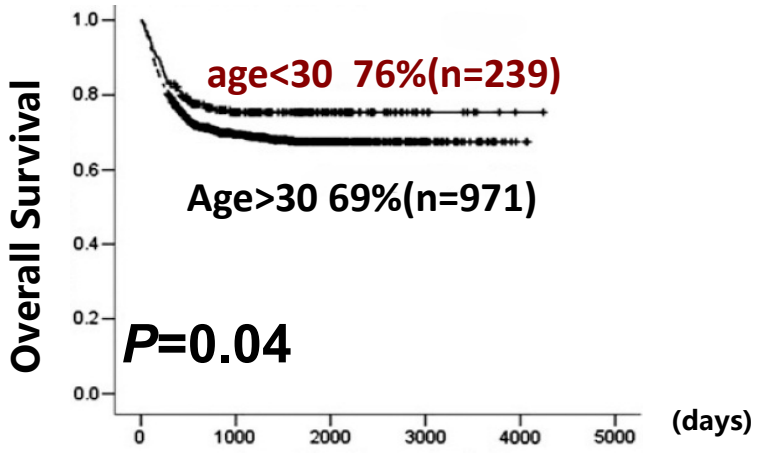
"G-CSF primed donor HSCs a stronger GVL effect…"

Reisner Y, et al. Blood. 2011; 118(23): 6006-17

Huang XJ. et al. Haematologica. 2007; 92(3) (Corresponding)
Huang XJ. et al. Sci China Life Sci. 2020;63(10) (Corresponding)
Huang XJ. et al. Biol Blood Marrow Transplant. 2015;21(11) (Corresponding)

Establishment of first widely applied donor selection algorithm

The Largest Haplo-HSCT cohort in the World (n=1210)



Younger Donor Preferred

Order	Donor Source
1st	Offspring/NIMA mismatch
2nd	Little brother/NIMA mismatch
3rd	Old sisiter/NIMA mismatch or father
4th	NIPA mismatch old sister or brother
last	Mother

Prof.Handgretinger
Commented in *Blood*

described in this study. Therefore, the analysis by Wang et al and their proposed algorithm for haploidentical donor selection will have a major impact on outcome for a large number of patients.

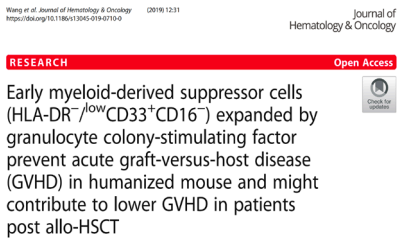
Algorithm has a major impact for large number of patients

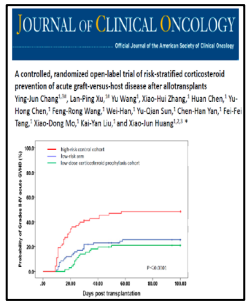
Handgretinger R, Blood. 2014; 124(6): 827-28

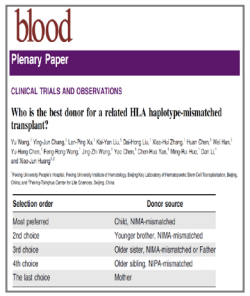
Huang XJ. et al. Blood. 2014; 124(6) (Plenary Paper) (Corresponding)

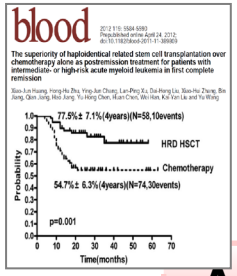
The First unmanipulated haplo-HSCT system--“Beijing Protocol”

Prize of National S&T progress(2014)









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Anti-Infection

Anti-Relapse

Donor Selection

GvHD Prophylaxis

Elucidate Poor graft function
Establish Novel Strategy

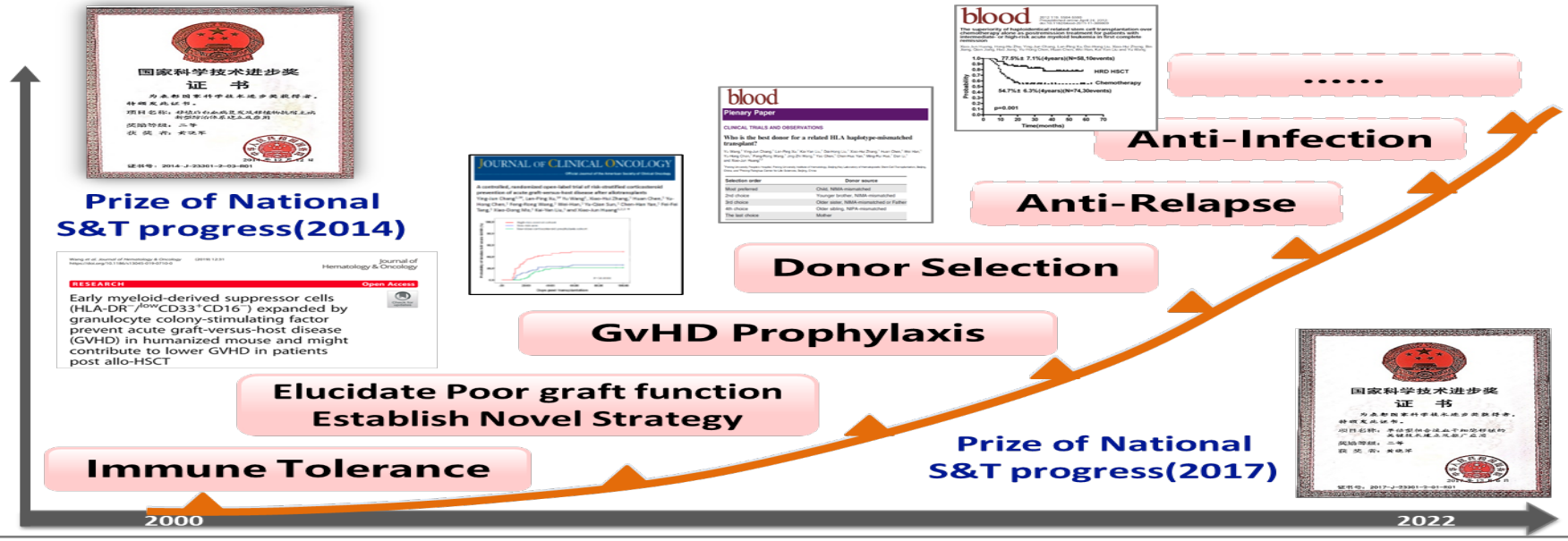
Immune Tolerance

Prize of National S&T progress(2017)

2000

2022

The First unmanipulated haplo-HSCT system--“Beijing Protocol”



Jeff Szer

Yoshihisa Kodera

Current and past president of Worldwide Network for Blood & Marrow Transplantation (WBMT)

Over the past 15 years, by using a combination of G-CSF–mobilized bone marrow and peripheral blood cells, as well as antithymocyte globulin administration for the prophylaxis of GVHD and graft rejection, the Beijing group initiated one of the earliest clinical trials to explore unmanipulated myeloablative haplo-HSCT for leukemia [8]. The extensive chronic GVHD 19% to 23%); haplo-HSCT achieved similar clinical efficacy as allo-HSCT from an HLA-identical sibling donor or matched unrelated donor and was found

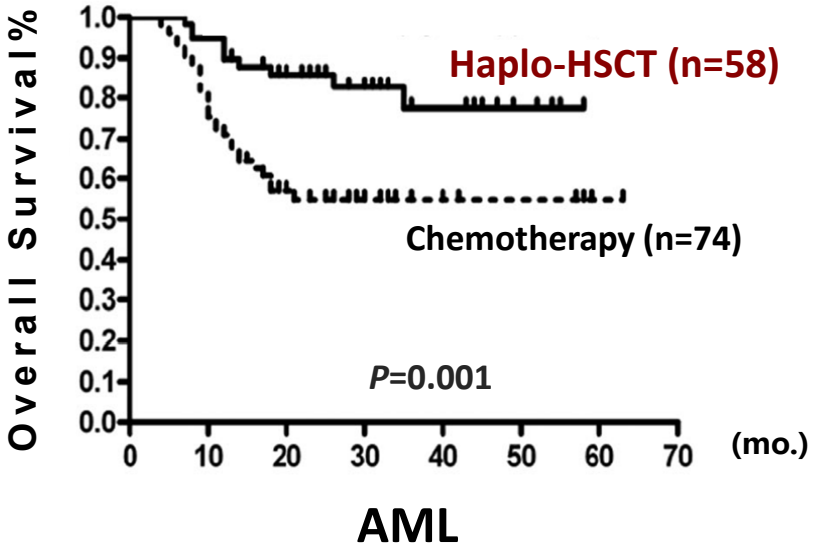
In recent years the Beijing Protocol has been improved in many aspects and developed into an integrated haplo-HSCT system. The indications for haplo-HSCT have been Beijing Protocol was shown to be a reliable treatment strategy for patients without a suitable HLA-matched donor for because of immunological or financial factors, thus providing the promise of a donor for almost every eligible patient. The

Apperley J, et al. Biol Blood Marrow Transplant. 2016; 22(1): 23-6

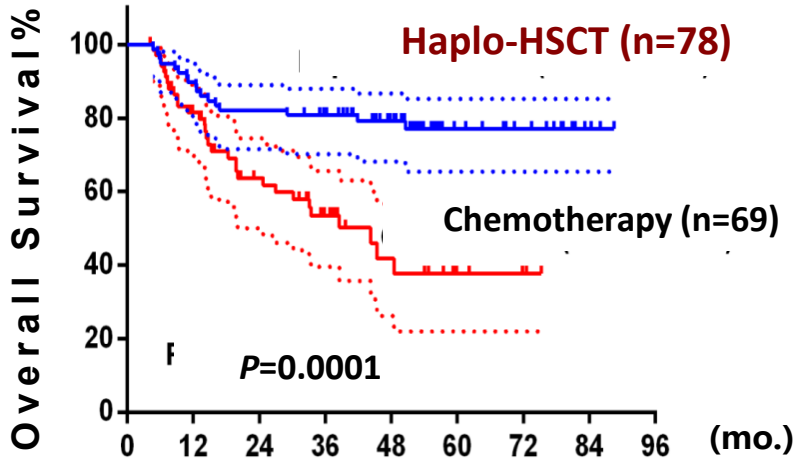
“integrated haplo-HSCT system, reliable treatment without HLA matched donor, promise of every eligible patient…”

Firstly enabling haplo-HSCT superior to chemotherapy

First Prospective Study



AML



Int AML

Overturning traditional concept "haplo-SCT is formidable"

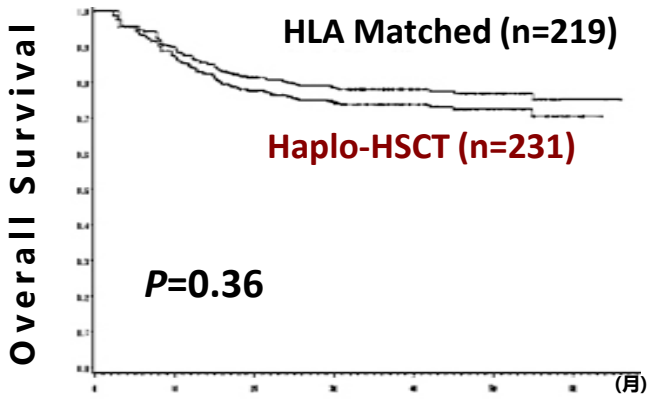
Form basis of new concept "haplo-SCT is feasible"

Huang XJ. et al. Blood. 2012; 119(23) (Corresponding)

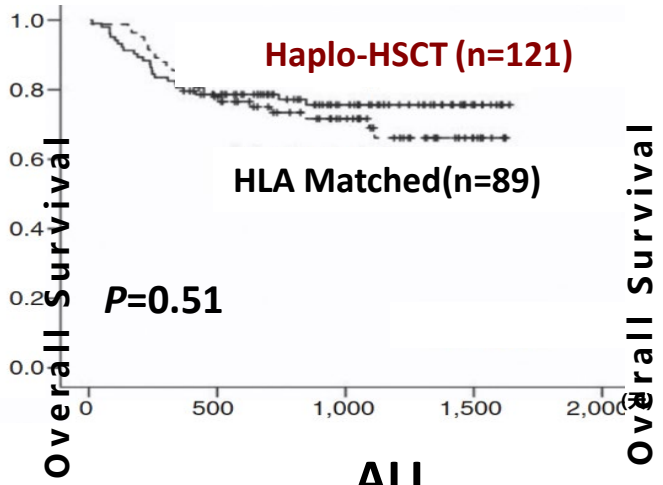
Huang XJ. et al. Clin Cancer Res. 2018; 25(6) (Corresponding)

Firstly enabling haplo-HSCT comparable to HLA matched HSCT

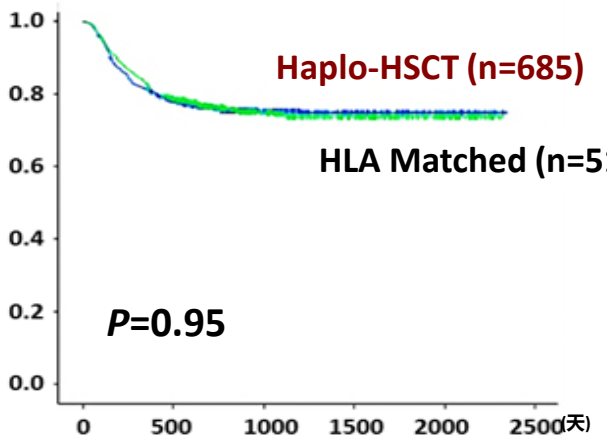
Prospective Multicenter Studies



AML



ALL



Acute Leukemia

Overturning traditional concept "haplo-SCT is formidable"

Form basis of new concept "haplo-SCT is feasible"

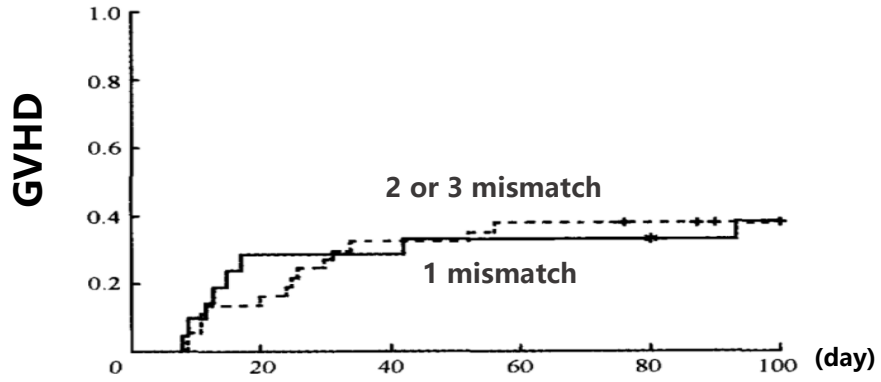
Huang XJ. et al. Blood. 2015; 125(25) (Corresponding)
Huang XJ. et al. Clin Cancer Res. 2016; 22(14) (Corresponding)
Huang XJ. et al. Leukemia. 2018; 32(2) (Corresponding)

AML: acute myeloid leukemia

ALL: acute lymphocytic leukemia

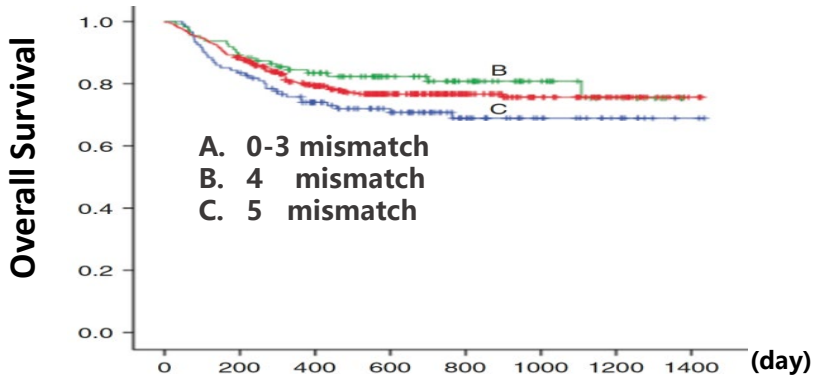
First time HLA disparity no longer affecting outcome

P=0.92



HLA mismatch **does not** affect GvHD

P=0.17



HLA mismatch **does not** affect OS

Firstly Report (58 cases) — 2004 *Peking U. J.*

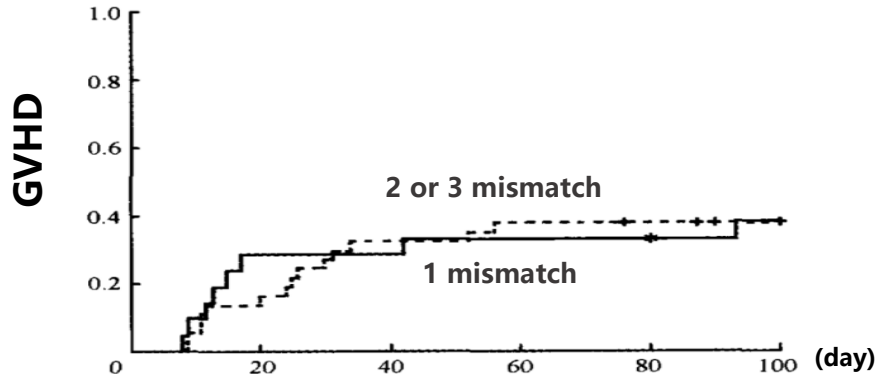
Prospective (219 cases) — 2009 *Clin Cancer Res*

Retrospective (595 Cases) — 2018 *BMT*

Large Prospective (1199 cases) — 2018 *Leukemia*

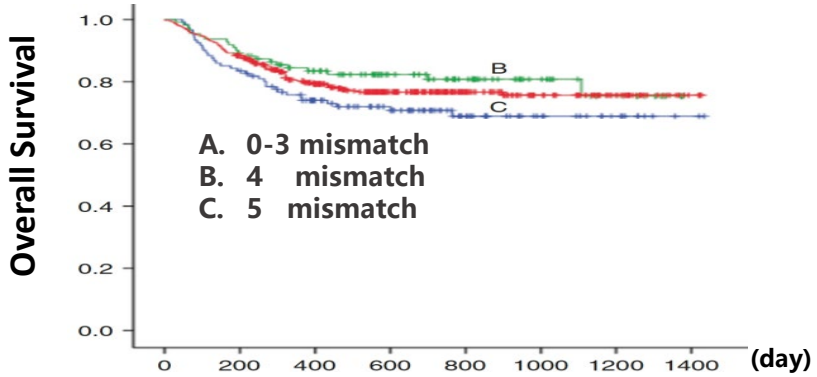
First time HLA disparity no longer affecting outcome

P=0.92



HLA mismatch **does not** affect GvHD

P=0.17



HLA mismatch **does not** affect OS

nature REVIEWS CLINICAL ONCOLOGY

Leonido Luznik (2016)

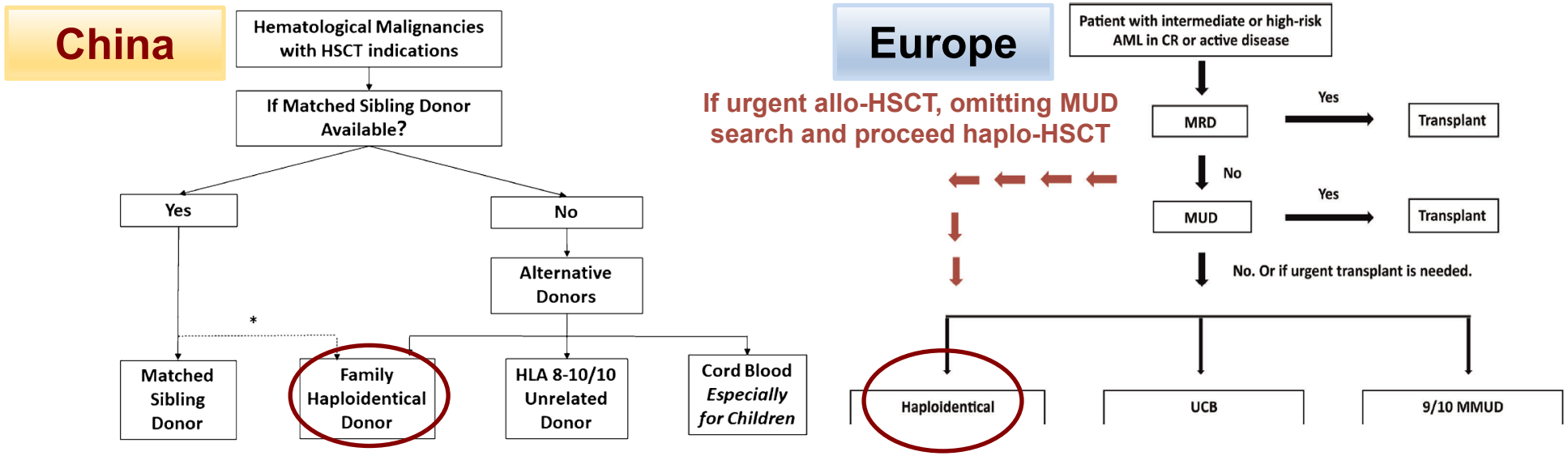
the extent of HLA disparity did not affect overall survival.[18,20,87]

"HLA disparity did not affect survival"

Kanakry CG, et al. Nat Rev Clin Oncol. 2016; 13(2): 132

HLA barrier bas been overcomed

“Beijing Protocol” updated Guidelines
Haplo-HSCT the first-line treatment for acute leukemia



Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

ASBMT

Indications Guidelines American Society for Blood and Marrow Transplantation (2015)

Majhail NS, et al. Biol Blood Marrow Transplant. 2015; 21(11): 1863-69

GUIDELINE ARTICLE

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Haplo-HSCT Consensus StatementEuropean Society for Blood and Marrow Transplantation(2017)

Lee CJ, et al. Haematologica. 2017; 102(11): 1810-22

Journal of Hematology & Oncology
Open Access

Consensus of indications, conditioning regimens and donor selection Chinese Society of Hematology

Zhang XH, et al. J Hematol Oncol. 2021;14(1):145.

Active in Academy and International Cooperation

International Meeting as Host President

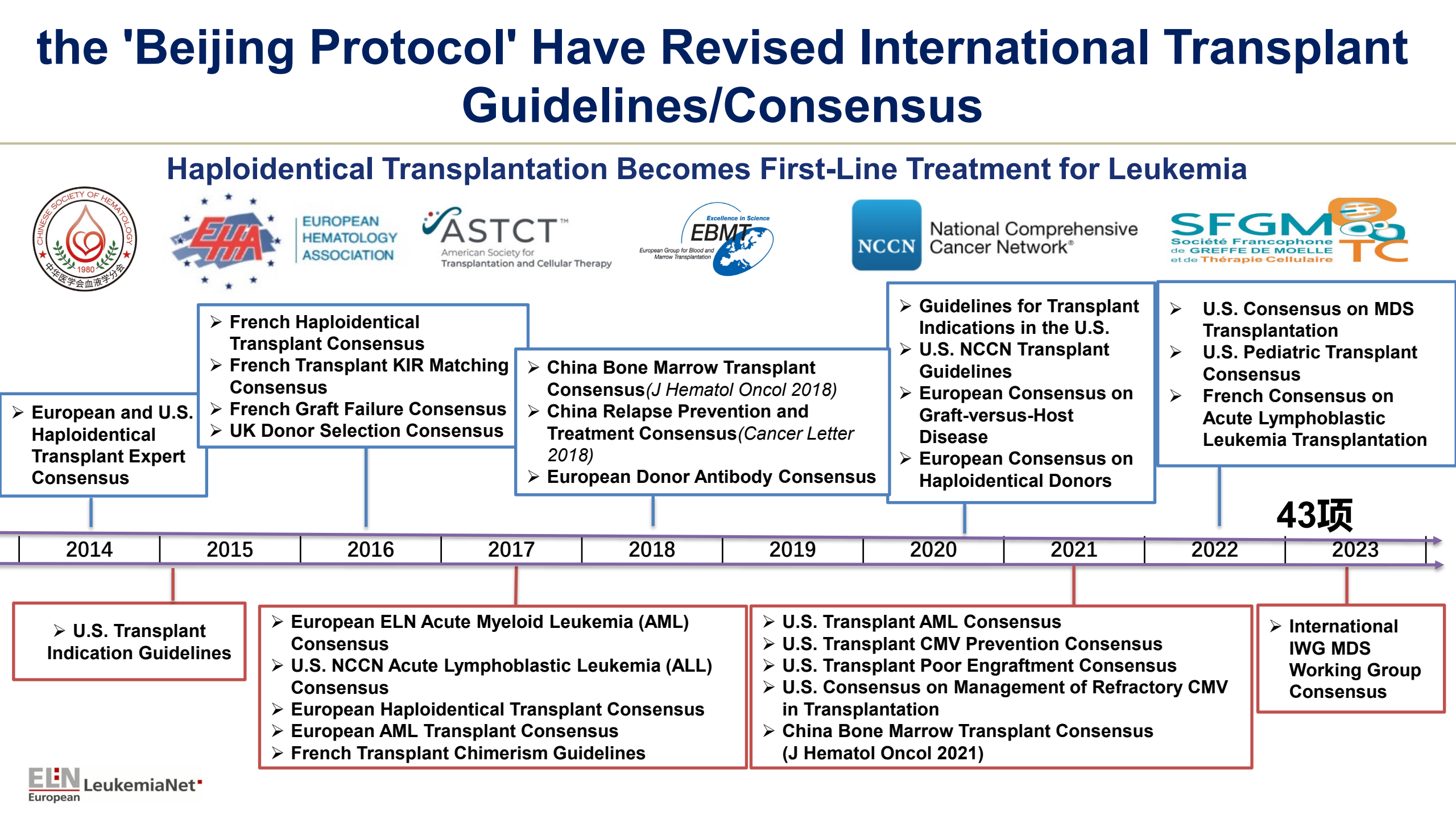
- 5th Worldwide Network for Blood & Marrow Transplantation (WBMT, 2018)
- 7th Meeting Asia Cellular Therapy Organization 2016
- 35th International Society of Hematology 2014
- 19th Asia-Pacific Transplant Meeting 2014
- ……

Invited Speaker in Europe and USA for consecutively recent 15 years

- 20th American Gene Therapy (ASGCT, 2017)
- 22th European Hematology (EHA, 2017)
- American Transplant & Cellular (ASTCT 2019)
- WBMT and EBMT 2021
- 48European Transplantation (EBMT, 2022)
- ……

the 'Beijing Protocol' Have Revised International Transplant Guidelines/Consensus

Haploidentical Transplantation Becomes First-Line Treatment for Leukemia



ELN European LeukemiaNet

"Beijing Protocol" Achieves Best Global Efficacy

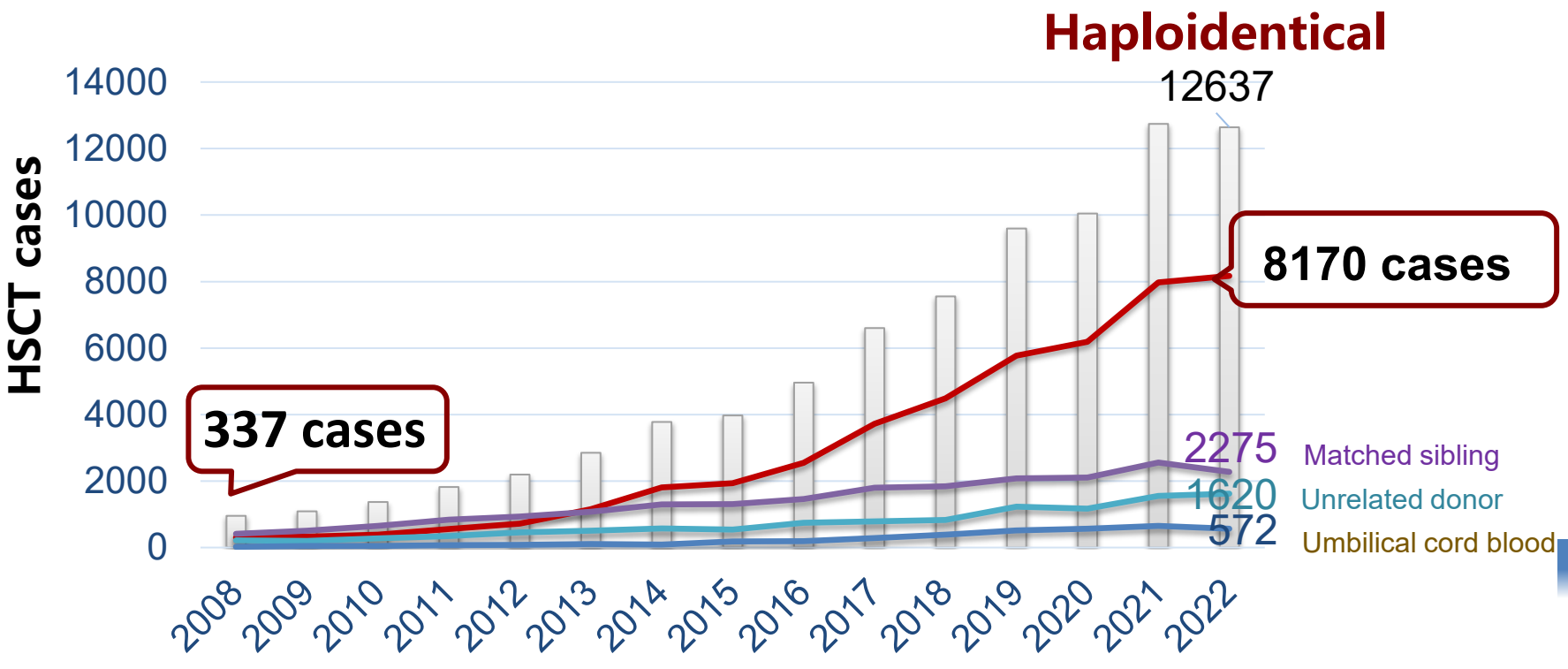
Ex Vivo T Cell Depletion	**Beijing Protocol** Granulocyte Colony-Stimulating Factor	**U.S. Protocol** Post-Transplant Cyclophosphamide
Earliest Reported	2004	2008
Clinical Efficacy		
- Transplantation Rate	99%	88-91%
- Graft-Versus-Host Disease	21-43%	16-42%
- Survival Rate	60-79%	40-65%
Key Milestones for Efficacy		
- Equivalent Efficacy to Full Match	2006	2013
- Superior Efficacy to Chemotherapy	2012	2014

Luznik, et al. Nat Rev Clin Oncol.2016; Huang XJ , Blood. 2015, J Clin Oncol.2016, Leukemia. 2017
Bashey A, et al. J Clin Oncol 2017; Mancusi A, et al. Blood. 2015; McCurdy SR, et al. Blood. 2015

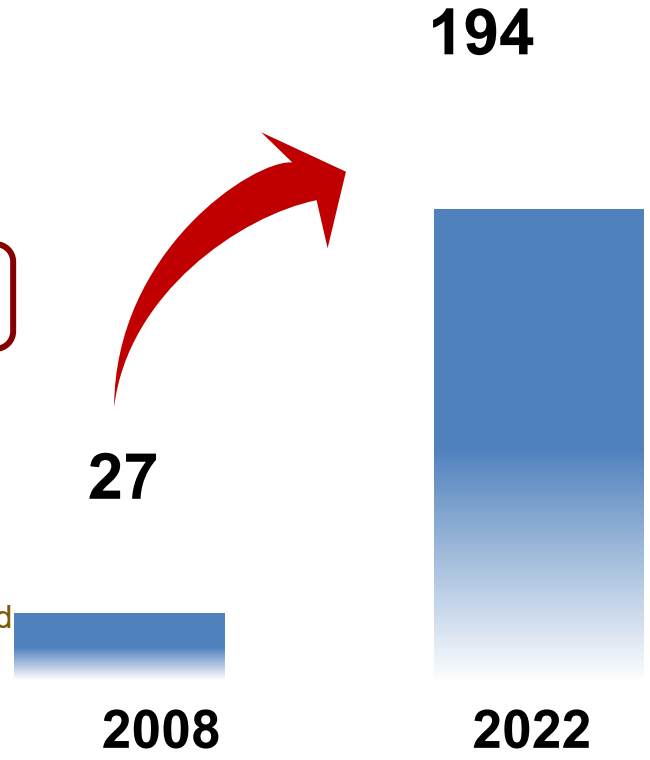
"Beijing Protocol" has become the first allo-HSCT model in China

"Beijing Protocol" was applied in 94% of haplo-SCT

Forty-six thousand cases completed in 15 years

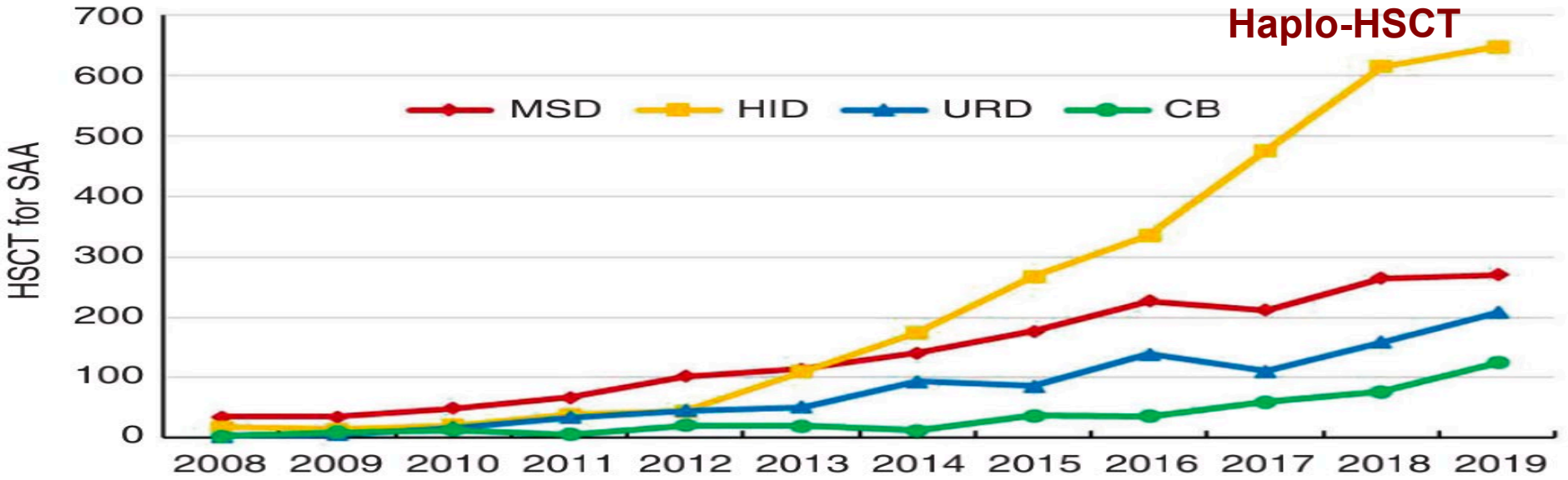


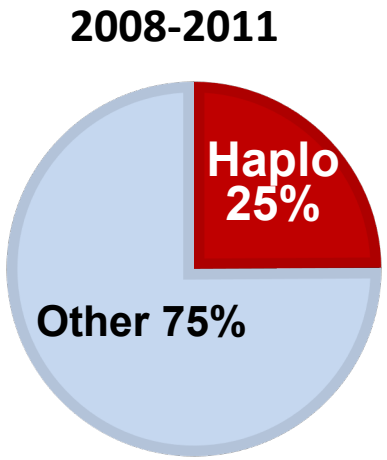
Transplant centers grew rapidly

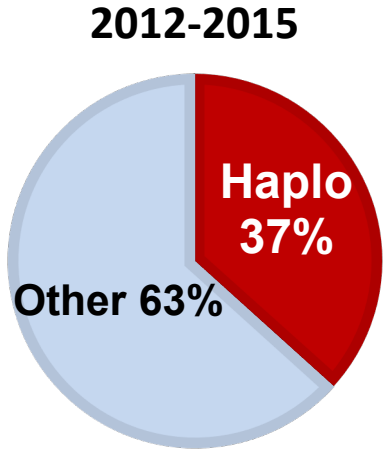


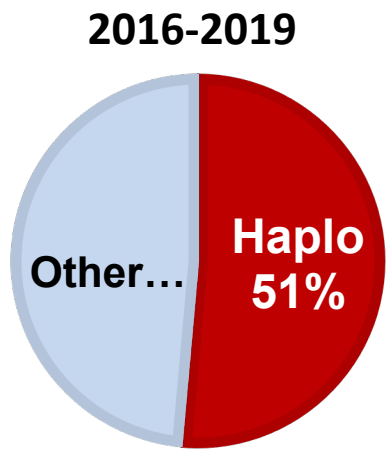
Since 2008, more than 600 visiting doctors have learned Beijing Protocol from mainland, Hong Kong, Malaysia, India...

Haplo-HSCT contributes to extension of HSCT indications



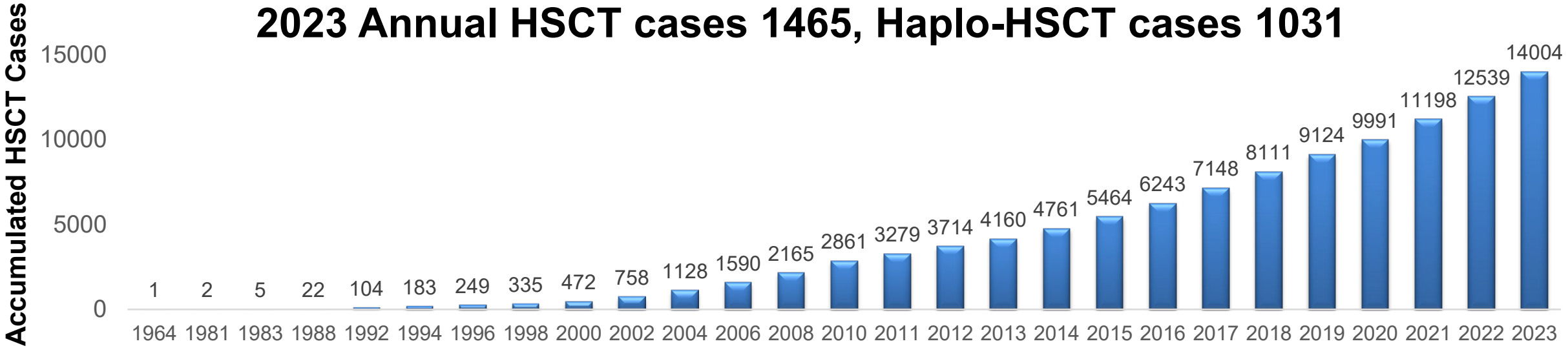


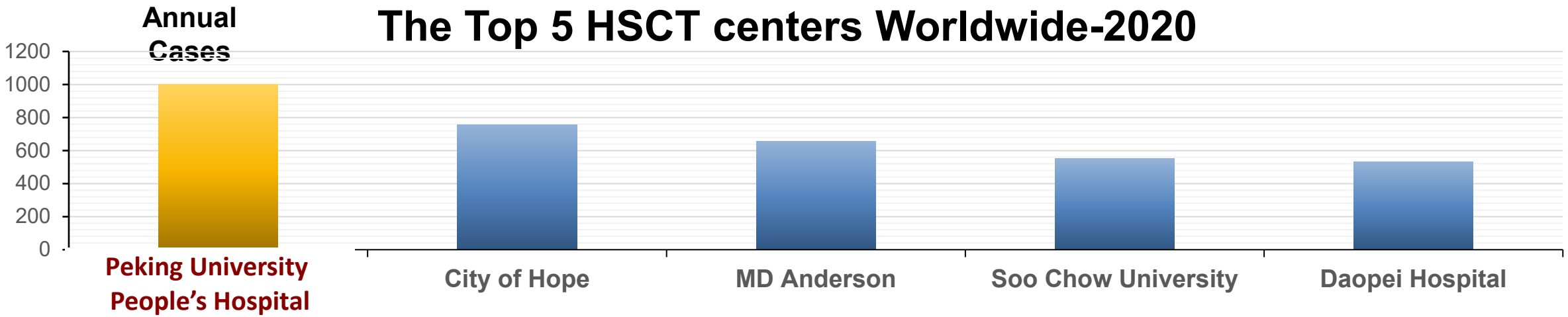




- *Huang XJ, et al. Bone Marrow Transplant. 2021.56(12) (Corresponding)*

The Largest HSCT Center Worldwide --- PUIH



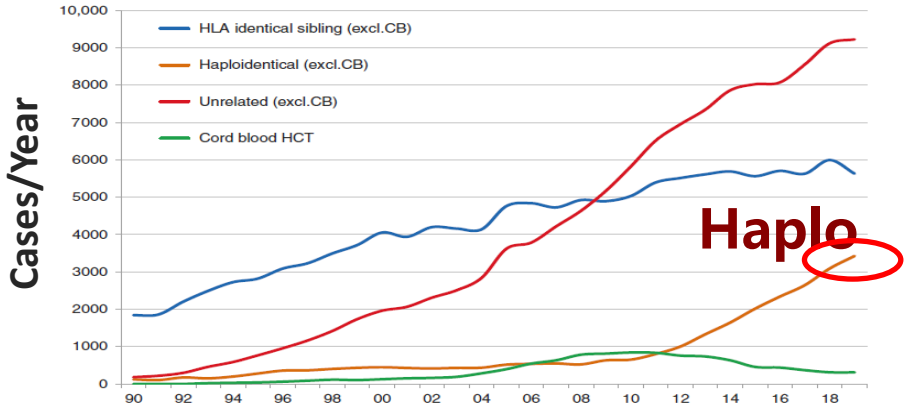


Lancet Haematol. 2022

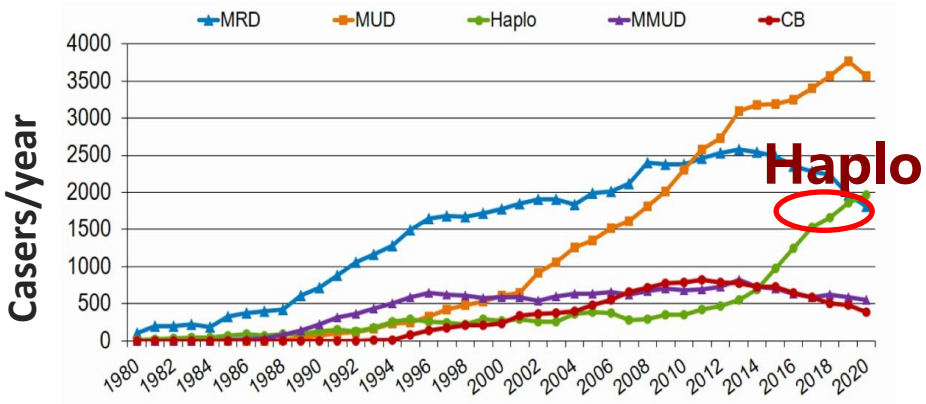
Transplant Cell Ther. 2023

CIBMTR summary slides, 2022

“Beijing Protocol” promotes rapid growth of haplo-HSCT worldwide



Europe Registry



USA Registry

blood

more than half of the HLA haplotype–mismatched transplantations performed worldwide will follow similar protocols as described in this study. Therefore, the

More than half of HLA mismatched HSCT follow similar protocol

Handgretinger R, Blood. 2014; 124(6): 827-28

Former President of European Hematology Association W.Fibbe

“Beijing Protocol” has become the new standard for Haplo-HSCT

W. Fibbe, 7th Annual Meeting of ACTO, 2016

“Beijing Protocol” promotes rapid growth of haplo-HSCT worldwide

Former Chairman of International Bone Marrow Transplant Registry Gale RP.

We should not forget what China has given us in these two decades including “Beijing protocol” for HLA-haplotype-matched transplants

Gale RP, J Hematol Oncol. 2018; 11(1):34

Former President of European Hematology Association W.Fibbe

“Beijing Protocol” has become the new standard for Haplo-HSCT

W. Fibbe, 7th Annual Meeting of ACTO, 2016

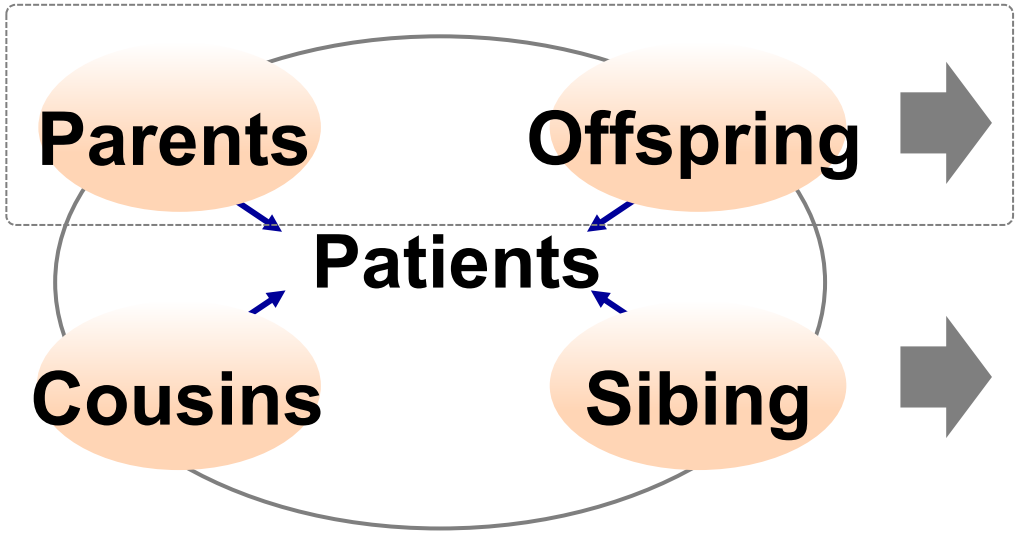
Beijing Protocol” Launches the New Era of Allo-HSCT

2023-10-5 International Academy for Clinical Hematology awarded Academician Xiaojun Huang **IACH International Collaboration Award**

“Beijing Protocol” Launches the New Era of Allo-HSCT

On February 23, 2024, the CIBMTR honored Academician Xiaojun Huang with the "Distinguished Service Award" in recognition of his exceptional contributions to international hematology through the establishment of the "Beijing Protocol."

“Beijing Protocol” Launches the New Era of Allo-HSCT



Offspring to/from Parents:
0% to almost 100%

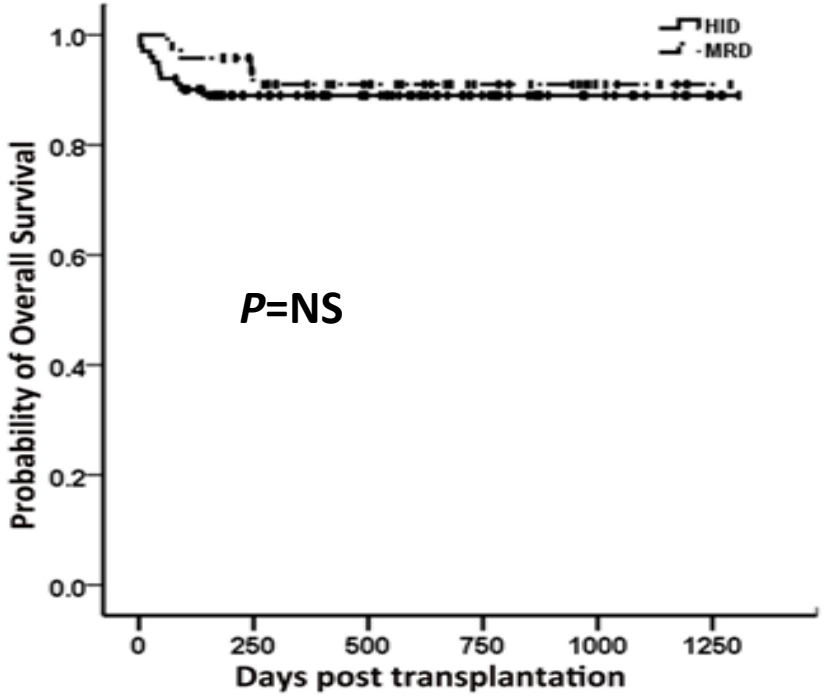
Sibling Donors
25% to 75%

“Beijing Protocol” prompted Haplo-HSCT From "Formidable” to “Feasible”

Everyone has a donor

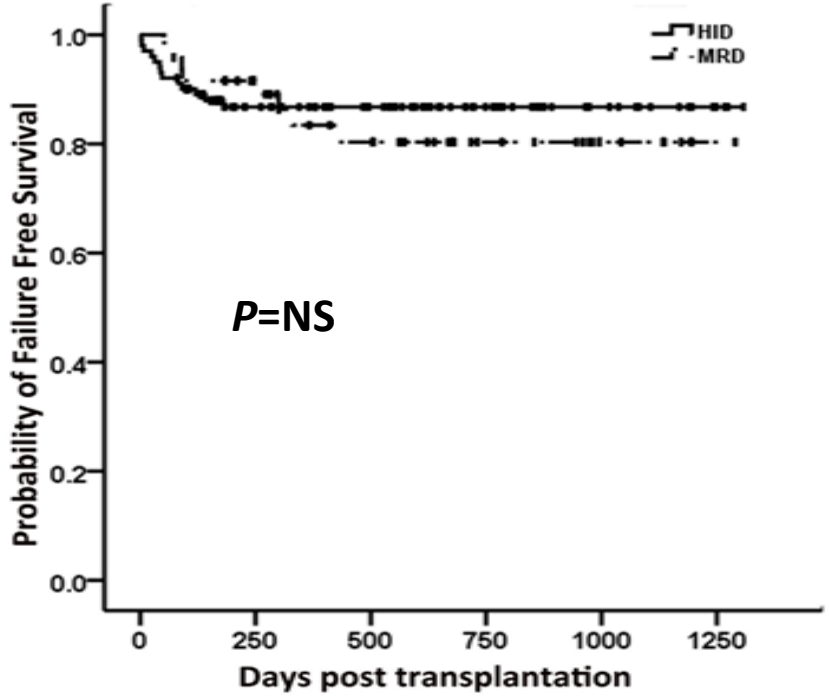
Comparable survival between haplo and ISD SCT in SAA as salvage treatment

OS



✓3-y OS: 89.0% vs 91.0%

FFS

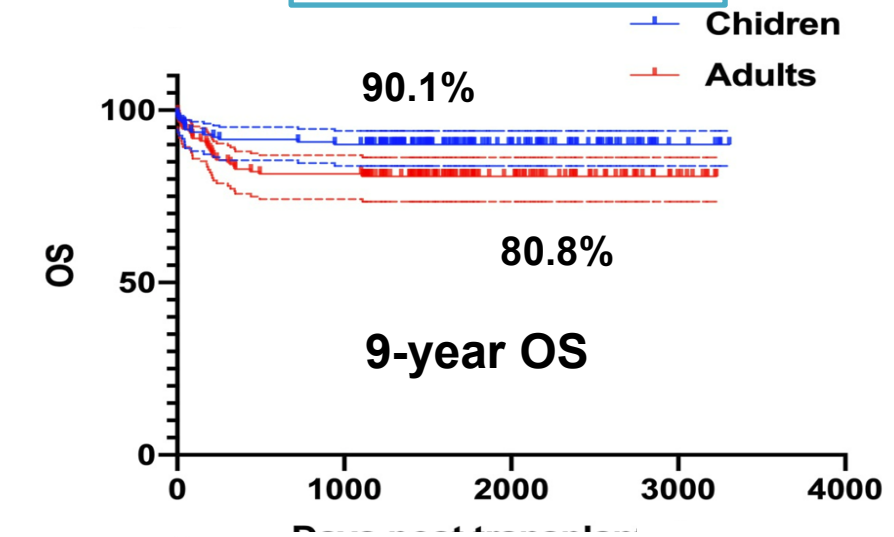


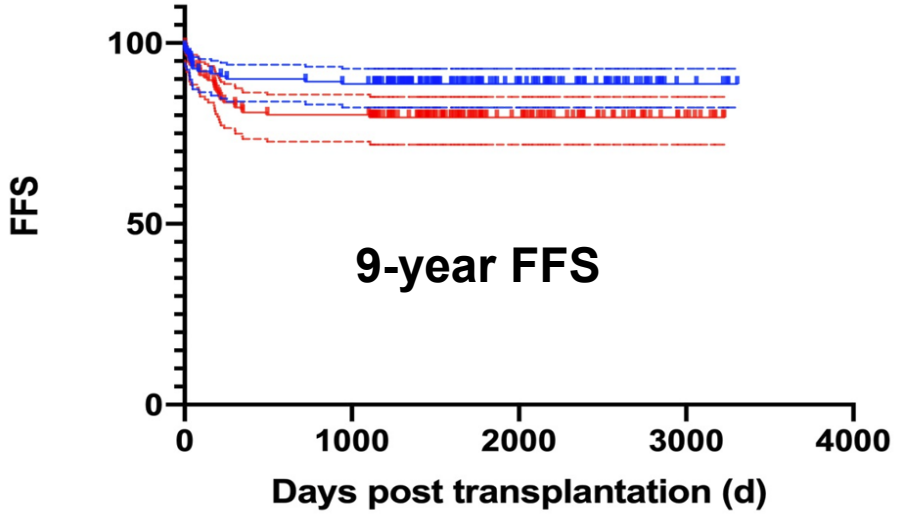
✓3-y FFS: 86.8% vs 80.3%

Xu LP,…, Huang XJ, et al. Br J Haematol. 2016*

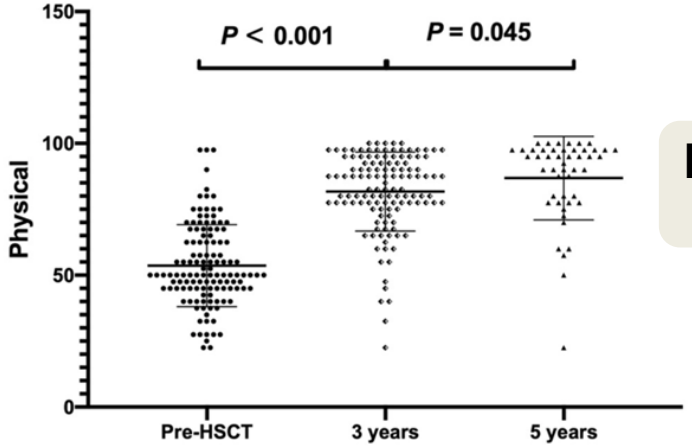
Long-term follow-up of salvage haplo-SCT in SAA

Survival

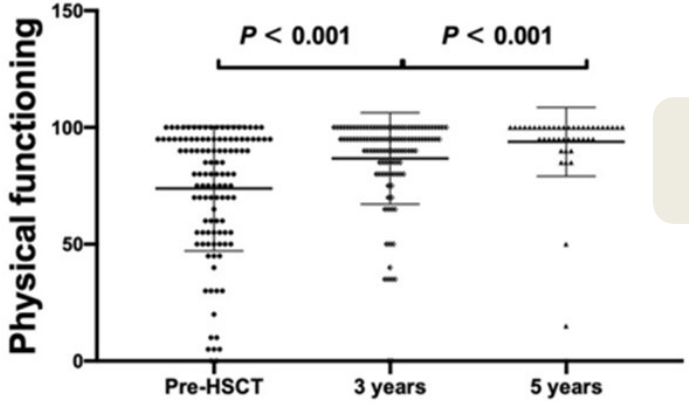




Quality of life



PedsQL 4.0 in children

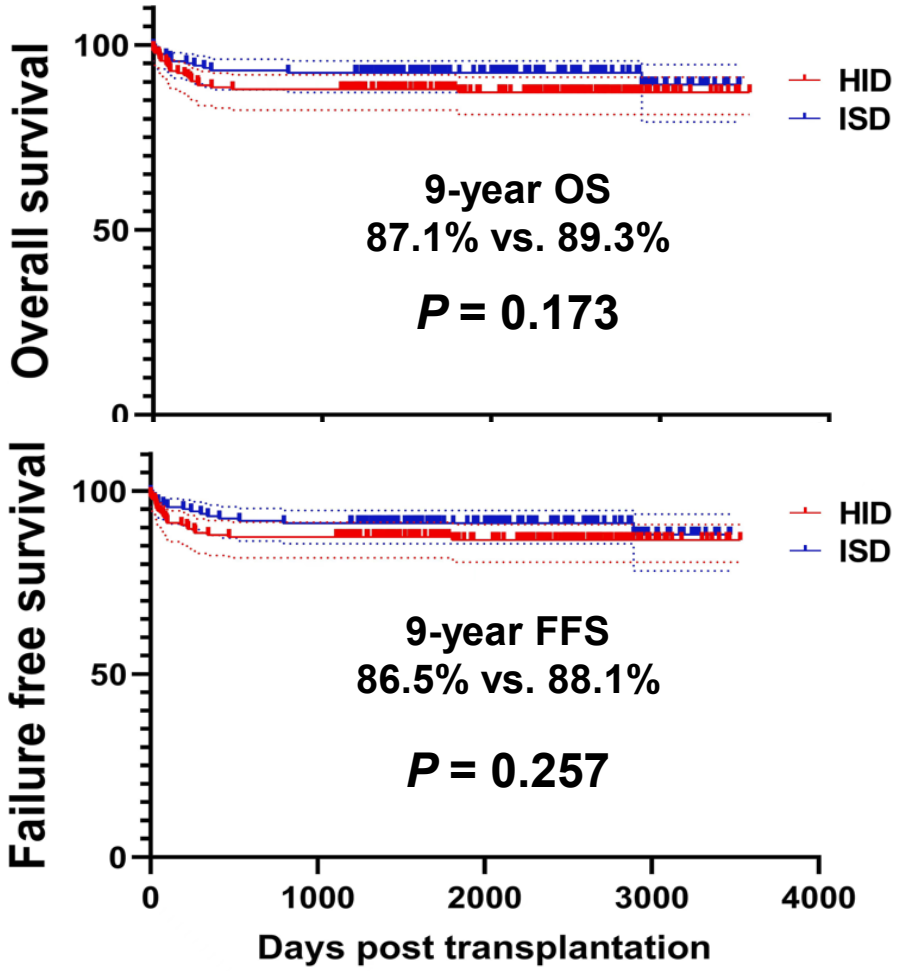


SF-36 in adults

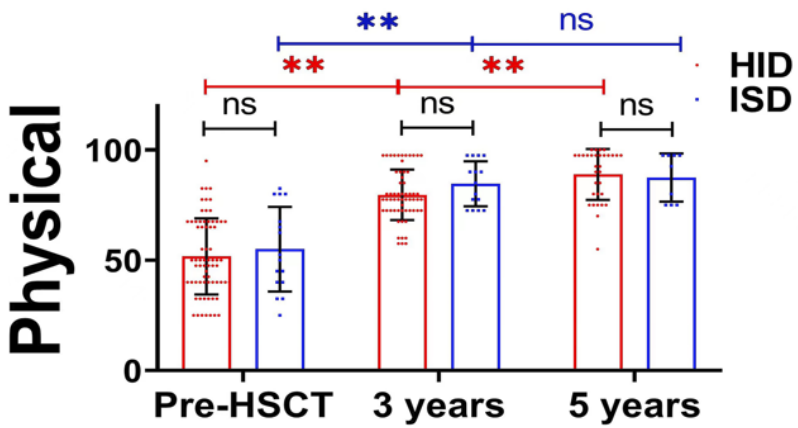
Huang XJ, et al. Science Bulletin. 2022

Comparable long-term outcomes in upfront haplo and ISD SCT for SAA

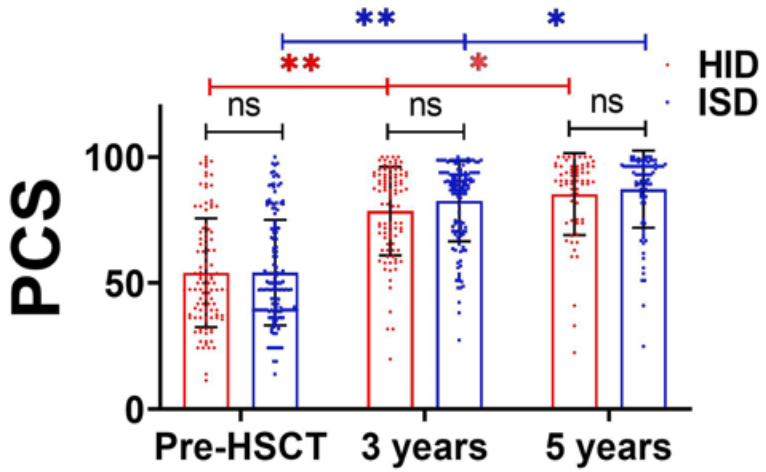
Survival



Quality of life



PedsQL 4.0 in children



SF-36 in adults

Xu ZL,…Huang XJ. et al. Haematologica. 2022*

Long-term outcomes of haplo-HSCT for AA: Expert commentary

Science Bulletin

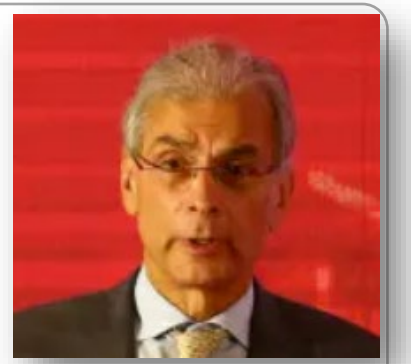
Prof. Arnon Nagler
Co-Chair of ALWP of the EBMT


Prof. Arnon Nagler

thus no wonder that professor Xiao-Jun Huang and his group pioneered the non T depleted haplo transplants for hematological malignancies in China paving the way for many other transplant centers in the world, establishing the G-CSF primed bone marrow and peripheral blood combined stem cell source be confirmed in additional SAA patient cohorts and in multicenter studies. In conclusion, treatment of severe aplastic anemia including with HSCT has improved significantly over the past 4 decades and the study by Dr. Xu Lang-Ping on behalf of his colleagues from the Peking University People's Hospital and Institute of Hematology, Beijing, China is an important step forward.

The NEW ENGLAND JOURNAL of MEDICINE

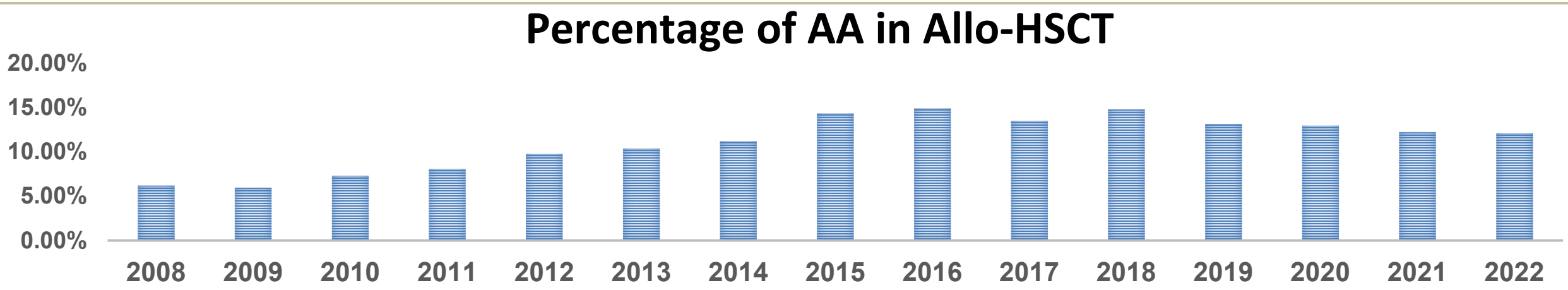
Prof. Neal S. Young
National Institutes Of Health

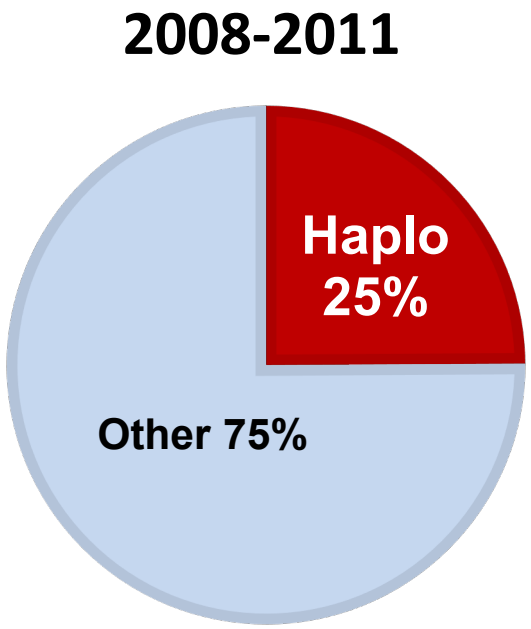


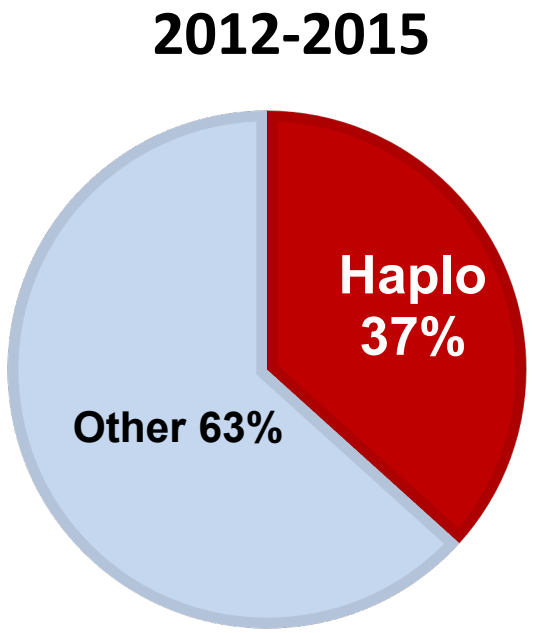
used to prevent GVHD. The results have been encouraging on the basis of extensive experience in Chinese centers, with much smaller series of transplant recipients in the United States and Europe (Table 3). Haploidentical transplantation has been advocated in China as first-line treatment for children.[92]

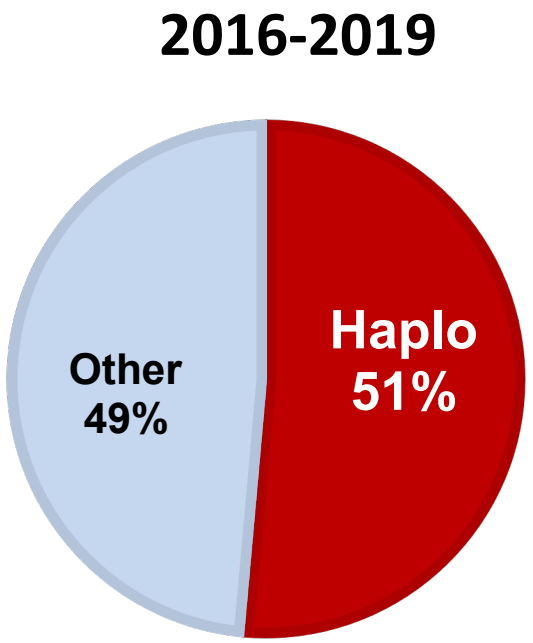
The results have been encouraging on the basis of extensive experience in Chinese centers…

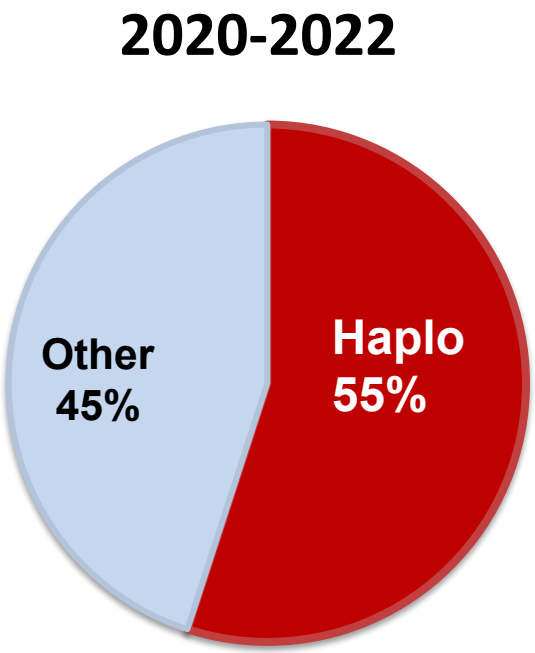
Increasing Haplo-HSCT for SAA in China





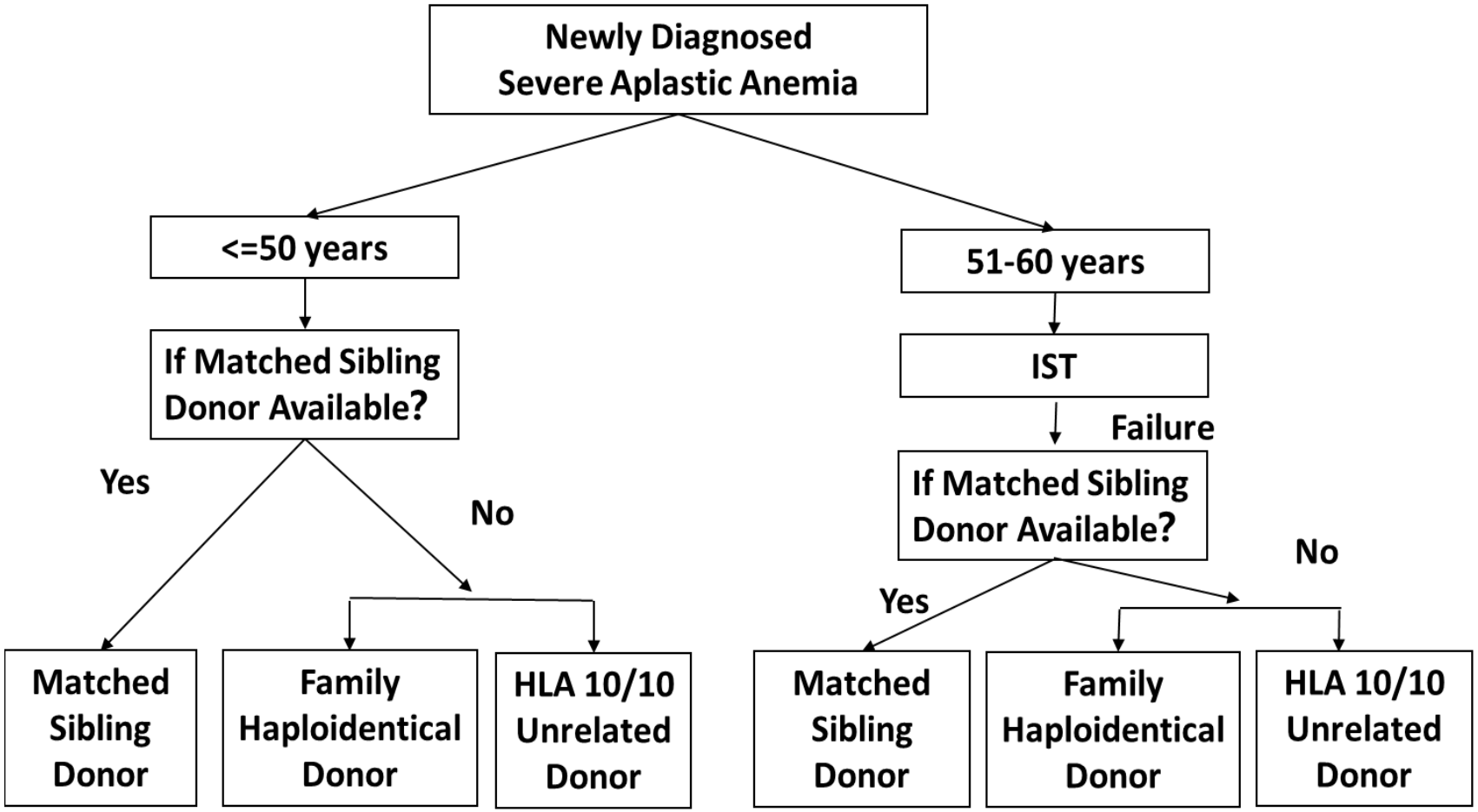






Xu LP, Huang XJ, et al. Bone Marrow Transplant. 2021.

Chinese Society of Hematology Recommendations



Haplo-HSCT for AA has been changed from second-line to first-line therapy.

Zhang XH, et al. J Hematol Oncol. 2021.

Summary

- Beijing Protocol has realized everyone has a donor
- Haplo-SCT has been increasingly applied

Allo-HSCT

Combination does better

Everyone has a donor

Haploidentical Donor

HLA matched Unrelated Donor

HLA matched Sibling Donor

CAR-T cell

Antibody

Target molecular agents