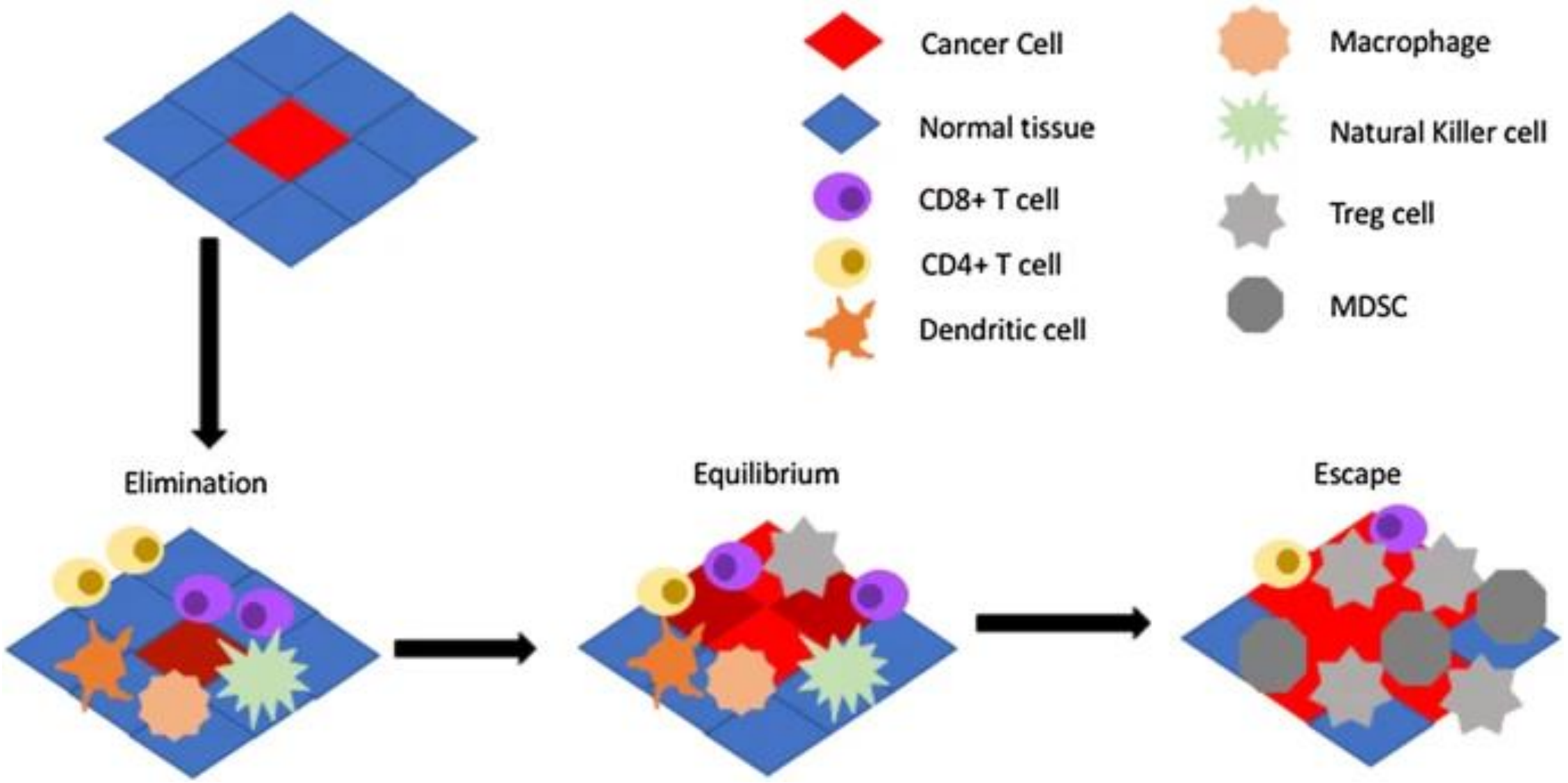
Advances in pediatric cancers ,thalassemi and hemophilia

Abolghasemi H
Professor of pediatrics
hematologist oncologist

Pediatric Cancer Immunotherapy

- Immunoediting consists of three different phases: elimination, equilibrium, and escape
- . Elimination phase : involves the innate and adaptive cells identifying the neoantigens, forming tumor-reactive T cells, and destroying cancer cells. Some tumor cells survive the elimination phase and enter the equilibrium stage.
- equilibrium stage: the tumor is held dormant by the adaptive immune system.
- escape phase: tumor cells evolve and evade the immune system, leading to the escape phase with subsequent cancer cell proliferation and/or T-cell exhaustion

Mechanism of immune evasion via immunoediting, with its three phases: elimination, equilibrium, and escape. MDSC myeloid-derived stem cell, Treg T-regulatory cell



The mechanisms behind the tumor cells evading the immune system

- loss of expression of tumor antigens and down-regulation of human leukocyte antigens (HLA) from tumor surfaces (so-called ‘edited’ tumor)
- recruitment of immunosuppressive regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), or tumor-associated M2-like macrophages, upregulation of inhibitory receptors (i.e., cytotoxic T lymphocyte associated protein 4 [CTLA-4]
- Programmed death receptor 1 [PD-1]) on T cells, or upregulation of inhibitory ligands (PD-L1) on tumor and/or stromal cells . By targeting this tumor microenvironment
- immunotherapies aim to counteract this escape phase and reinvigorate the patient’s immune system to recognize and eliminate cancer cells

Pediatric Cancer Immunotherapy

- immunomodulatory agents immunomodulatory agent is liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE)
- Antibody and antibody like therapy
- adoptive cell therapy including CAR-T therapy, NK cell, and tumor-infiltrating lymphocytes (TIL) therapy
- bispecific T-cell engagers
- oncolytic virotherapy
- checkpoint inhibition: anti-PD1 antibody, pembrolizumab, for the treatment of both adults and children with refractory classic HL

Antibdy therapy

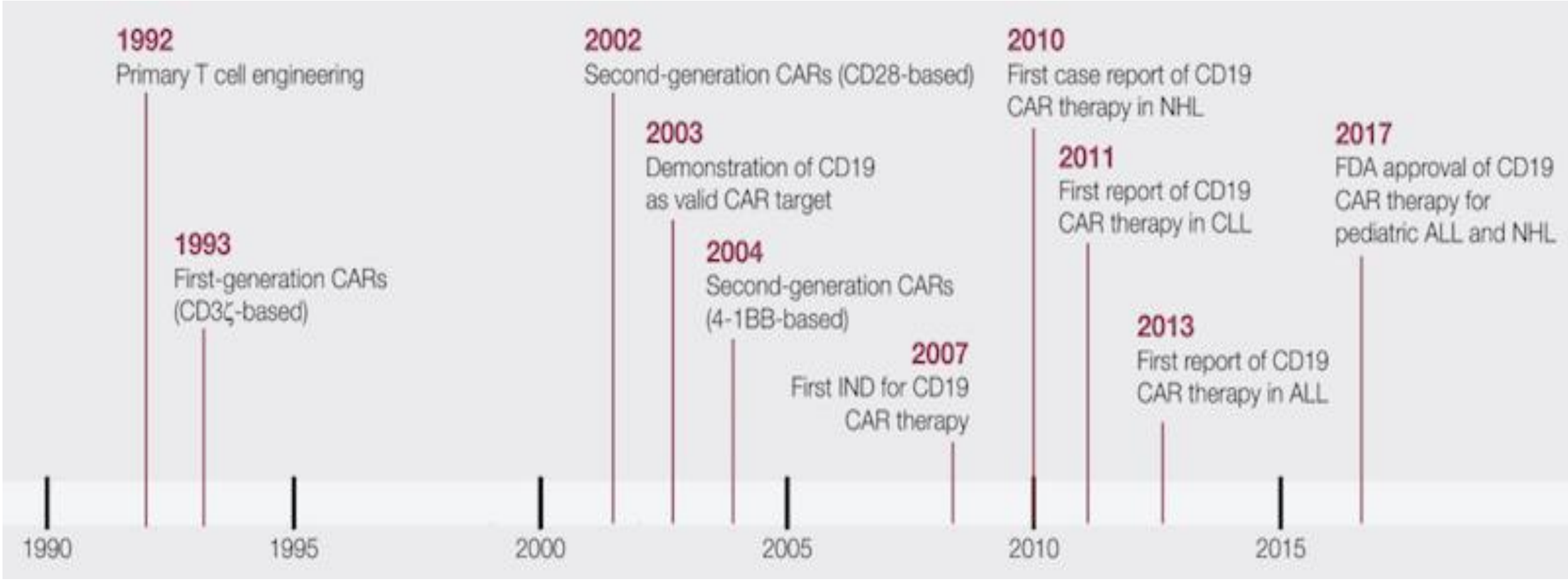
- Anti CD20 or rituximab for nonhodgkin lymphoma
- Anti CD 30 or brentuximab vedotin for relapsed Hodgkin lymphoma
- Anti-CD33 mAb interest was renewed with promising data in pediatric AML, but now is primarily utilized as BiTE therapy
- Anti CD22 for ALL
- CD19/antiCD3 BiTE, blinatumomab, was FDA approved in 2017 for the treatment of relapsed or refractory B-cell ALL
- anti-GD2 mAb dinutuximab, which is FDA approved for neuroblastoma.

- checkpoint inhibition therapy is FDA approved in very limited subsets of pediatric patients, such as those with melanoma, Hodgkin lymphoma, and biallelic mismatch repair deficiency.
- Chimeric antigen receptor T cell (CAR-T) therapy is FDA approved for some pediatric patients with leukemia but challenges remain in leveraging such technology for patients with brain tumors and neuroblastoma.
- Issues of importance are the investigation of combinations of immunotherapies, the identification of predictive biomarkers, and specific toxicities of immunotherapies in pediatric patients.

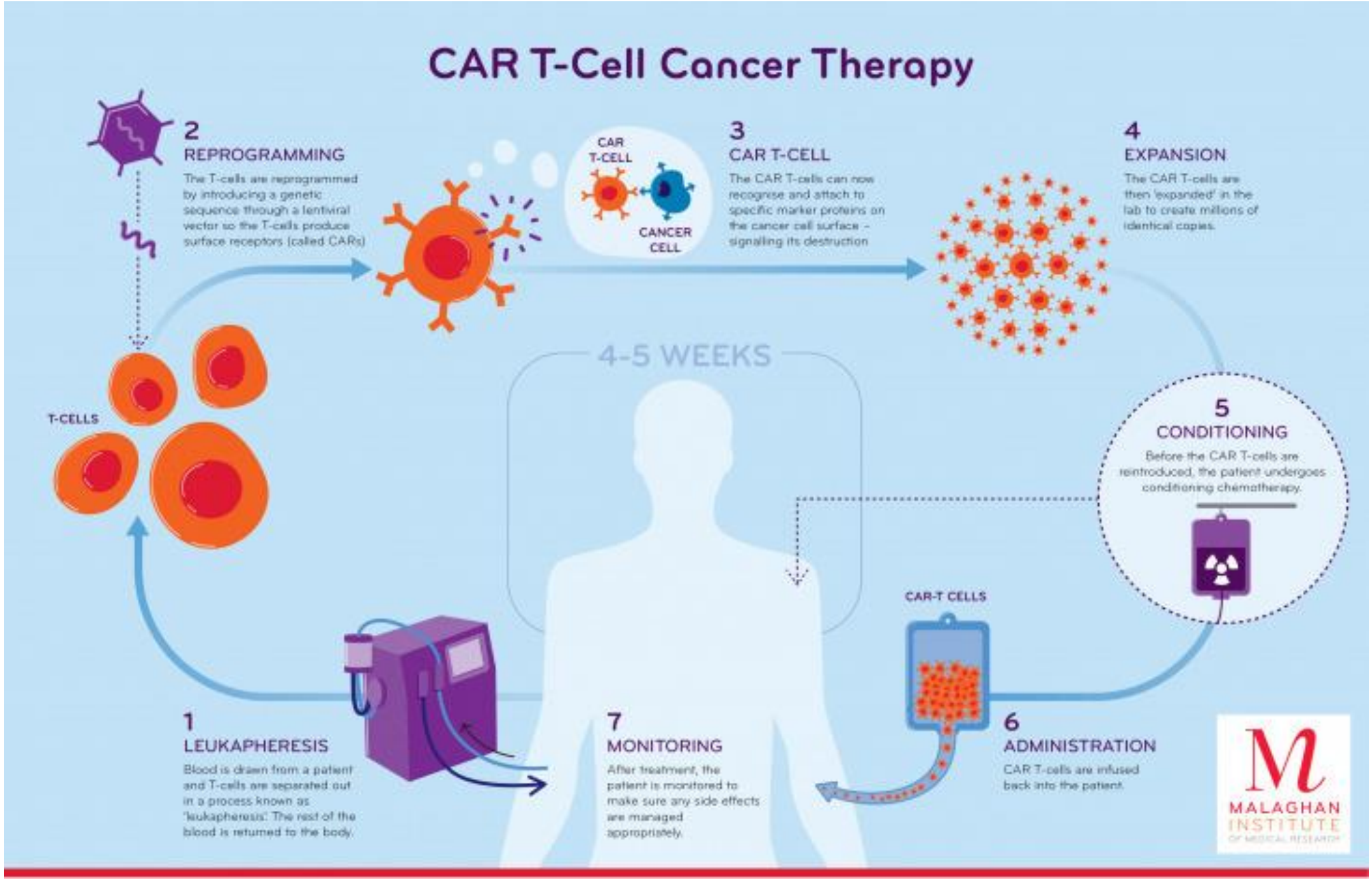
Chimeric Antigen Receptor (CAR) T-cell therapy

- genetic modification of patient's autologous T-cells to express a CAR specific for a tumor antigen, following by ex vivo cell expansion and re-infusion back to the patient. CARs are fusion proteins of a selected single-chain fragment variable from a specific monoclonal antibody and one or more T-cell receptor intracellular signaling domains.
- This T-cell genetic modification may occur either via viral-based gene transfer methods or nonviral methods, such as DNA-based transposons, CRISPR/Cas9 technology or direct transfer of in vitro transcribed-mRNA by electroporation

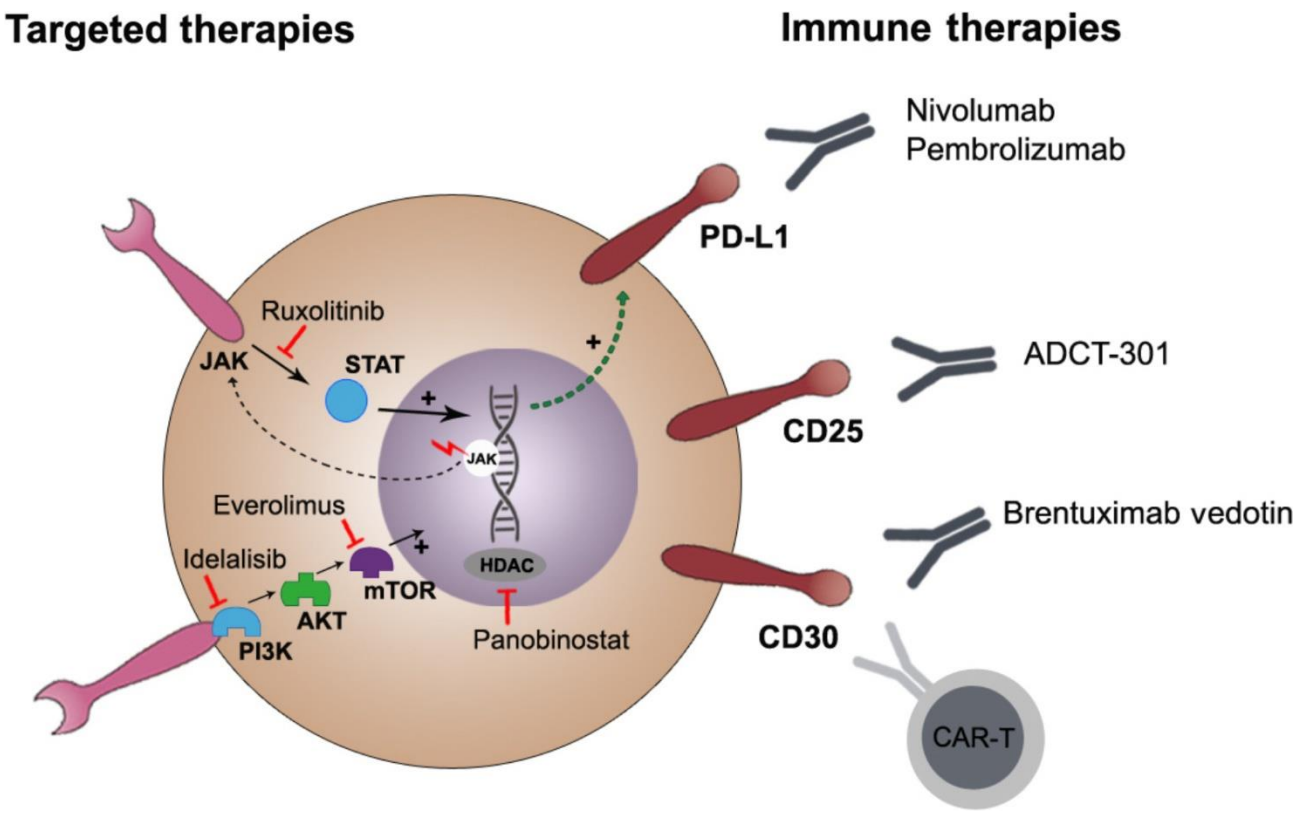
A Cure for Cancer? How CAR T-Cell Therapy is Revolutionizing Oncology



CAR T-Cell Cancer Therapy



Novel therapeutic agents for relapsed classical Hodgkin lymphoma



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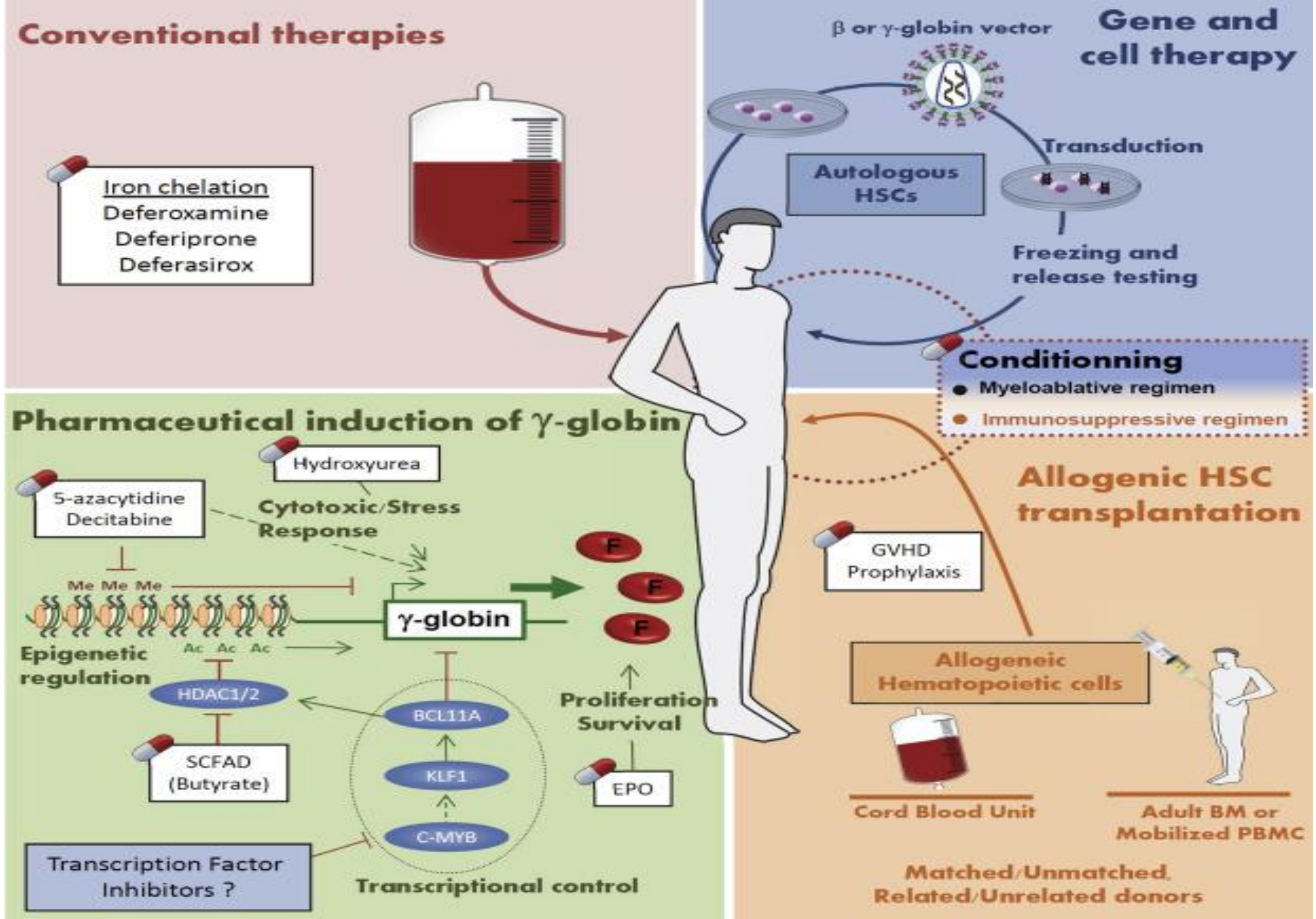
thalassemia

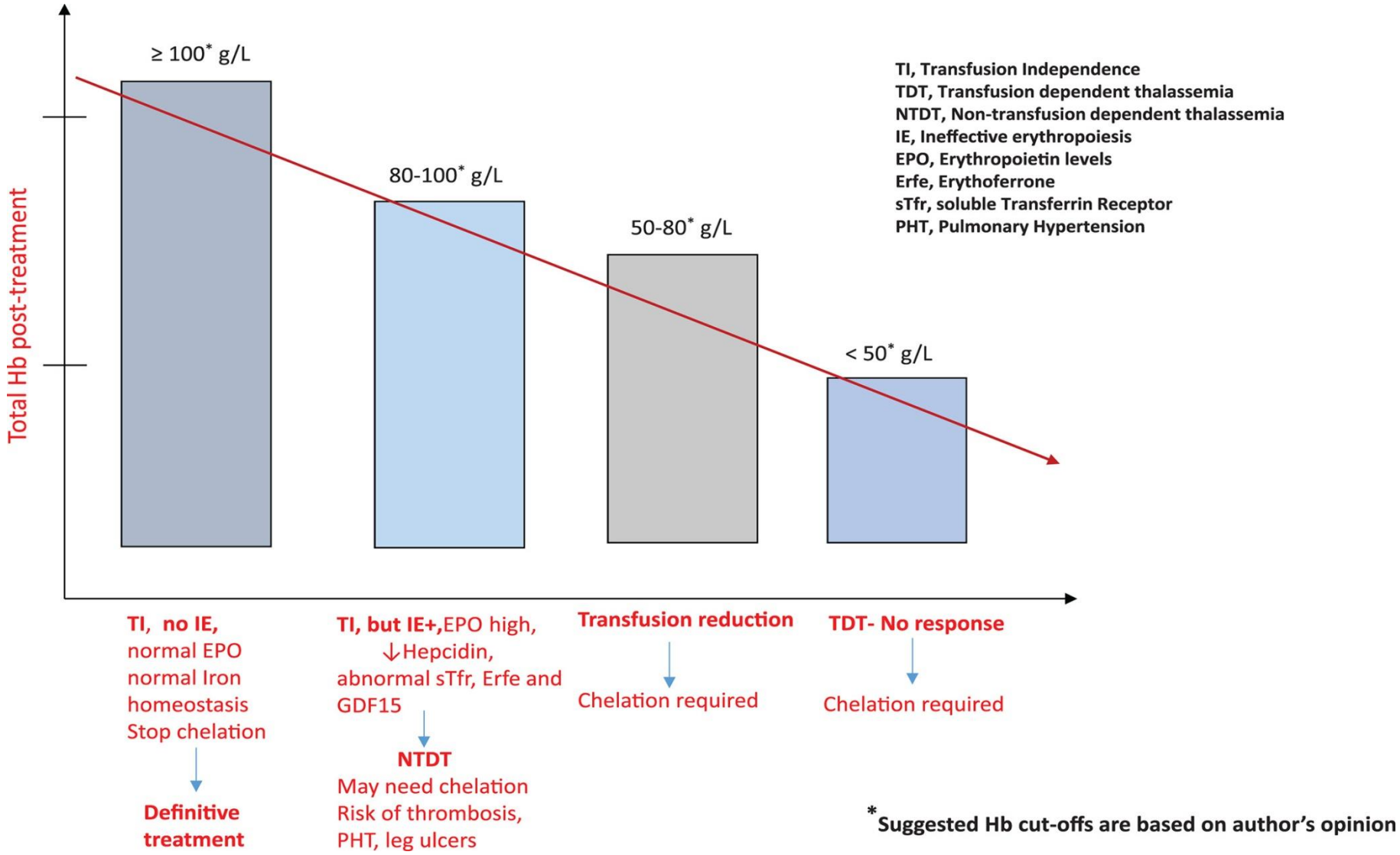

Conventional therapies
Iron chelation
Deferoxamine
Deferiprone
Deferasirox
β or γ-globin vector
Gene and cell therapy
Transduction
Autologous HSCs
Freezing and release testing
Conditionning
Myeloablative regimen
Immunosuppressive regimen
Pharmaceutical induction of γ-globin
Hydroxyurea
5-azacytidine
Decitabine
Cytotoxic/Stress Response
Me Me Me
γ-globin
Epigenetic regulation
Ac Ac Ac
HDAC1/2
SCFAD (Butyrate)
BCL11A
KLF1
C-MYB
Transcription Factor Inhibitors ?
Transcriptional control
F
F
F
Proliferation Survival
EPO
Allogenic HSC transplantation
GVHD Prophylaxis
Allogeneic Hematopoietic cells
Cord Blood Unit
Adult BM or Mobilized PBMC
Matched/Unmatched, Related/Unrelated donors

•. 2018 Apr 19;378(16):1479-1493.
doi: 10.1056/NEJMoa1705342.

Gene Therapy in Patients with Transfusion-Dependent β-Thalassem

- Recent advances in genome sequencing, an understanding of the control and regulation of the HBB gene along with improvements in vector biology and manufacturing, availability of new gene-editing nucleases that can lead to sufficient degree of gene modifications in HSPCs to achieve meaningful clinical benefit, has finally led to active clinical trials in patients.
- In two phase 1–2 studies, we obtained mobilized autologous CD34+ cells from 22 patients (12 to 35 years of age) with transfusion-dependent β-thalassemia and transduced the cells ex vivo with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA) with a T87Q amino acid substitution (HbAT87Q). The cells were then reinfused after the patients had undergone myeloablative busulfan conditioning. We subsequently monitored adverse events, vector integration, and levels of replication-competent lentivirus. Efficacy assessments included levels of total hemoglobin and HbAT87Q, transfusion requirements, and average vector copy number

Gene therapies for transfusion dependent β-thalassemia: Current status and critical criteria for success



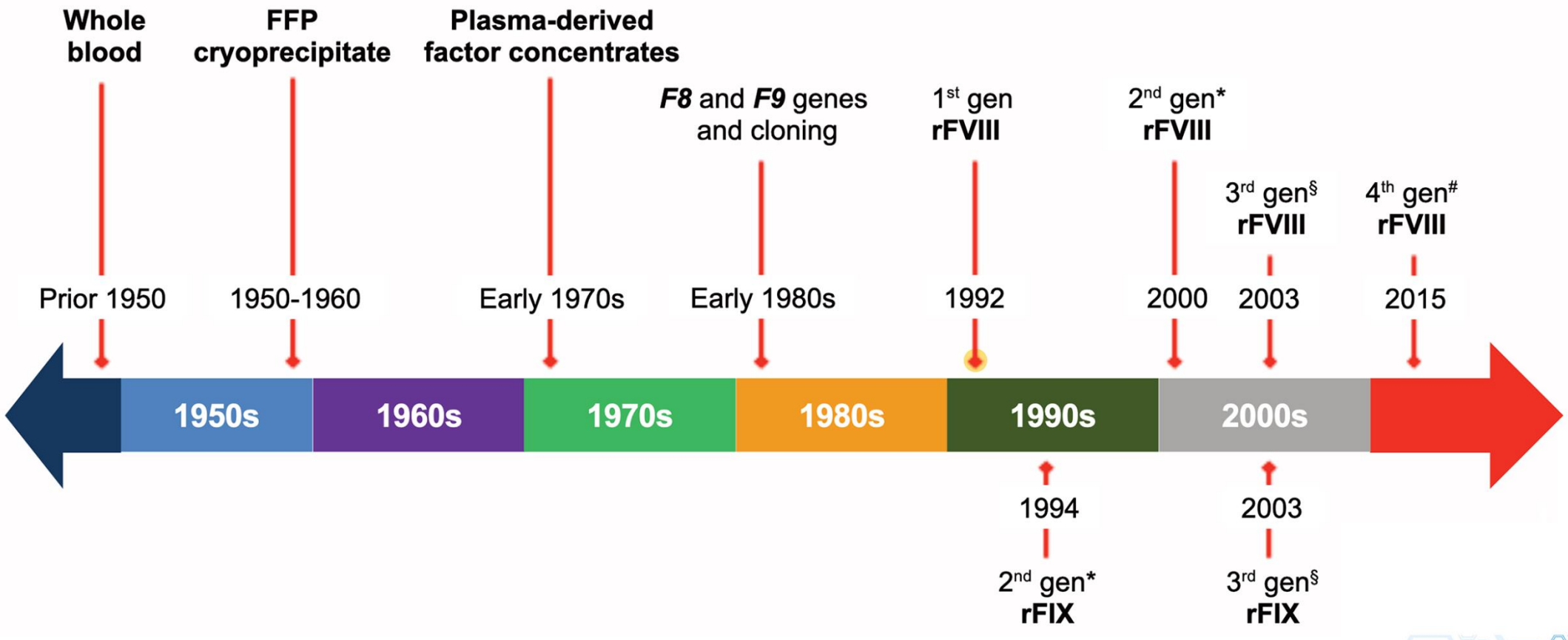
American Journal of Hematology, Volume: 95, Issue: 9, Pages: 1099-1112, First published: 19 June 2020, DOI: (10.1002/ajh.25909)

Table 2. Summary of Outcomes in the 22 Study Patients.*

Patient No.	Genotype	Last Study Visit	HbA^{T87Q} at Last Visit	Total Hemoglobin at Last Visit	Still Receiving Transfusions	Time since Last Transfusion†
		mo after infusion		*g/dl*		*mo*
1102	β^E/β^0	36	5.4	10.5	No	35.2
1103	β^0/β^0	24	8.7	9.8	Yes	NA
1104	β^E/β^0	30	4.8	10.1	No	31.6
1106	β^0/β^0	30	8.2	9.0	No	14.1
1107	β^0/β^0	30	4.1	8.6	Yes	NA
1108	β^0/β^+	24	9.6	12.1	No	30.6
1109	β^0/β^X	24	5.7	12.5	No	27.8
1110	β^0/β^0	24	4.3	8.8	Yes	NA
1111	β^E/β^0	24	8.0	13.7	No	26.5
1113	β^0/β^0	21	2.6	11.3	Yes	NA
1115	β^0/β^0	18	7.2	9.0	Yes	NA
1117	β^E/β^0	15	6.3	11.1	No	12.5
1118	β^E/β^0	12	3.4	8.2	No	11.3
1119	β^+/β^+	18	5.6	9.7	No	15.8
1120	β^E/β^0	18	3.6	9.3	No	15.8
1121	β^+/β^+	15	1.1	10.6	Yes	NA
1122	β^0/β^0	15	0.4	10.3	Yes	NA
1123	β^0/β^0	12	6.8	10.2	No	13.5
1201	β^E/β^0	36	8.2	11.3	No	41.9
1202	β^E/β^0	36	10.0	12.9	No	38.7
1203	β^+/β^+	21	6.6	8.3	No	20.4
1206	β^E/β^0	18	8.4	11.7	No	20.3

* Listed are the values a median of 26 months (range, 15 to 42) after drug product infusion. NA denotes not applicable.
† The time since the last red-cell transfusion was calculated according to the data cutoff date, which might have been later than the last study visit.

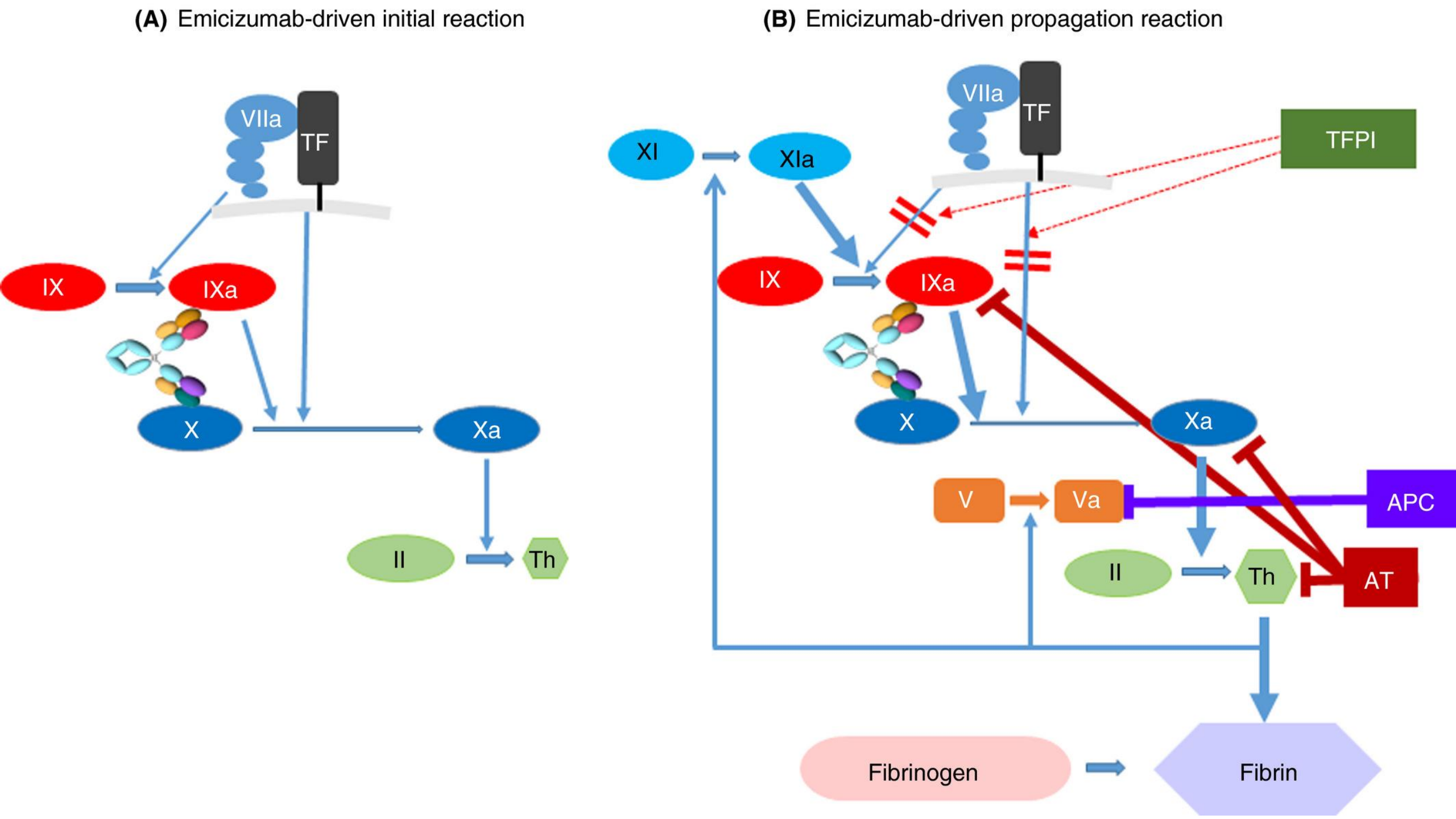
Evolution of Hemophilia Treatment



Flora Peyvandi, MD, PhD
University of Milan - Milan, Italy

essentials

- Bispecific antibody, emicizumab, recognizes activated factor IX (FIXa) and activated factor X (FXa), and promotes FIXa-catalyzed activation of FX in the absence of factor VIII.
- Phase 3 studies demonstrated reduced bleeding rates irrespective of the inhibitor.
- Emicizumab is well tolerated, although isolated thromboembolic and thrombotic microangiopathic complications may occur.
- Remaining questions include when to start, monitoring, supplementary hemostatic treatment and immune tolerance induction


(A) Emicizumab-driven initial reaction
VIIa
TF
IX
IXa
X
Xa
II
Th
(B) Emicizumab-driven propagation reaction
VIIa
TF
TFPI
XI
XIa
IX
IXa
X
Xa
V
Va
APC
II
Th
AT
Fibrinogen
Fibrin

Gene therapy in hemophilia

Hemophilia provides an attractive target for gene therapy studies, due to the monogenic nature of these disorders and easily measurable endpoints (factor levels and bleed rates)

All successful, pre-clinical and clinical studies to date have utilized recombinant adeno-associated viral (AAV) vectors for factor VIII or IX hepatocyte transduction

Recent clinical data have presented normalization of factor levels in some patients with improvements in bleed rate and quality of life.

Advances and challenges for hemophilia gene therapy

The main toxicity seen within these studies has been early transient elevation in liver enzymes, with variable effect on transgene expression.

There are a number of phase III studies currently recruiting; however, there may be some limitations in translating these data to clinical practice, due to inclusion/exclusion criteria.

AAV-based gene therapy is one of a number of novel approaches for treatment of hemophilia with other gene therapy (in vivo and ex vivo) and non-replacement therapies progressing through clinical trials.

Availability of these high-cost novel therapeutics will require evolution of both clinical and financial healthcare services to allow equitable personalization of care for persons with hemophilia.

Paul Batty, David Lillicrap
Human Molecular Genetics, Volume 28, Issue R1, October 2019, Pages R95–R101