Advances in Gene Therapy for Sickle Cell Disease and Thalassemia (Cell Therapy Beyond Cancer)

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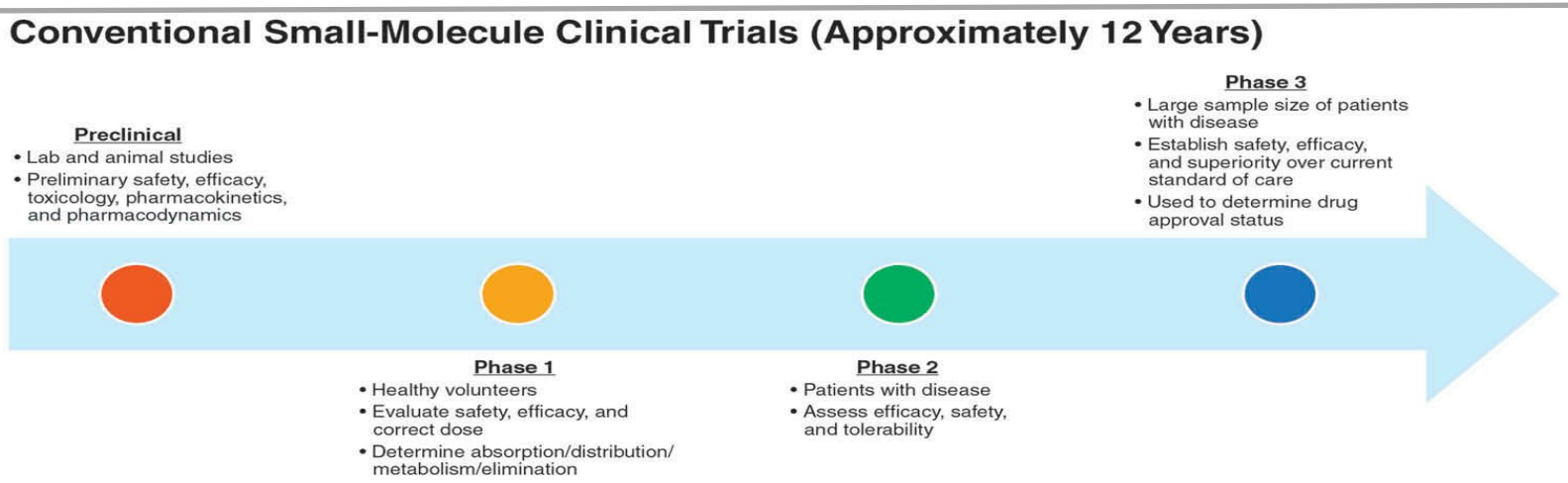
Faculty Disclosures

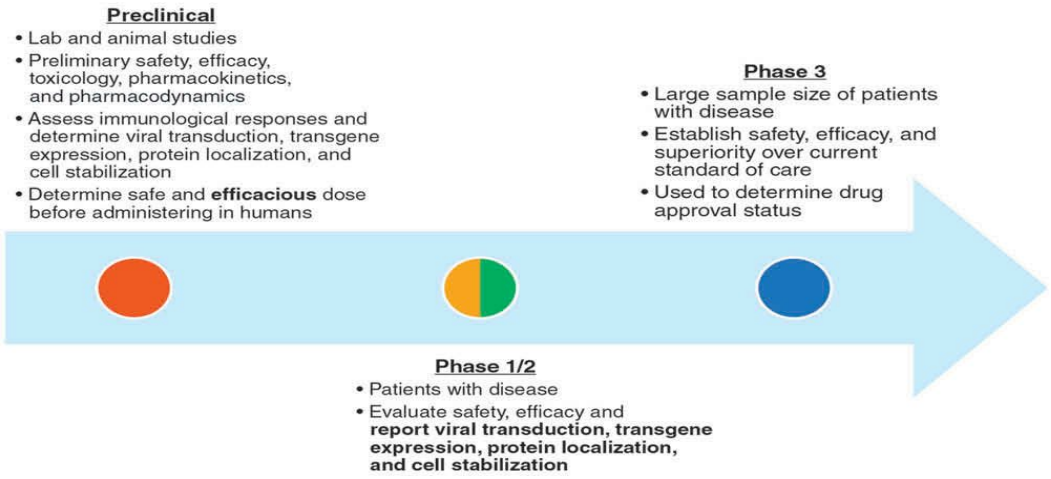
- Stephan A. Grupp, MD, PhD
  - **Consulting Fees:** Novartis, Allogene, Adaptimmune, TCR2, Cabaletta, Juno, CBMG, GlaxoSmithKline, Cellectis, J&J/Janssen, CRISPR/Vertex, Roche, Jazz, TCR2, Cellectis, Allogene, and Cabaletta
  - Toxicity management and CAR T **patents** managed by CHOP/U Penn policies
  - **Contracted Research:** Kite, Novartis, Servier, Vertex

Points to Ponder

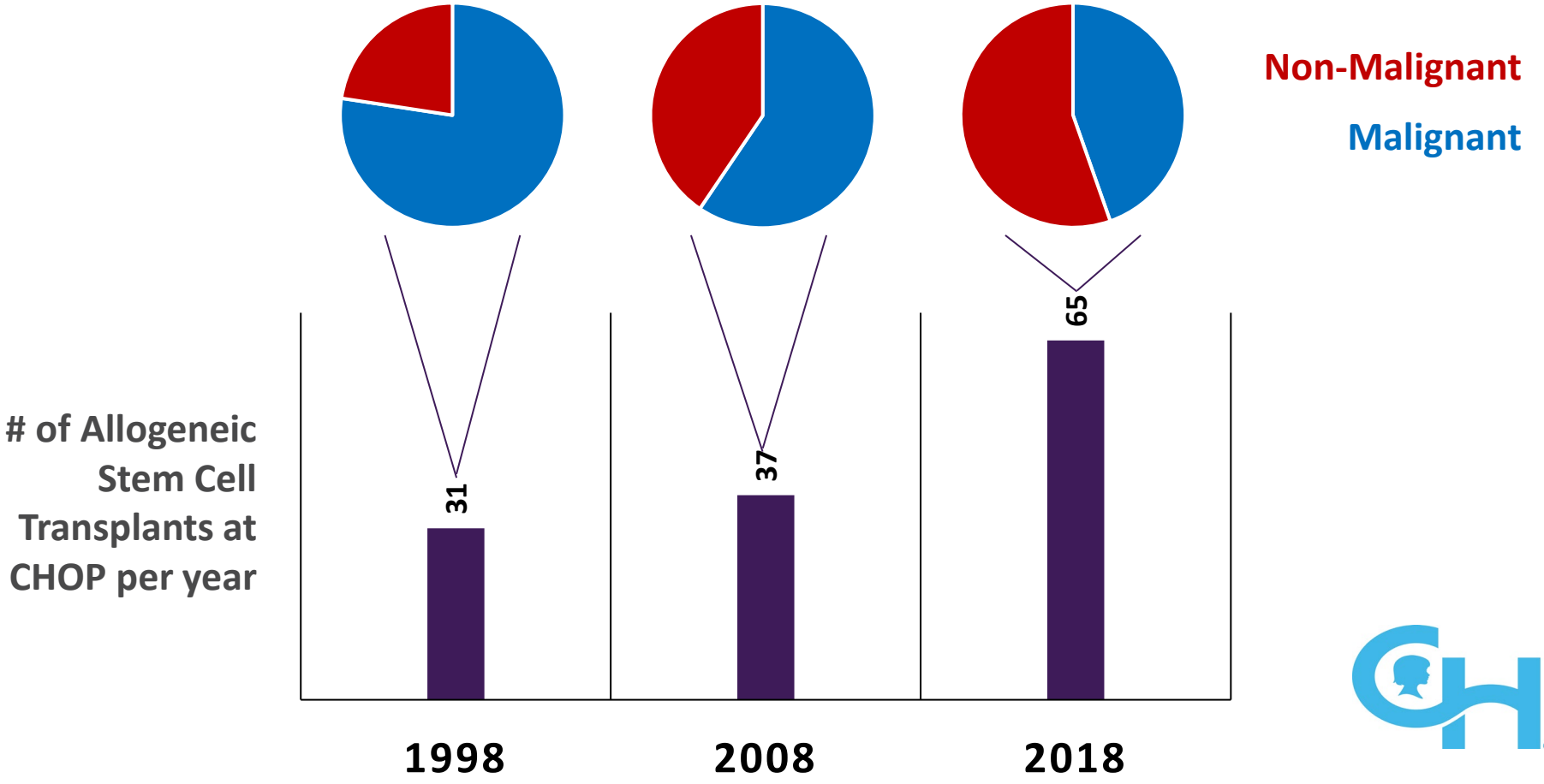
- Many gene therapies are being developed for rare diseases
  - Sparse rare disease patient populations, disease heterogeneity, and geographic dispersion create difficulties in enrolling representative, homogenous cohorts for clinical studies
- Many of these diseases are chronic, progressive diseases, affecting infants and children
- Challenges inherent to gene therapy: cell collection, manufacturing, access, centers of excellence, genotoxicity

Clinical development for conventional small-molecule drugs vs. gene therapy





Pediatric BMT:
Increased Focus on Non-Malignant Diseases



Sometimes knowing the molecular basis of a disease isn't enough…

November 25, 1949, Vol. 110 SCIENCE 543

Sickle Cell Anemia, a Molecular Disease[1]

Linus Pauling, Harvey A. Itano,[2] S. J. Singer,[2] and Ibert C. Wells[3]

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California[4]

THE ERYTHROCYTES of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in the partial pressure of oxygen. When the oxygen pressure is lowered, these cells change their forms from the normal biconcave disk to crescent, holly wreath, and other forms. This process is known as sickling. About 8 percent of American Negroes possess this characteristic; usually they exhibit no pathological consequences ascribable to it. These people are said to have sicklemia, or sickle cell trait. However, about 1 in 40 (*4*) of these individuals whose cells are capable of sickling suffer from a severe chronic anemia re-

that form from normal erythrocytes. In this condition they are termed promeniscocytes. The hemoglobin appears to be uniformly distributed and randomly oriented within normal cells and promeniscocytes, and no birefringence is observed. Both types of cells are very flexible. If the oxygen or carbon monoxide is removed, however, transforming the hemoglobin to the uncombined state, the promeniscocytes undergo sickling. The hemoglobin within the sickled cells appears to aggregate into one or more foci, and the cell membranes collapse. The cells become birefringent (*11*) and quite rigid. The addition of oxygen or carbon monoxide to these cells reverses these

Non-cancer Applications of Engineered Cell Therapy

- Closest to FDA approval are products for sickle cell disease and related disease of thalassemia, plus cALD
- These are autologous products which are gene modified bone marrow stem cells
- Examples of
  - gene addition/insertion (lentiviral vector)
  - gene editing (CRISPR)

Therapy Options for Severe Sickle Cell Disease a Decade Ago

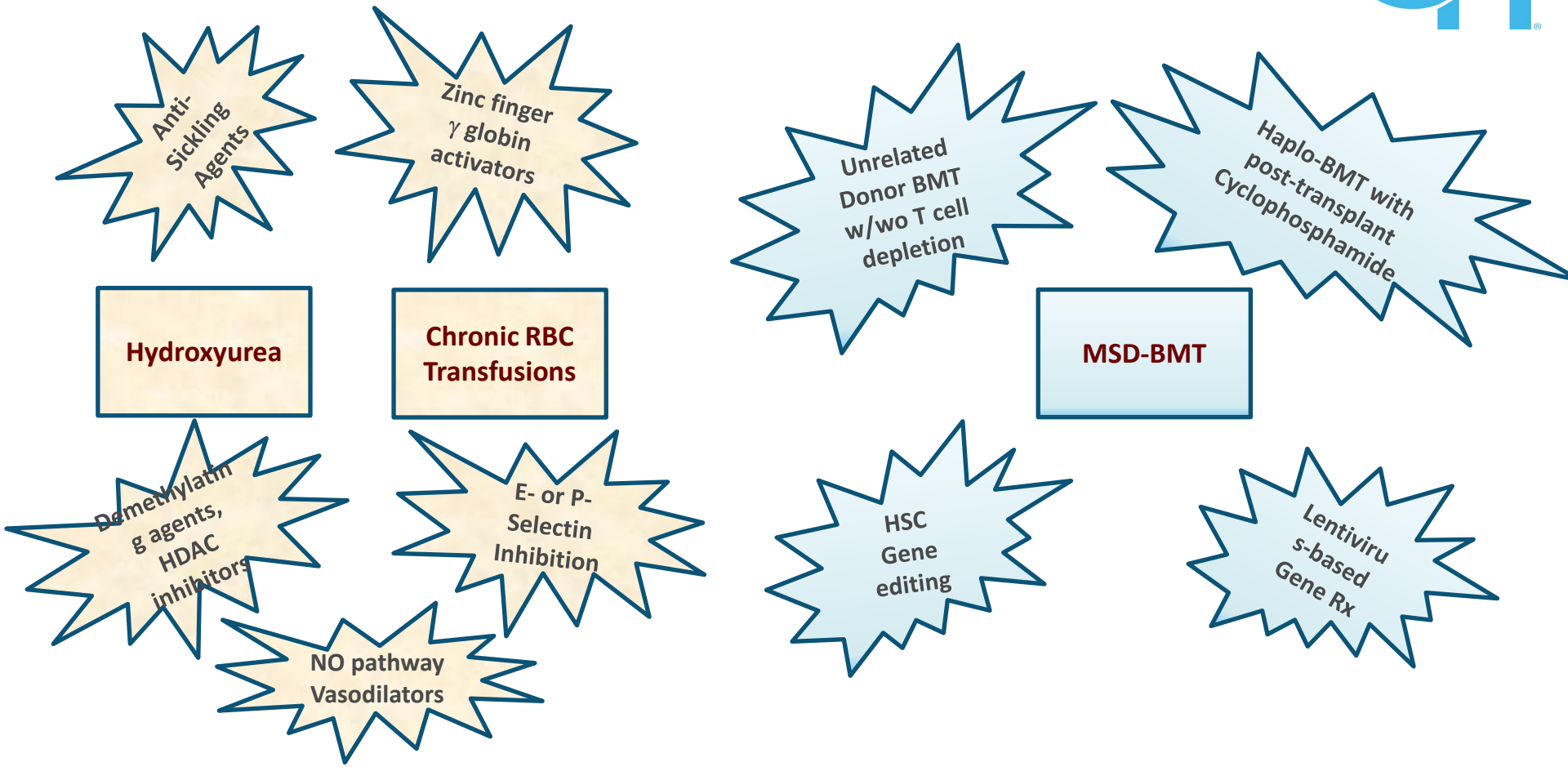
Hydroxyurea (HU)

Chronic Red Blood Cell (RBC) Transfusions

Matched Sibling Donor (MSD)-BMT*

***Only an option for 18% of patients with SCD** *(Mentzer et al. AM J Pediatr Hematol Oncol, 1994)*

Therapy Options for Severe SCD in 2022!



Eligibility for MSD-BMT: Sickle Cell Disease

Traditional Criteria: Required pre-existing complications

- **Cerebrovasculopathy**
  - Stroke
  - Abnormal TCD Velocity
  - Progressive Silent Infarctions with Cognitive Impairment
  - Over 50% stenosis of ≥ 2 arterial segments on MRA imaging
- **Vaso-occlusive episodes, typically > 2 per year x 2 years of:**
  - Acute Chest Syndrome
  - Vaso-occlusive Pain requiring admission and/or IV pain medication
  - Splenic Sequestration
  - Priapism
- **Other**
  - Pulmonary Hypertension, Avascular Necrosis, Retinopathy

***Today: Still need history of severe complications to meet criteria for gene therapy and URD-SCT, but…**

Should we be waiting for complications to pursue MSD-BMT in SCD?

Early HLA Matched Related Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease: A Sickle Transplant Alliance for Research (STAR) Trial

Study Co-Chairs:
Kimberly Kasow, DO
Emily Meier, MD, MSHS

Eligibility:

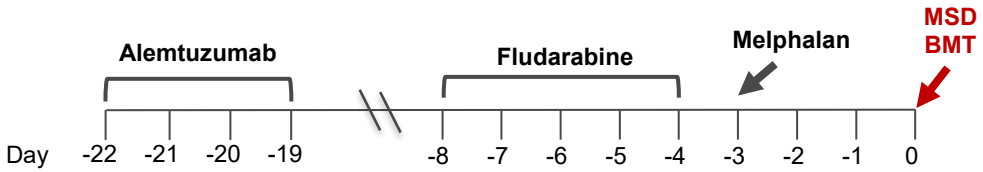
- HbSS or HbSβ^0
- Patient and donor < 10 years of age

Why Are More Patients/Families Pursuing Curative Stem Cell Therapy?

- Because optimal medical treatment and screening does not always prevent disease progression/complications
  - **Sickle Cell Disease:** acute and chronic pain, stroke, chronic lung disease, priapism, avascular necrosis, decreased life expectancy.
  - **Thalassemia Major:** Extramedullary hematopoiesis, burden of lifelong transfusion visits every 3-4 weeks.
- Because non-curative treatments can cause their own problems
  - **Hydroxyurea:** hepatic effects, myelosuppression gonadal/teratogenicity, malignancy risk???
  - **Transfusions/chelation:** alloimmunization, transfusional iron overload, osteopenia
  - **Newer biologics: Expense. L**ong-term side effects unknown?
- Because curative technologies are now more widely available!!

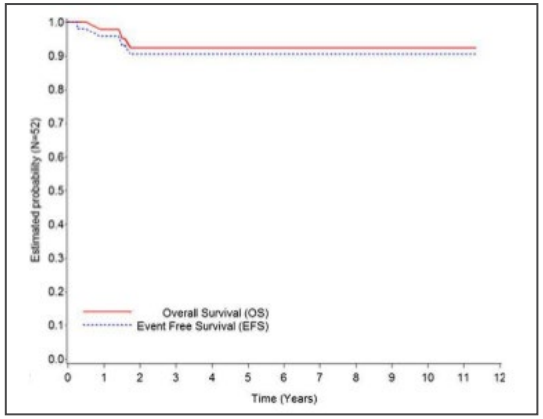
2008 to Present: Reduced Intensity Conditioning MSD-BMT for SCD

➢ **Cooperative U.S. Group:** (King, Bunin et al. *Am J Hematol*, 2015)



GVHD prophylaxis:
- CsA/tacrolimus
- Mycophenolate

43 patients (1-20 y/o); Transplant period 2003 – 2014 Median follow-up 3.5 years
Sickle cell free survival: 91% **(100% survival in age <14 years)**
Graft Rejection 2% Transplant-related mortality: 5.7%
Major problem #1: CMV infections/disease ➢ Cause of death in two patients
Major problem #2: Severe GVHD if age 14 or older ➢ ~40% risk of chronic extensive GVHD



Active Stem Cell Based Gene Therapy Clinical Trials for Non-Malignant Diseases

Hemoglobinopathies

Product	Sponsor	Strategy	Diseases	Age (y)
Lentiglobin BB305	bluebird bio	LV Gene addition: β-globin	SCD, BTM	2-50
BCH_BB-LCR shRNA(miR)	Boston Children's	LV Gene addition: shRNA targeting BCL11a	SCD	3-40
Lenti/G-βAS3-FB	UCLA	LV Gene addition: β-globin	SCD	>18
GLOBE1	Multiple	LV Gene addition: β-globin	SCD, BTM	5-35
TNS9.3.55	Mem Sloan Kettering	LV Gene addition: β-globin	BTM	>18
CSL200	CSL Behring	LV Gene addition: γ-globin + shRNA734	SCD	18-45
CTX001	Vertex	CRISPR-CAS9 Gene editing: BCL11a	SCD, BTM	12-35
OTQ923/HIX 763	Novartis	CRISPR-CAS9 Gene editing: BCL11a	SCD	2-40
BIVV003	Bioverativ	ZFN Gene editing: BCL11a	SCD	18-40

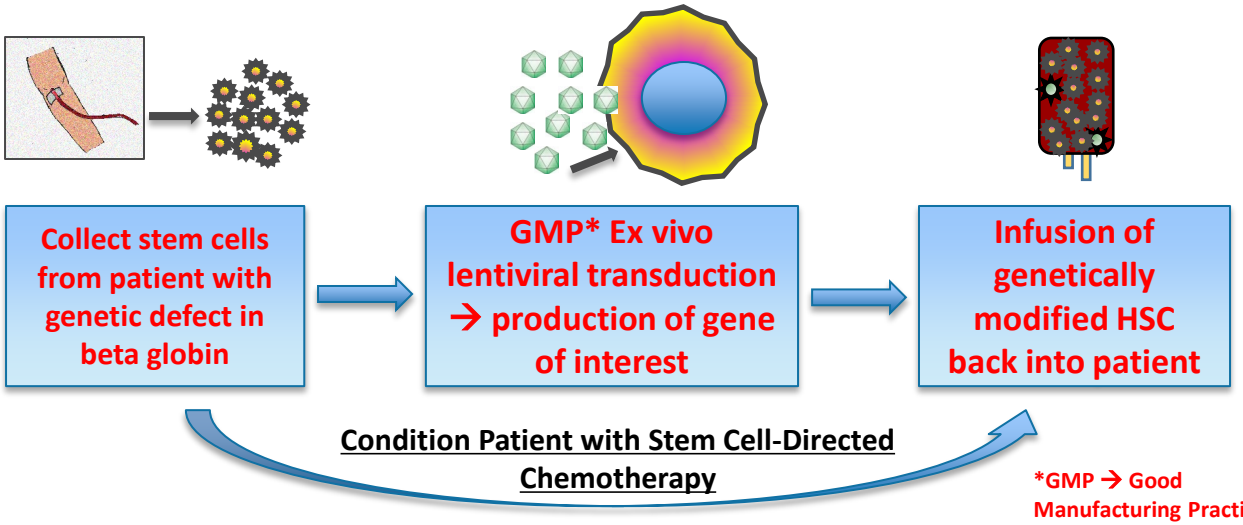
Primary Immune Deficiencies

Product	Sponsor	Strategy	Diseases	Age (y)
OTL-101	Orchard	LV Gene addition: ADA	ADA-SCID	< 18
AProArt	UCSF	LV Gene addition: DCLRE1C	Artemis-SCID	> 2mth
SIN-LV-RAG1	Leiden Univ	LV Gene addition: RAG1	RAG-1 SCID	< 2
G2SCID	Boston Child	LV Gene addition: IL2RG	X-linked SCID	≤ 5
CL20-i4-EF1α-hγc-OPT	Multiple (Mustang)	LV Gene addition: IL2RG	X-linked SCID	varies
OTL-103	Orchard	LV Gene addition: WAS	Wiskott-Aldrich	> 5
G1XCGD	Genethon	LV Gene addition: CYBB	X-linked CGD	> 2

Neurologic, Metabolic, and BMF Disorders

Product	Sponsor	Strategy	Diseases	Age (y)
OTL-200	Orchard	LV Gene addition: Arylsulfatase A	MLD	0-7
Lenti-D	bluebird bio	LV Gene addition: ABCD1	cALD	0-17
IDUA	IRCCS San Raffaele	LV Gene addition: α-L-iduronidase	MPS-1 (Hurler's)	0-11
RP-L401	Rocket	LV Gene addition: TCIRG1	Infantile Osteopetrosis	> 1mth
RP-L102	Rocket	LV Gene addition: FANCA	Fanconi Anemia	> 1

Lentivirus Based Gene Therapy for Hemoglobin Disorders

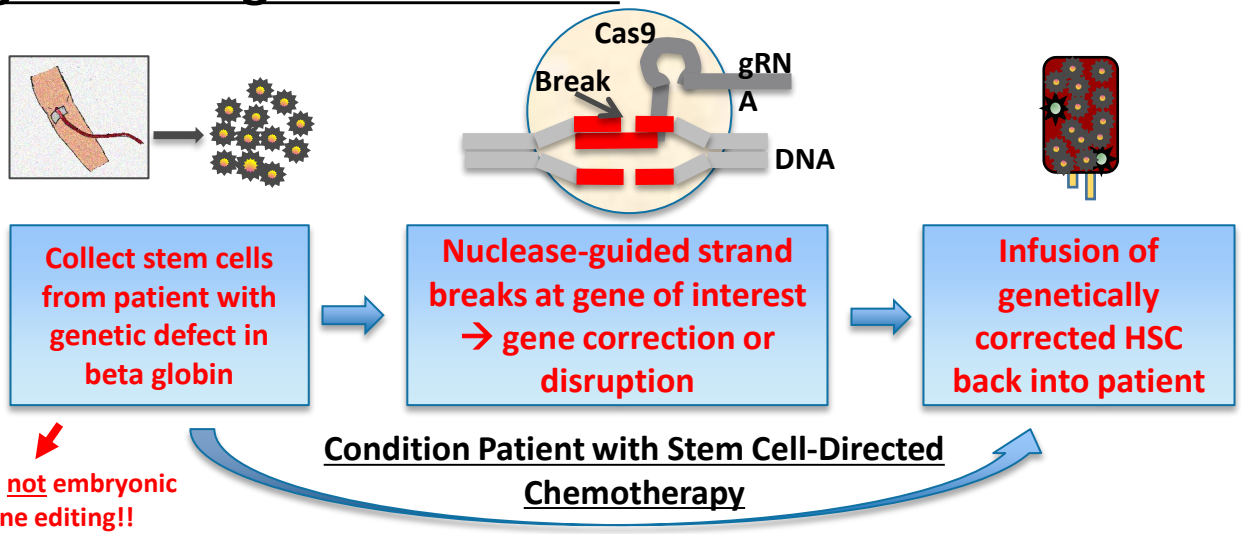


*GMP → Good Manufacturing Practice regulations per Code of Federal Regulations (CFR)

Options for Gene Addition

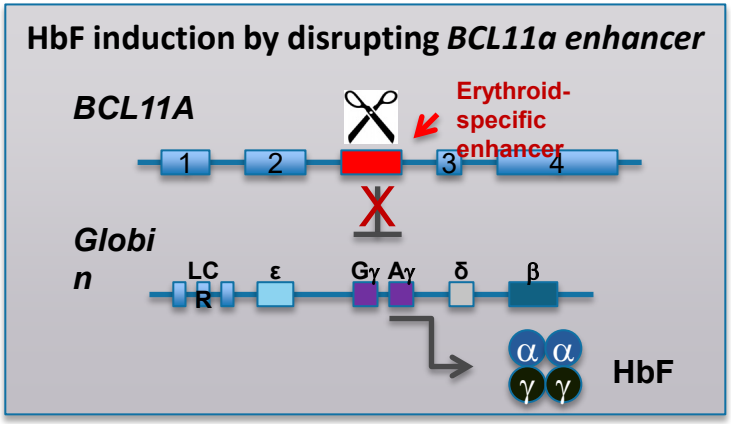
1. β-globin: increases HbA (NCT02140554)
2. γ-globin: increases HbF (NCT02186418)
3. Short hairpin(sh)RNA (miR) targeting *BCL11A* enhancer: increases HbF (NCT03282656)

Gene Editing for Hemoglobin Disorders



Goals of gene editing

1. Gene correction: difficult, needs homologous recombination (inefficient, no current trials)
2. Gene disruption by error-prone non-homologous end joining (NHEJ) creation of insertions/deletions (efficient, currently in trials)



Allogeneic HSCT versus Gene Therapy: How to Decide?

	Allo HSCT	Gene Therapy
Myeloablation Risks	Present	Present
Speed of Engraftment	Faster	Slower, particularly platelets
Alloimmunity Risk	Present	None
Infection Risk	Higher	Lower
Medication Burden	Higher	Lower
Degree of Phenotype Correction	Typically complete (if full chimerism achieved)	Often partial correction (but this may be ok for many diseases)
GVHD	High	None

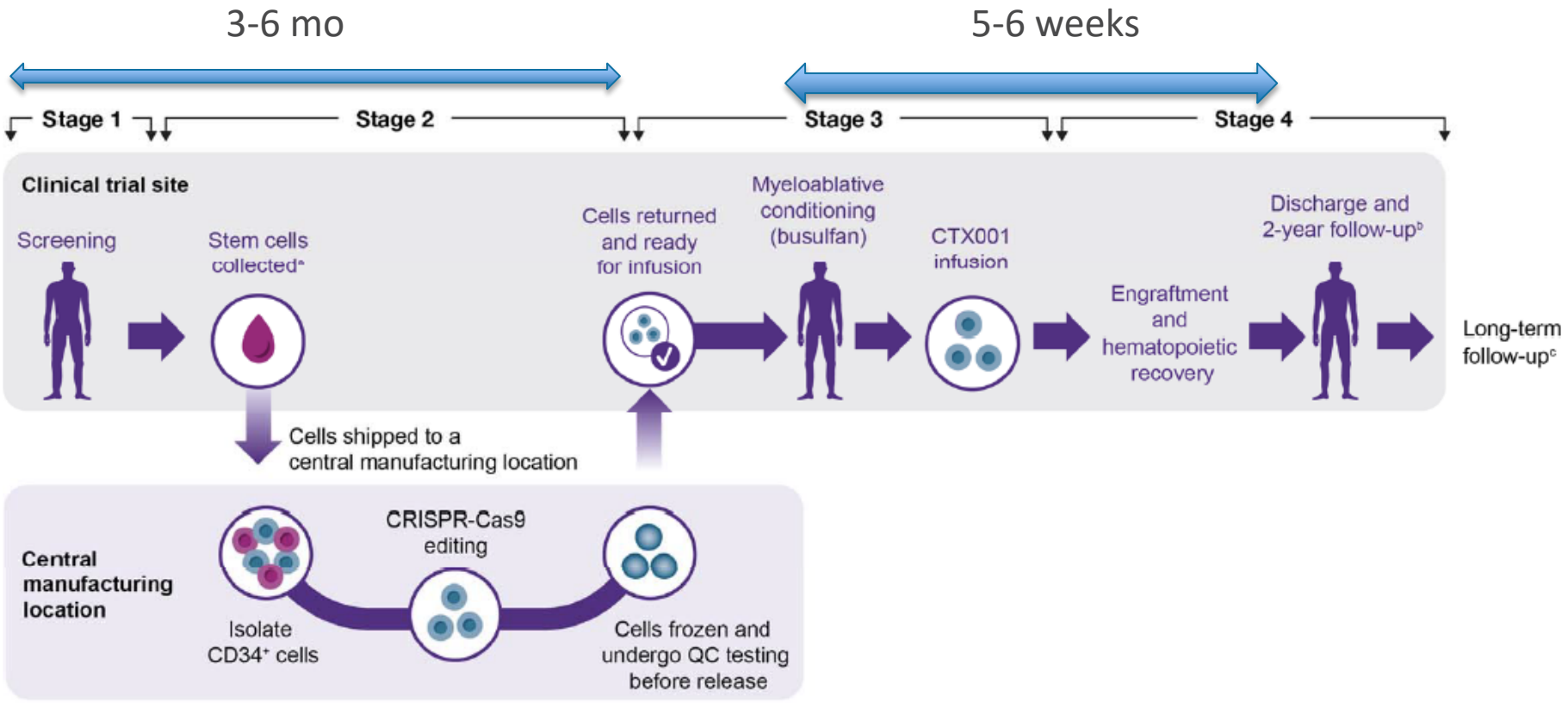
- **Biggest Problem for allo HSCT: GVHD/infection**
- **Biggest Problem for Gene Therapy: Access**
  - Trial slots, post-approval capacity, insurance?
- **Problem for BOTH: reproductive toxicity**

Current and Future Challenges for Gene Therapy

- **Availability**
  - **Current:** limited trial slots
  - **Future:** limited manufacturing capacity?
- **Exportability**
  - Conditioning/infusion straightforward
  - Collection requires specialized expertise
- **Long Term Follow-up**
  - Coordinating network of centers likely needed
- **In The Future…**
  - Head to head comparisons with Allo-BMT
  - Elimination of alkylating agent conditioning?

Recommendation: **Recent results from gene therapy trials demonstrate safety and promising early efficacy. Eligible patients interested in curative therapy should seek consultation to learn more about these studies.**

Sickle cell gene therapy transplant process



Adapted from The New England Journal of Medicine, Frangoul H et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia, 384., 252-260. Copyright © (2020) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

QC, quality control.

[a]Patients enrolled in CLIMB SCD-121 received plerixafor only. Back-up cells kept at site as a safety measure;

[b]Patients will be followed for 24 months after CTX001 infusion with physical exams, laboratory and imaging assessments, and adverse event evaluations;

[c]All patients who receive CTX001 will be followed for 15 years overall in a long-term follow-up study (NCT04208529) after completion or withdrawal from CLIMB SCD-121.

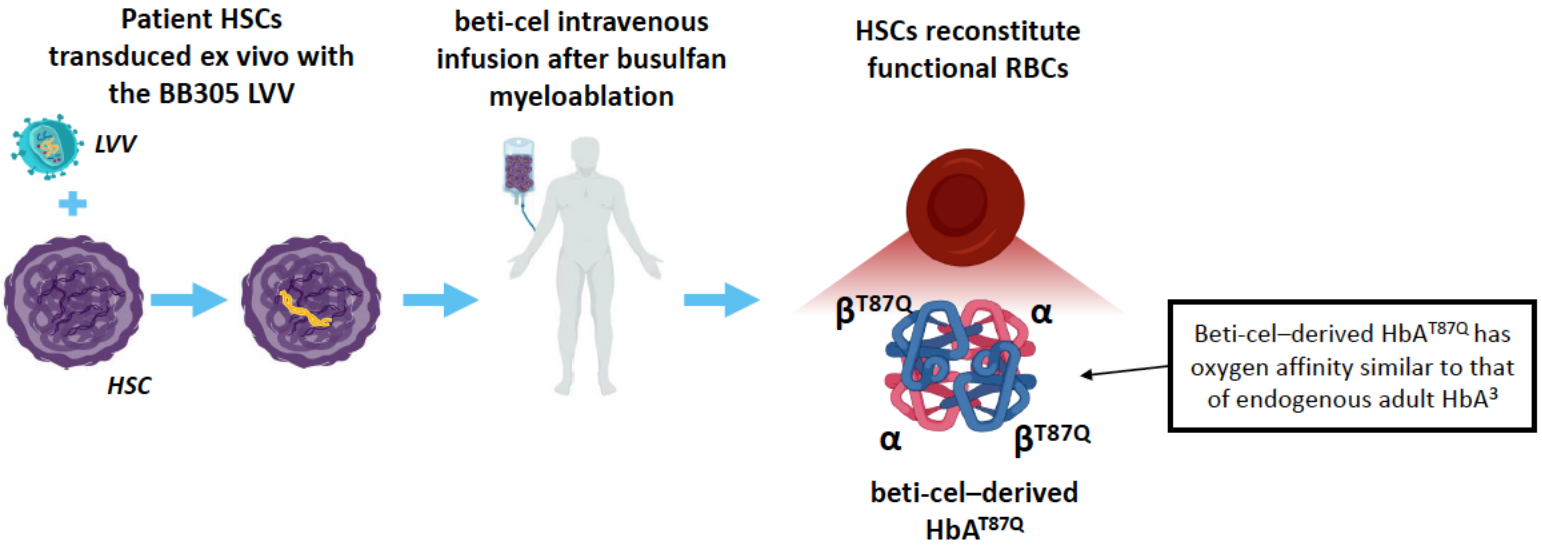
6

bbb beta-thal study – gene addition

Thompson et al. ASH 2021. Abstract 148177

Betibeglogene autotemcel (beti-cel) ex vivo gene therapy for TDT

- Transfusion-dependent β-thalassemia (TDT) is a severe, progressive genetic disease caused by mutations in the β-globin gene resulting in absent or significantly reduced adult hemoglobin, HbA, that normally accounts for approximately 95% of the total Hb in the blood of adults after 6 months of age[1,2]



1. Paramore C, et al. *Patient.* 2021;14(2):197-208. 2. Thomas C, et al. *Continuing Education in Anaesthesia. Critical Care & Pain.* 2012;12(5):251-6. 3. Pawliuk R, et al. *Science.* 2001;294(5550):2368-71.
HbA, adult hemoglobin; Hb, hemoglobin; HSC, hematopoietic stem cell; LVV, lentiviral vector; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia.

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

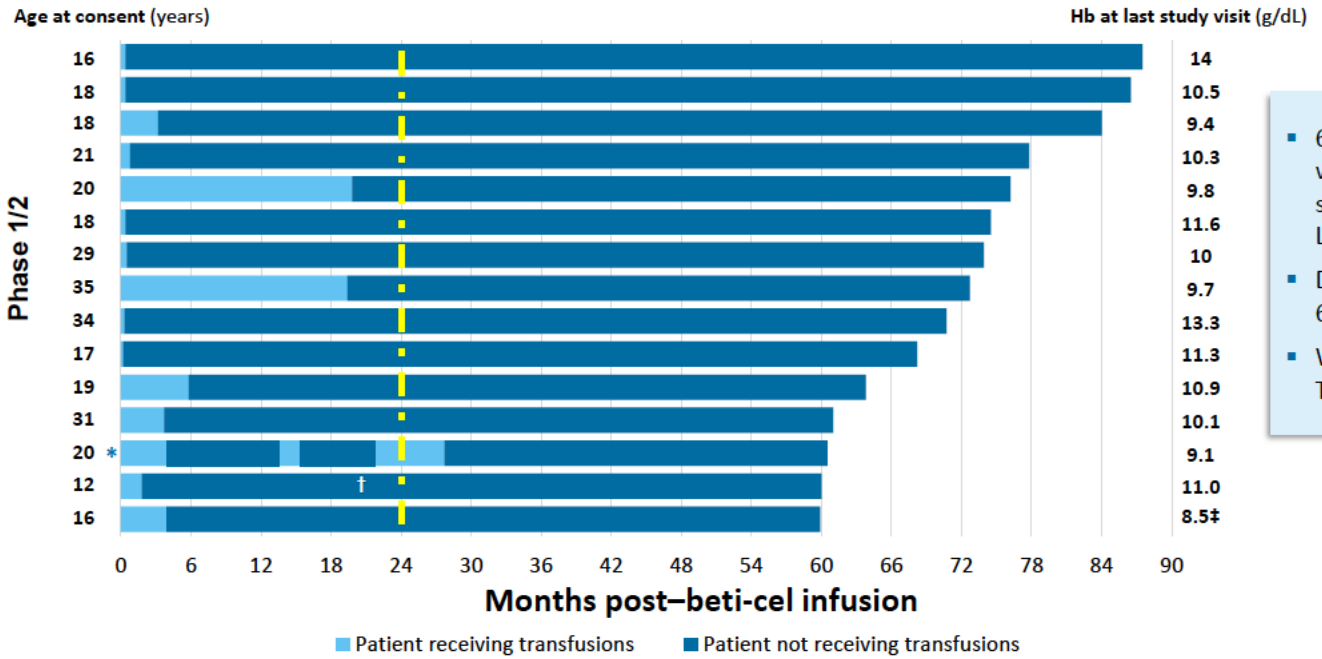
A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller, E. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, L. Caccavelli, J.-S. Diana, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarré, 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

bbb beta-thal study

Thompson et al. ASH 2021. Abstract 148177

Phase 1/2 studies: maintenance of TI for up to 7 years of follow-up

Transfusion status in phase 1/2 patients enrolled in LTF-303 who achieved TI



- 68.2% (15/22) of patients who completed a phase 1/2 study and enrolled in LTF-303 achieved TI
- Duration of ongoing TI: 65.91 (19.8 – 84.5) months
- Weighted average Hb during TI: 10.3 (9.1 – 13.2) g/dL

*Patient diagnosed with HIV-1 infection approximately 22 months after beti-cel infusion. †Patient had a single transfusion for an acute event of *Bartonella* infection. ‡Represents patient's total unsupported hemoglobin at last study visit; this patient's weighted average hemoglobin during TI was 9.3 g/dL. TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months). Yellow dotted line denotes completion of parent study and enrollment in LTF-303.

CRISPR gene editing trial for Hemoglobinopathies - Vertex

ASH 2020: CRISPR and Vertex's Potential Cure for Sickle Cell Disease and More Glimmers of Hope

Published: Dec 07, 2020 | By Mark Terry

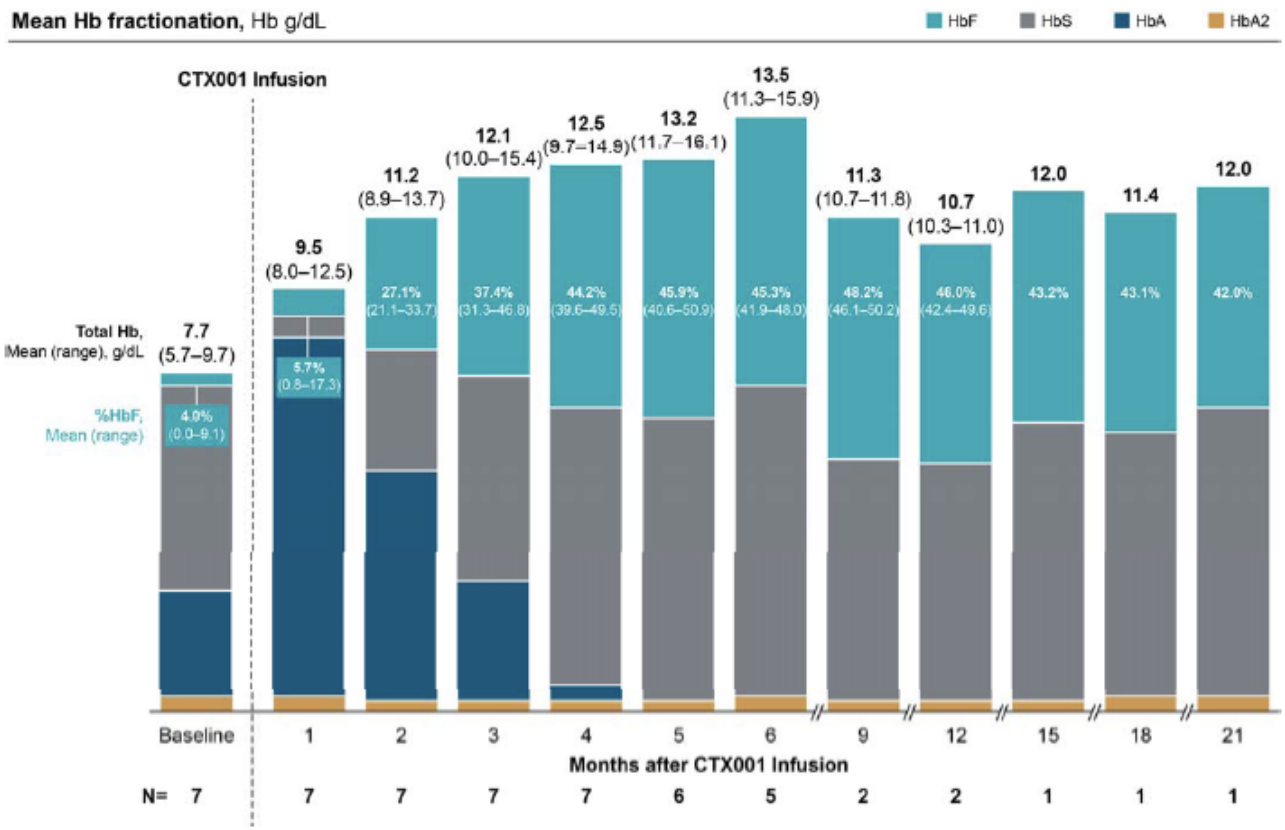
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

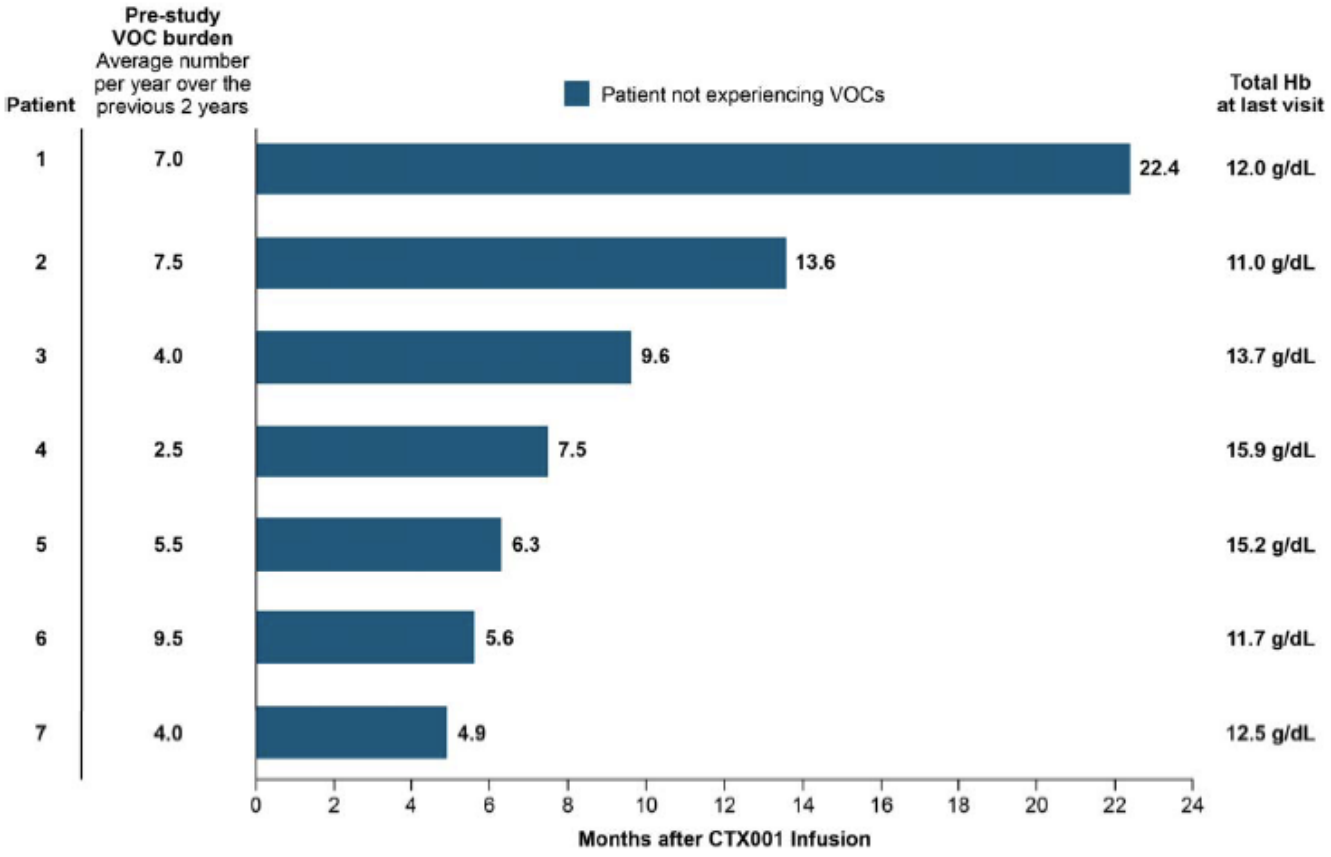
CTX001 gene editing – sustained increases in Hb/HBF



Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin.
Bars show mean Hb in g/dL, labels indicate mean proportion of HbF as a percentage of total Hb.

- Increases in total Hb and HbF occurred early and were maintained over time; mean %HbF increased to >30% by 3 months following infusion

CTX001 – sickle cell patients VOC free



- All 7 patients have remained VOC-free from CTX001 infusion to the time of this analysis, with up to 22.4 months of total follow-up

Hb, hemoglobin; VOC, vaso-occlusive crisis.

11

CTX001 sickle cell current conclusions

- All patients (N=7) have been VOC-free from the time of CTX001 infusion, with a follow-up of 4.9 to 22.4 months
- The safety profile of CTX001 is generally consistent with that of myeloablative conditioning and autologous hematopoietic stem cell transplant
- All patients demonstrated clinically meaningful increases in total Hb and HbF which occurred early and have been maintained over time
- After CTX001 infusion, high levels of BCL11A edited alleles in CD34+ bone marrow cells were maintained
- Major data update due this year

Lentiviral transduction concerns

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Acute Myeloid Leukemia Case after Gene Therapy for Sickle Cell Disease

Sunita Goyal, M.D., John Tisdale, M.D., Manfred Schmidt, Ph.D., Julie Kanter, M.D., Jennifer Jaroscak, M.D., Dustin Whitney, Ph.D., Hans Bitter, Ph.D., Philip D. Gregory, Ph.D., Geoffrey Parsons, Ph.D., Marianna Foos, M.S., Ashish Yeri, Ph.D., Maple Gioia, A.L.M., Sarah B. Voytek, Ph.D., Alex Miller, B.S., Jessie Lynch, M.S., Richard A. Colvin, M.D., Ph.D., and Melissa Bonner, Ph.D.

bluebird bio Announces Temporary Suspension on Phase 1/2 and Phase 3 Studies of LentiGlobin Gene Therapy for Sickle Cell Disease (bb1111) (news release). Cambridge, MA: bluebird bio, Inc; Feb. 16, 2021

bbb lentiviral transduction concerns

- No genotoxicity in CAR T, but concerns exist in transduced HSC
- No US approval (approved → pulled in EU)

-then-

- AML years after SCD therapy (also MDS) → FDA hold
- Vector in blasts
- Integration site is VAMP4, which should be innocuous
- Back off FDA hold
- Risk-benefit considerations in cALD product

bluebird bio Announces Temporary Suspension on Phase 1/2 and Phase 3 Studies of LentiGlobin Gene Therapy for Sickle Cell Disease (bb1111) (news release). Cambridge, MA: bluebird bio, Inc; Feb. 16, 2021

bbb eli-cel for cALD summary (gene addition)

- **Eli-cel may offer an alternative to allo-HSCT in patients with early cerebral disease:** In most patients, eli-cel stabilizes neurologic disease and shows a favorable safety profile with up to 83.7 months of follow-up

Efficacy outcomes in ALD-102/LTF-304

- 91% of evaluable patients (29/32) were alive and MFD free at Month 24
- Of 32 patients, 30 had stable NFS, 26 had stable Loes scores, and 29 were GdE(-) at last visit

Safety outcomes in ALD-102/LTF-304 and ALD-104

- The treatment regimen had a safety/tolerability profile primarily reflective of the known effects of mobilization/apheresis and conditioning
- The following AEs are considered possibly related to eli-cel drug product: 3 SAEs (BK viral cystitis and pancytopenia) and 2 non-serious AEs (vomiting)
- As of August 2021, 2 ALD-104 patients, each with a predominant clone[a] with insertions into *MECOM*, developed MDS, likely mediated by Lenti-D LVV insertion; an additional patient treated in ALD-102/LTF-304 has a predominant clone, which so far has been consistent with benign clonal expansion
- No GVHD, graft failure, or evidence of replication-competent lentivirus were reported with eli-cel treatment

[a] > 50% clonal contribution to whole blood or any blood cell lineage.

E, adverse event; allo-HSCT, allogeneic hematopoietic stem cell transplantation; GdE, gadolinium enhancement; GVHD, graft-versus-host disease; LVV, lentiviral ector; MFD, major functional disability; NFS, Neurologic Function Score; SAE, serious adverse event

Data as of March 2021; ongoing studies with an open database.

Opportunities for Improvement in Cell Therapy

- Cost!
- Manufacturing is first generation. There are HUGE opportunities for better MFG – speed, success rates, cost of goods, automation
- How do we pay for this?
  - Tisa-cel $475K, Zolgensma $2.1M betibeglogene autotemcel (EU) €1.5M
  - Value-based pricing: tis-cel (ALL) has a value/outcome based agreement
  - Pay over time models

Opportunities for Improvement

- What we need: outcomes-based PLUS pay over time
- Need a way to:
  - Enhance patient access: short term hospital costs, co-pays, travel to COE if needed
  - Finance these expensive therapies, access capital
  - Assess if we really need a middleman who doesn't touch the product
  - Amortize over 5 (?) years
  - Assess efficacy and STOP payment if efficacy not maintained

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release August 30, 2017

FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

Biotech

stellar CAR-T efficacy data steamrolls safety doubts to power landmark cancer therapy toward approval

Lessons from the first commercial CAR T site

- Centers of excellence!
- It's not easy, but no one ever did this before
- Setting up contracting between the hospital and the drug company is a new challenge
- Hospital is a supplier? A service provider?
- Foundation for the Accreditation of Cellular Therapy (FACT)
  - Joint Accreditation Committee, International Society Cell and Gene Therapy and European Society for Blood and Marrow Transplant (JACIE)
- Every company wants to be different
- We need standardization

Post Marketing in CAR T

- Tisa-cel (Kymriah) and axi-cel (Yescarta) have had manufacturing issues
- Tisa-cel MFG issues were worse (NHL>>ALL) but basically now resolved
- Some issues with true manufacturing failures
- Some issues with “out of spec” – still have a useful product but now it’s free

Toxicity Reporting After Approval

- Large effect sizes have meant that CAR T indications are FDA approved in single arm trials, on <100 patients
- Further data collection is paramount
- 15 year follow-up needed, but no RCL/RCR testing now required
- Data will not be collected in a research setting with research budgets and direct regulatory mandates on the centers
- Excessive, inconsistent, or conflicting data requests from companies or health authorities in the commercial setting may interfere with getting necessary data #Askforeverythinggetnothing

Questions?

grupp@chop.edu