bluebirdbio™

Transforming the Lives of Patients
WITH SEVERE GENETIC DISORDERS

Stem Cells
Regenerative Medicine Congress 2014

September 15, 2014

Forward Looking Statement

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," and other similar expressions are intended to identify forward looking statements. For example, all statements we make regarding the initiation, timing, progress and results of our preclinical and clinical studies and our research and development programs, our ability to advance product candidates into, and successfully complete, clinical studies, and the timing or likelihood of regulatory filings and approvals are forward looking. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These statements are also subject to a number of material risks and uncertainties that are described in our most recent quarterly report on Form 10-Q, as well as our subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Summary - Key Messages

- Potential for **one-time transformative** treatments for **severe genetic and orphan diseases**
- Encouraging **clinical safety and efficacy data** in beta thalassemia and CCALD with growing clinical pipeline
- **Industrialized gene delivery platform** across people, production, development and deployment
- **Disruptive gene addition and gene editing technologies** with broad product and deal potential
- **Industry leading team** and **culture** funded for success

Ethan – Why We Do What We Do

Ethan

Aidan

Cameron

Our Vision – Make Hope a Reality

Seeking to transform the lives of patients with severe genetic and orphan diseases through the development of innovative gene therapy products.

Time is Now – Rapidly Evolving Landscape

Private GT Companies

AskBio
AUDENTES
Spark THERAPEUTICS
CALIMMUNE engineering immunity
ReGenX BIOSCIENCES
GenSight
DIMENSION THERAPEUTICS
JUNO THERAPEUTICS

Active in Gene Therapy

Celgene
NOVARTIS
BIOMARIN
Baxter
Shire
genzyme
sanofi aventis
biogen idec
Celladon
gsk
AGTC
uniQure
Kite Pharma
AVALANCHE BIOTECH

Clinical Data Maturing*

Lenti	ALD N=5	Science 2009 — Hematopoietic Stem Cell Gene Therapy with a Lentiviral Vector in X-Linked Adrenoleukodystrophy	MLD N=9	*Lenti*
Lenti	B-Thal N=7	nature September 2010 — Transfusion independence and *HMGA2* activation after gene therapy of human β-thalassaemia	WAS N=12	*Lenti*
AAV	Hem B N=14	The New England Journal of Medicine — Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B	ALL&CLL N=>100	*Lenti*

Science 2013 — Therapeutic Benefit in Metachromatic Leukodystrophy by Lentiviral Hematopoietic Stem Cell Gene Therapy

Science 2013 — Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome

The New England Journal of Medicine — Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

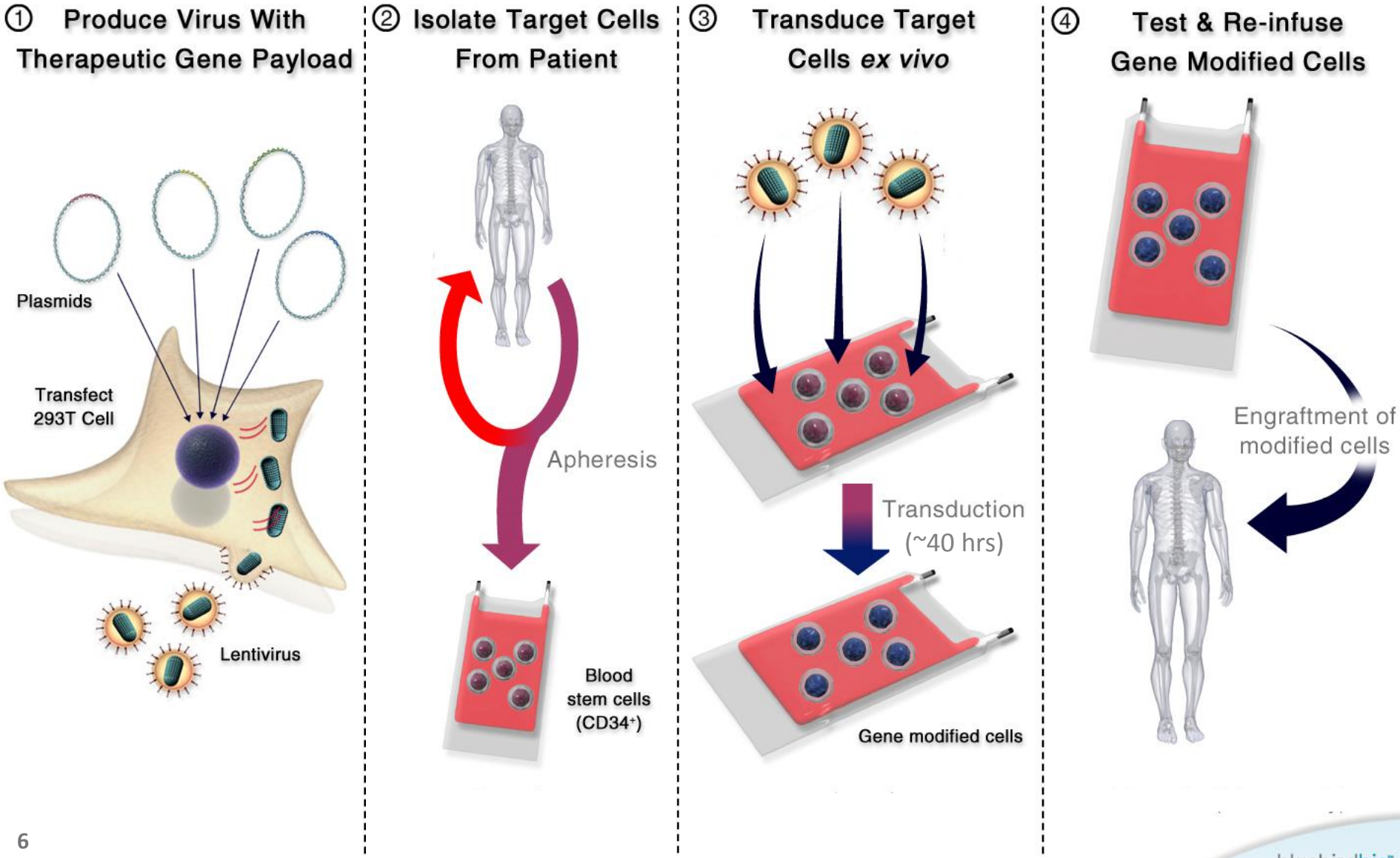
* Patient numbers reflect aggregate patients treated by indication as of ESGCT 2013

bluebird Pipeline

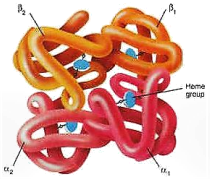
Products	Program Area	Preclinical	Phase I/II	Phase II/III	Rights
Lenti-D	CNS Diseases				
	Childhood Cerebral ALD – Starbeam Study*				Worldwide
LentiGlobin™	Hematologic Diseases				
	β-thalassemia/SCD (France) – HGB-205 Study**				Worldwide
	β-thalassemia (U.S.) – Northstar Study**				
	Sickle Cell Disease (U.S.) – HGB-206 Study				
CAR-T Cells	Oncology				
	Hematologic/Solid Tumors				Global Celgene Collaboration
Early Pipeline	Research				
	Undisclosed + Gene Editing				Worldwide

* The Phase II/III Starbeam Study is our first clinical study of our current Lenti-D viral vector and product candidate.
** The Phase I/II HGB-205 and Northstar Studies are our first clinical studies of our current LentiGlobin viral vector and product candidate.

Produce Virus With Gene Payload



β-Thalassemia: *Disease Overview*



Disease

- Monogenic, severe anemia
- Loss or reduced β-globin production
- Poor quality of life
- Shortened lifespan

Current Treatment

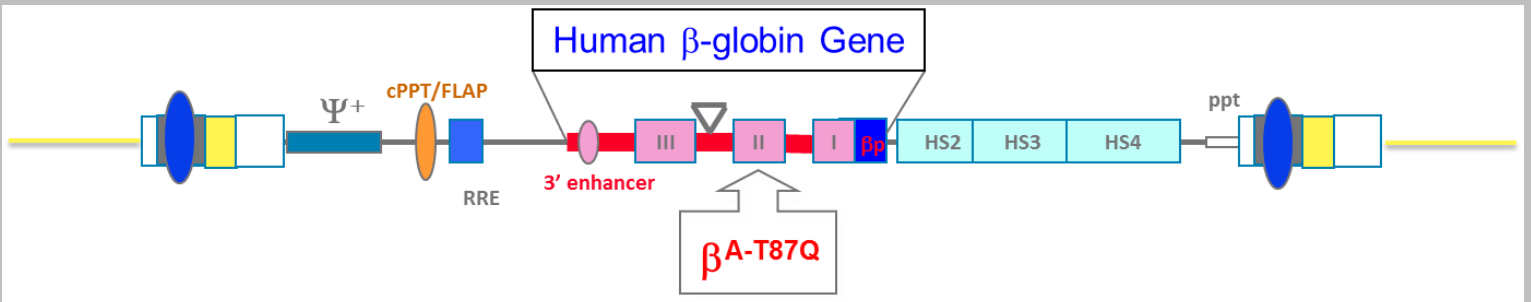
- Chronic transfusions and iron chelation
  - Not curative
  - Iron overload leads to organ failure
- Allo transplant (rarely)
  - Match uncommon
  - High morbidity / mortality due to graft versus host disease

Epidemiology

- Global β-thalassemia prevalence (symptomatic) ~288K; incidence ~60K
- US/Europe β-thalassemia prevalence (treated) ~15K; incidence ~1.5K
  - 60-80% severe/major
- Affects people of Mediterranean, Middle Eastern, South Asian and SE Asian descent

β-Thalassemia: Innovative Product Design

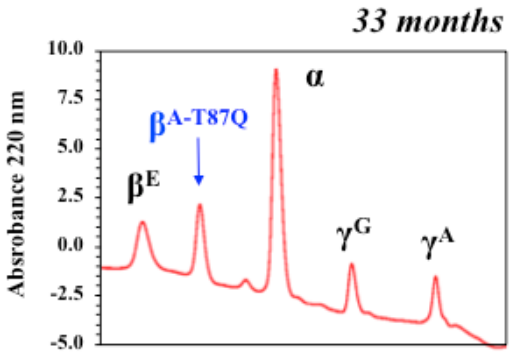
Philippe Leboulch



- Biomarker for transgene expression via blood sample
- Provides anti-sickle properties (published Science 2001)

Lineage Specific Expression

(Erythrocytes)



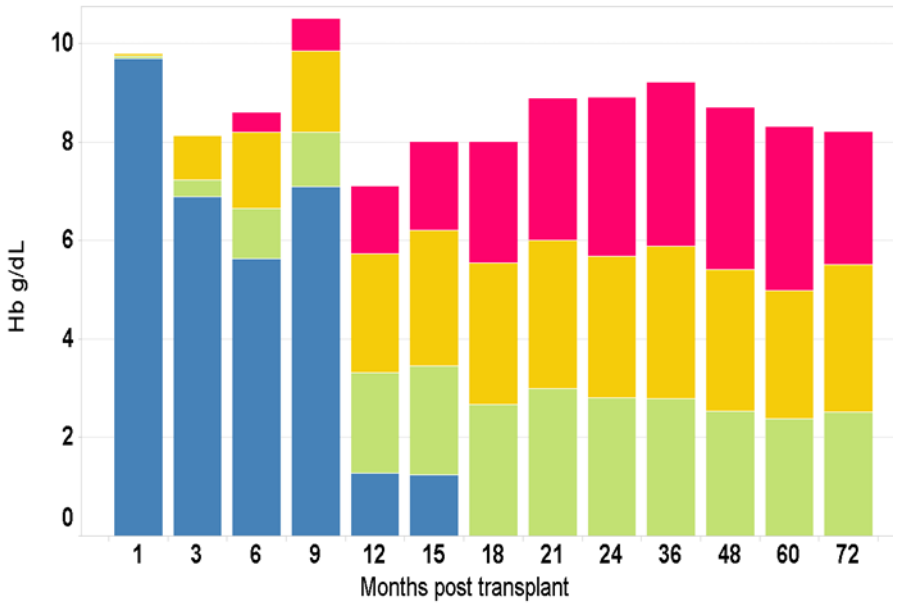
Science *December 2001*

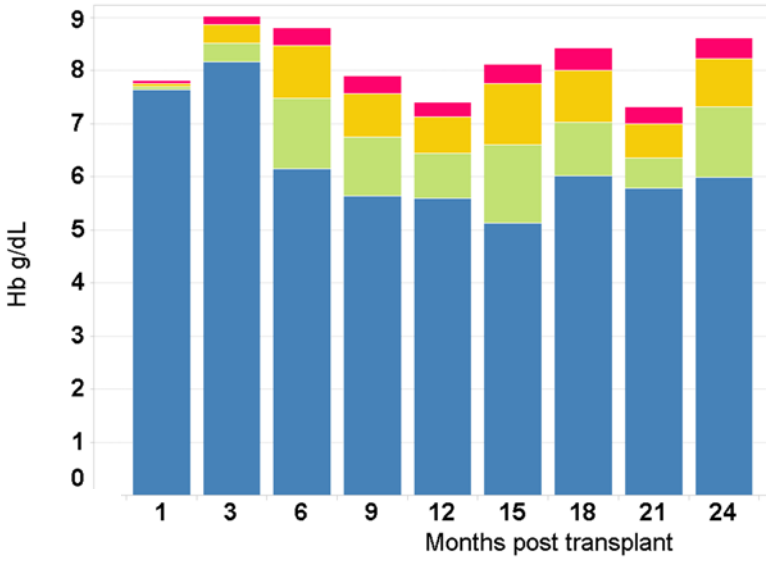
Correction of Sickle Cell Disease in Transgenic Mouse Models by Gene Therapy

Robert Pawliuk,[1,2] Karen A. Westerman,[1,2] Mary E. Fabry,[3] Emmanuel Payen,[4] Robert Tighe,[1,2] Eric E. Bouhassira,[3] Seetharama A. Acharya,[3] James Ellis,[5] Irving M. London,[1,6] Connie J. Eaves,[7] R. Keith Humphries,[7] Yves Beuzard,[4] Ronald L. Nagel,[3] Philippe Leboulch,[1,2,4,8*]

β-Thalassemia: Promising Clinical LG001 Data

2007	2007	2007	2011	2013/2014
Subject One (Untreated, no transplant)	**Subject Two** (Low cell dose, no engraftment)	**Subject Three** (Transfusion independent 6 yrs)	**Subject Four** (β87 expression)	HGB-205 /Northstar Studies First Patients Transplanted
Non-Evaluable		*Evaluable*		





HbA
HbE
HbF
HbB-A-T87Q

β-Thalassemia: Development Plan Summary

Product Enhancements	Results
• Improved process • Selective vector changes • No transgene changes	✓ 25 to 30-fold reduction in non-infectious viral particles ✓ 3x vector copy number increase

	Northstar Study	HGB-205
Trial Location	US, Australia	France
Phase	I/II	I/II
N	15	7
Indication	β-thalassemia major	β-thalassemia major & sickle cell disease
Sites	Multi-center	1
Status	First Patient Transplanted	First Patient Transplanted

Preliminary HGB-205 data was presented at the EHA Congress (June 14, 2014)

HGB-205 Study : Improved transduction efficiency demonstrated

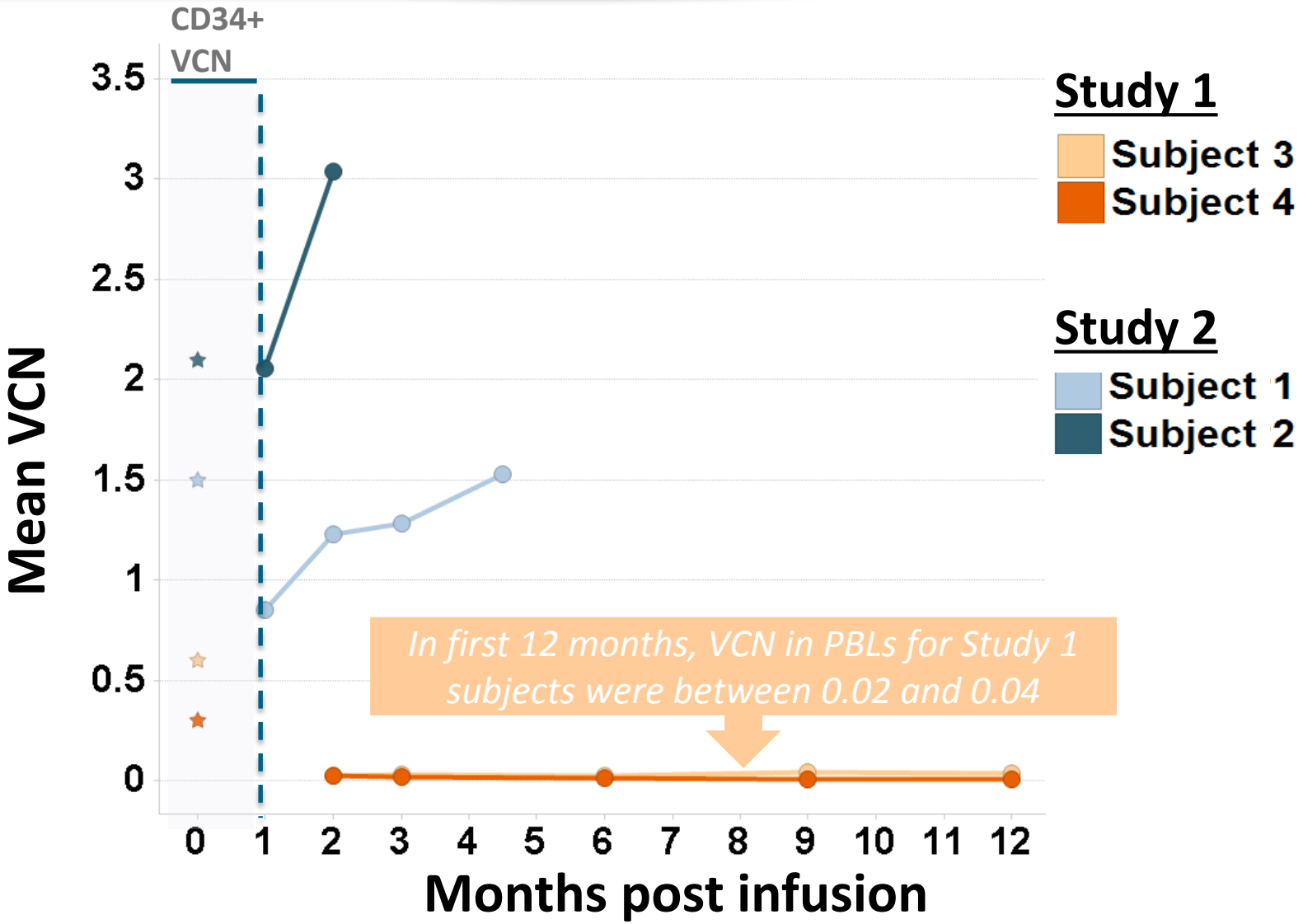
	Subject 1	Subject 2	Subject 3
Study	HGB-205	HGB-205	LG001
Vector	BB305	BB305	HPV569
Age of Enrollment	18	16	18
Genotype	β0/βE	β0/βE	β0/βE
CD34+ VCN	1.5	2.1	0.6
CD34+ cell dose ($x10^6$/kg)	8.9	13.6	4.9*

* Subject 3 source of CD34+ cells was bone marrow versus periphery

- 2.5-3.5 times increase in transduction efficiency seen in HGB-205

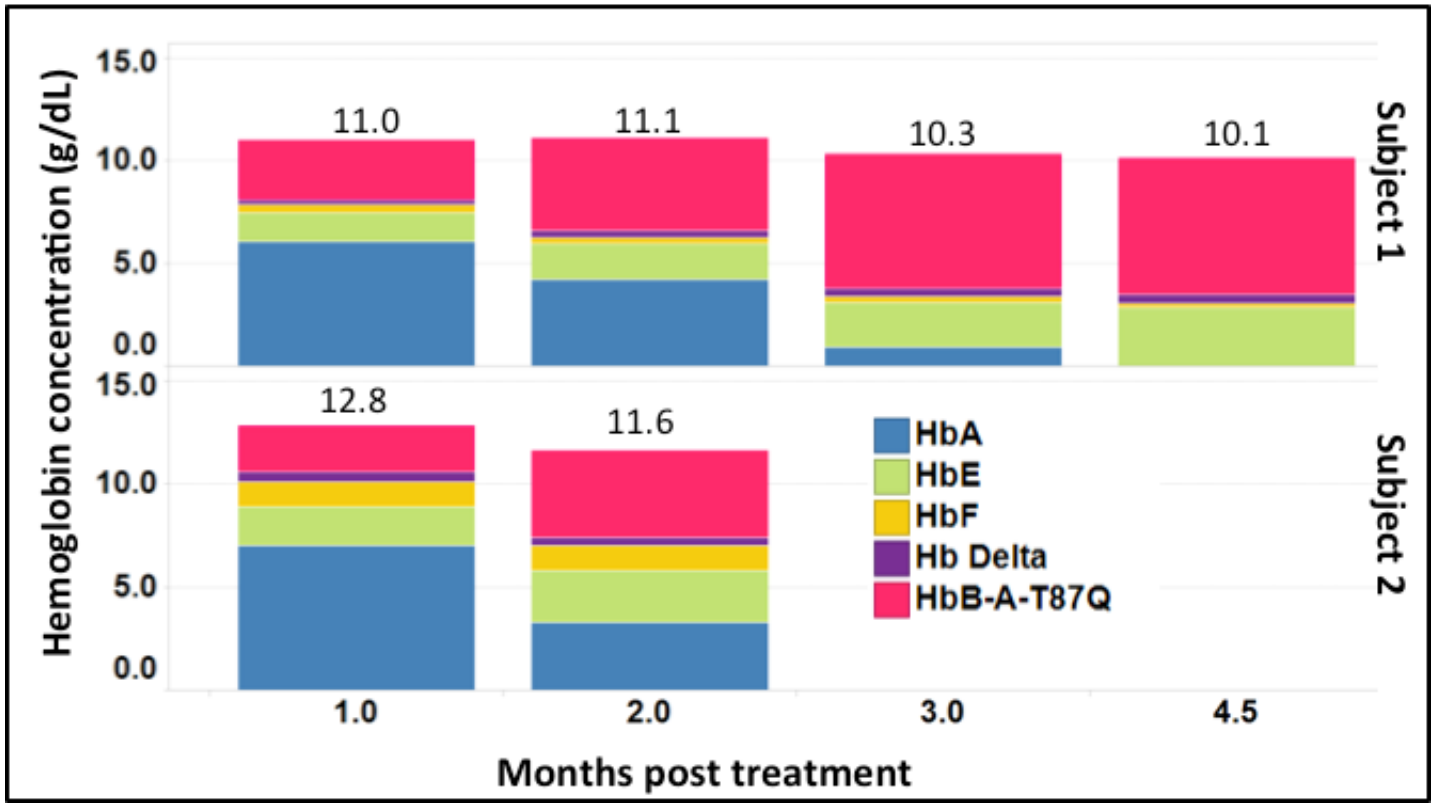
M. Cavazzana *et al* European Hematology Association Congress oral presentation (June 14, 2014)

HGB-205 Study: Higher VCNs pre and post infusion



M. Cavazzana *et al* European Hematology Association Congress oral presentation (June 14, 2014)

HGB-205 Study : Early and high production of $\beta^{A\text{-}T87Q}$-globin resulting in rapid transfusion-independence at near normal Hb levels in both patients

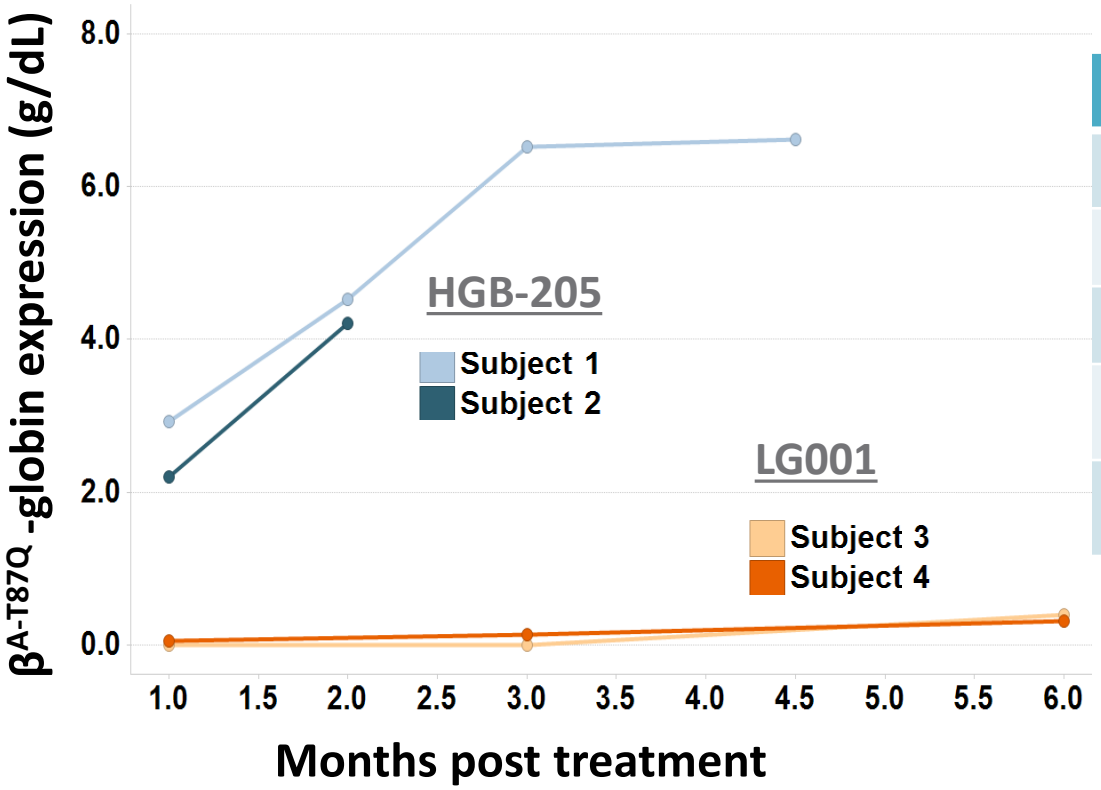


- Subject 1: producing 6.6 g/dL of $\beta^{A\text{-}T87Q}$ -globin at 4.5 months
- Subject 2: producing 4.2 g/dL of $\beta^{A\text{-}T87Q}$ -globin at 2 months

Both subjects are transfusion independent

M. Cavazzana *et al* European Hematology Association Congress oral presentation (June 14, 2014)

HGB-205 Study : Rapid production of $\beta^{A\text{-}T87Q}$-globin leading to transfusion independence



RBC transfusion Independence			
	Subject 3	Subject 1	Subject 2
Study	LG001	HGB-205	HGB-205
Vector	HPV569	BB305	BB305
Day of last transfusion	Month 12	Day 10	Day 12
Duration since last transfusion	>6 years	>125 days	>48 days

- Rapid production of therapeutic globin (weeks as opposed to one year)
- Both subjects in HGB-205 have near normal hemoglobin levels without transfusion (neither subject has required a transfusion post-engraftment)

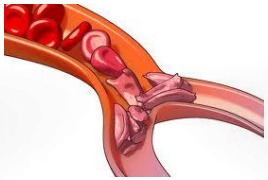
M. Cavazzana *et al* European Hematology Association Congress oral presentation (June 14, 2014)

HGB-205 Study : Conclusions

- Demonstrated improved manufacturing process and superior transduction efficiency with BB305 vs prior HPV569 vector
- Early and high production of $\beta^{A\text{-}T87Q}$-globin resulting in rapid transfusion-independence at near normal Hb levels in two patients
- Initial safety profile is consistent with autologous transplantation
- Next steps for LentiGlobin program
  - Complete enrollment - 3 treated; 10 of 22 enrolled across HGB-205 and Northstar Studies
  - Initiate HGB-206 Study in SCD - HGB-205 data gives growing reason to believe in the potential to treat sickle cell disease

M. Cavazzana *et al* European Hematology Association Congress oral presentation (June 14, 2014)

Sickle Cell Disease: Program Summary



Disease

- Monogenic, severe anemia
- Polymerization of β-globin chains deforms / sickles red blood cells
- Poor quality of life
  - Pain crises, stroke, splenomegaly
- Shortened lifespan

Current Treatment

- Non curative treatments
  - Hydroxyurea
  - Blood transfusions
  - Pain management
- Allogeneic HSCT option
  - Match uncommon
  - High morbidity / mortality

Epidemiology

- US/EU Prevalence ~150K
- US/EU incidence ~3K
- Global prevalence ~25M
- Global incidence ~300K

IND Active for HGB-206 Study

HGB-206 Study Plan

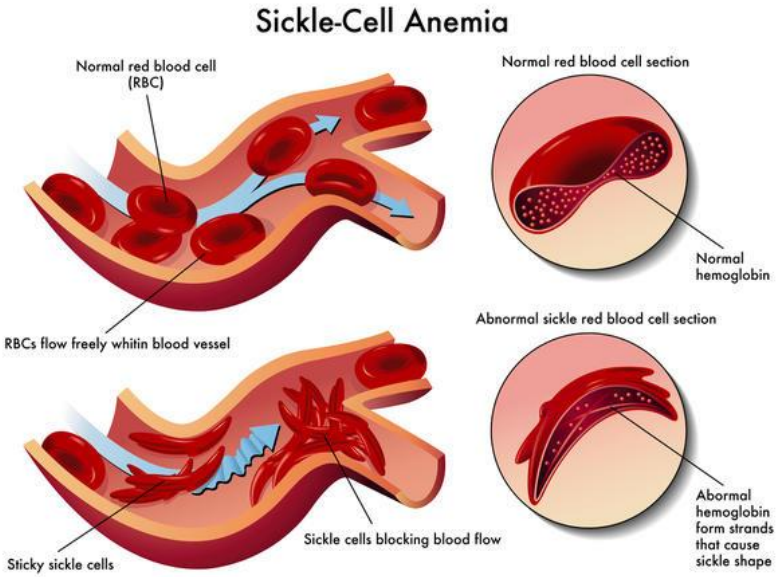
	HGB-206
Trial Location	US
Phase	I
N	8
Indication	Severe sickle cell disease
Clinical Endpoints	Primary : safety Secondary : clinical events*
Sites	Multi-Center
Status	Active IND

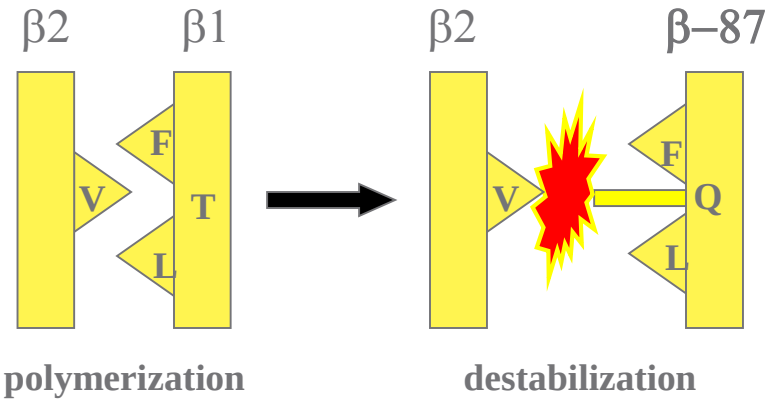
*Measure red cell function tests, hemolysis markers, frequency of clinical events secondary to SCD (e.g. severe vaso-occlusive crises, strokes etc.)

Plan to enroll SCD patient in HGB-205 or HGB-206 in 2014

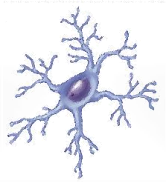
Evidence for why BB305 globin may work for sickle cell disease

- BB305 globin incorporates an anti-sickling amino acid that is found in fetal hemoglobin (glutamine at position 87)
- Anti-sickling activity of $\beta^{A\text{-}T87Q}$-globin has been demonstrated in a mouse model of SCD (Science 2001)
- Elevated fetal hemoglobin from hereditary persistence of fetal hemoglobin (HPFH) has shown clinical benefit





Lenti-D: Childhood Cerebral Adrenoleukodystrophy (CCALD) Disease Overview



Disease

- Ultra-orphan, X-linked, monogenic, neurological disorder
- Mutated ABCD1 peroxisomal transporter results in toxic buildup of very long chain fatty acids (VLCFA)
- Leads to cerebral inflammation & demyelination

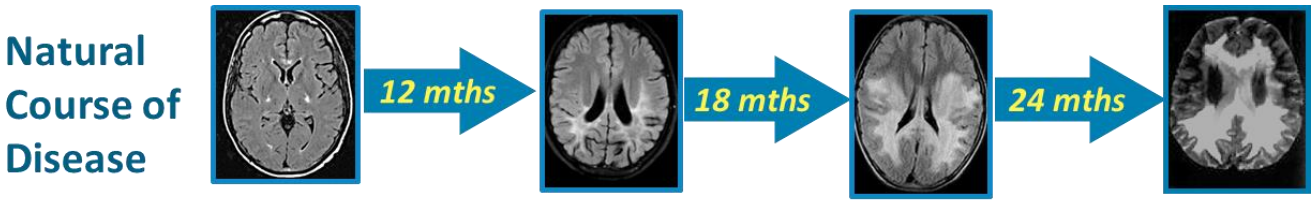
Current Treatment

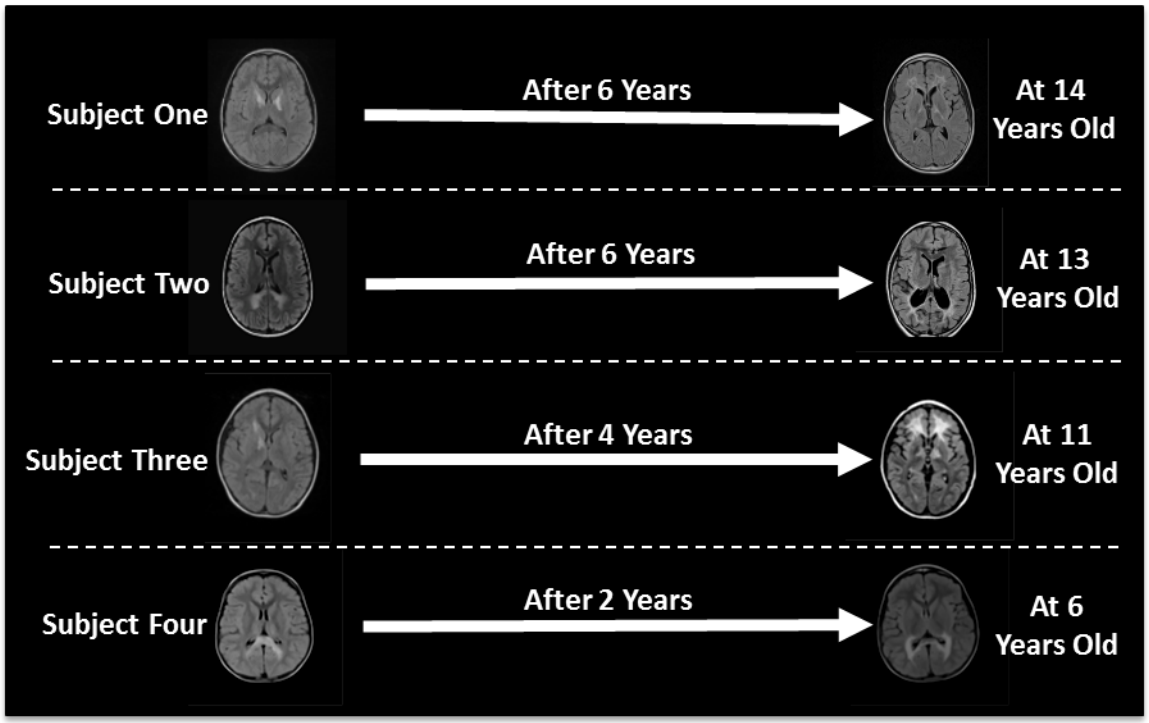
- Untreated cerebral ALD leads to dismal outcomes (vegetative state and death)
- Allogeneic stem cell transplant standard for CCALD (if possible)

Epidemiology

- CCALD most severe form of ALD
- ALD Incidence : 1 in 20,000 (live births)
- Cerebral disease
  - CCALD accounts for 30-40% of ALD
  - AMN accounts for 40-45% of ALD with 40% cerebral
  - ACALD accounts for 5% of ALD

Promising Clinical Data – CCALD (TG04.06.01 Study)





- NFS / Loes currently stable in all patients
- Gad resolved in 3 out of 4 patients
- Efficacy results comparable to allogeneic transplant
- No gene therapy-related adverse events

NFS – Neurological Function Score
Gad – gadolinium enhancement

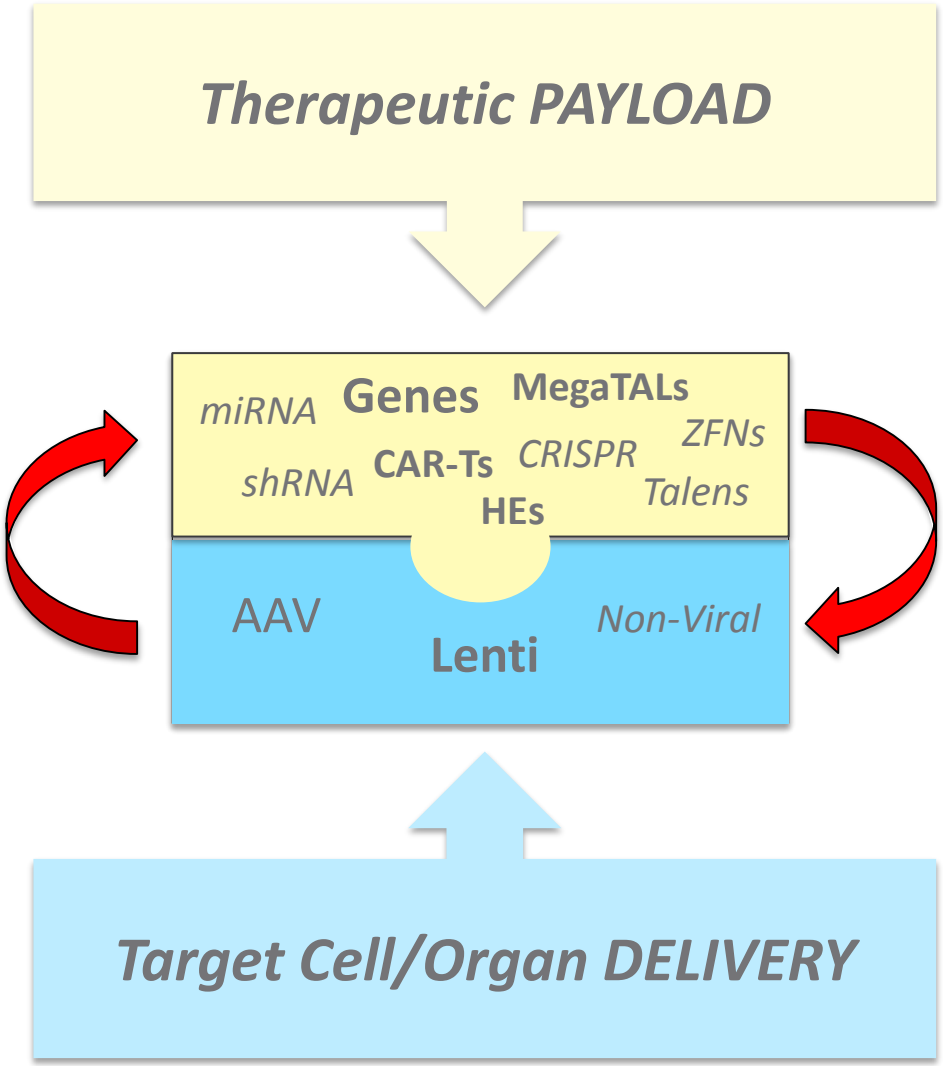
Starbeam Study – Phase II/III Design

Open label, multi-center, single arm global study

Design	*Primary Endpoints*	*Secondary Endpoints*
• 15 Patients • Age ≤ 17 • Gad Positive • Loes Score 0.5 – 9 • NFS ≤ 1	• % of Boys With Major Functional Disabilities (MFDs) at 24 Months After Transplant	• Neurological Functional Score (NFS) • Gad +/- • Loes Score • Safety

- ✓ First patient enrolled (October 2013)
- ✓ Multiple clinical sites open
- Anticipate completion of enrollment in 2015

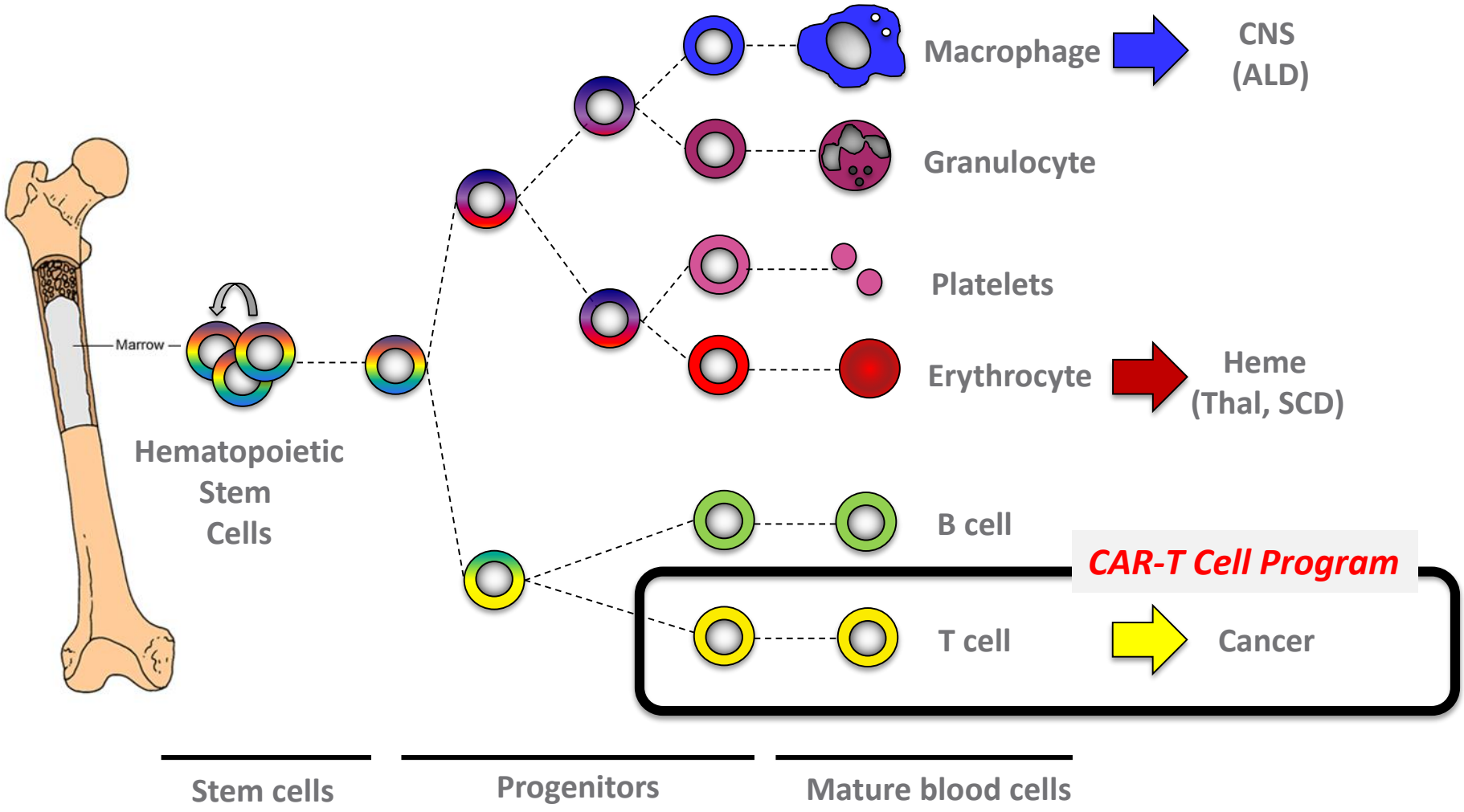
Looking Forward: Convergence of Gene Therapy Technologies



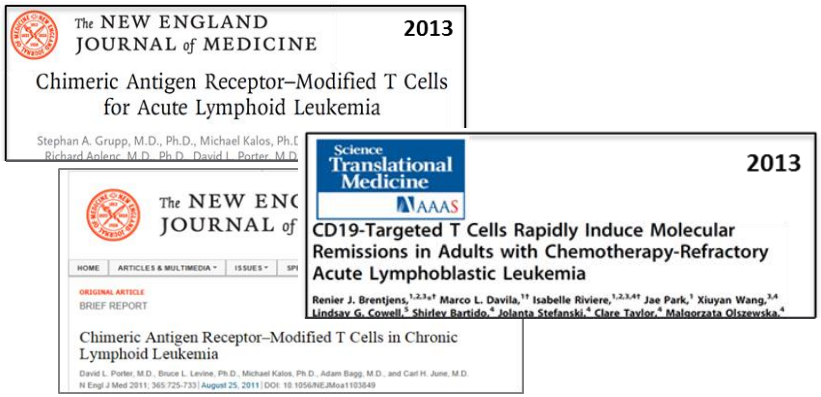
Our Strategic Intent

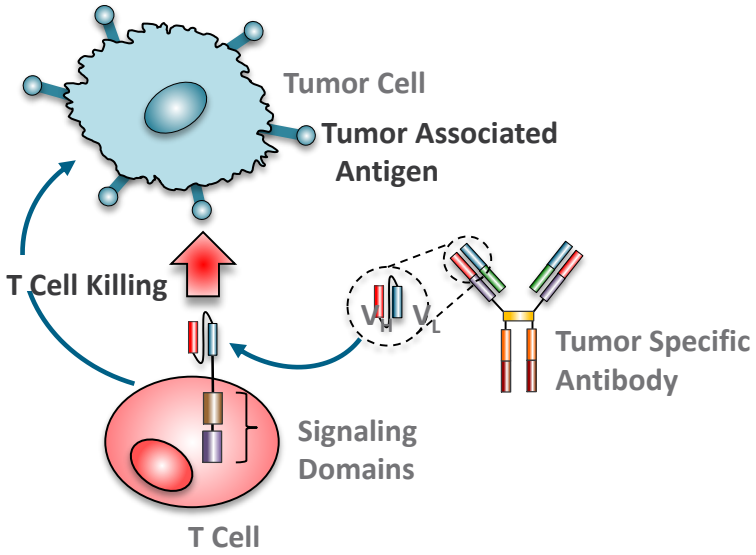
- Lead the "Gene Therapy" revolution
- Take advantage of growing understanding of disease etiology (genetics) and evolving technologies
- Versatile R&D Strategy – **Right Tool for the Right Job**
- Lever leading gene therapy team, capabilities and resources
- Plant 'seeds' in promising areas of technology innovation

Lentiviral Stem Cell Platform



Chimeric Antigen Receptor (CAR) T Cells



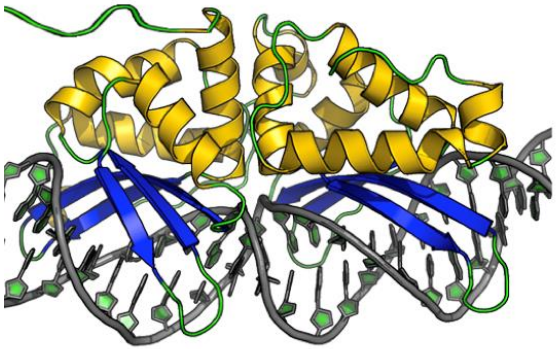


Collaboration Highlights

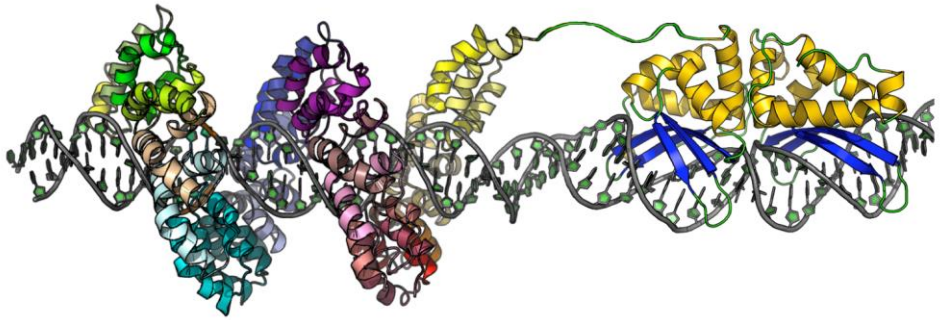
- ✓ $75M upfront payment; 3 yrs (up to 6yrs)
- ✓ bluebird right to 50/50 co-develop, co-promote and profit share in the US
- ✓ bluebird is responsible through Phase I

Pregenen Acquisition
Homing Endonucleases and MegaTALs Editing Tools

Homing Endonucleases



MegaTAL



- All gene-editing technologies share common features of a DNA binding domain and a DNA cleavage domain
- Acquired expertise in homing endonucleases (HE) and MegaTALs
  - Robust nuclease discovery platform and proprietary database
  - Broad IP portfolio
- Multiple advantages of HE and MegaTALs
  - Naturally occurring gene-editing proteins
  - Highly specific and efficient activity
  - Compact size allows for delivery of multiple proteins
- Broad range of therapeutic applications
  - Complimentary to existing indications

Recent and Upcoming News Flow

2013

- ☑ Signed global Oncology collaboration with Celgene
- ☑ Completed IPO
- ☑ Initiated phase II/III Starbeam Study
- ☑ Initiated two phase I/II Thal studies (Northstar & HGB-205)
- ☑ First patient transplanted in Starbeam Study
- ☑ First patient transplanted in Thal HGB-205 study

2014

- ☑ **First patient transplanted in Northstar Study**
- ☑ **Filed IND for sickle cell disease (SCD) study**
- ☑ **Preliminary Thal HGB-205 data at EHA**
- ☑ **Acquired gene-editing company, Pregenen**
- ❑ **Enroll first SCD patient in HGB-205 or HGB-206 (2014)**
- ❑ **Preliminary Thal Northstar & HGB-205 data (late 2014)**
- ❑ **Various clinical publications**

2015

- ❑ Complete enrollment of Starbeam Study
- ❑ Complete enrollment Thal Northstar & HGB-205
- ❑ Preliminary SCD data

Financial Summary

28.6M Shares Common Stock O/S 7/29/14	2013 Fiscal Year End 12/31/2013 (Audited)	Second Quarter 2014 6/30/2014 (Unaudited)
Cash and Cash Equivalents	$206.3M	**$285.5M***
Revenues	$20.1M	$6.3M
R&D Expenses	$31.0M	$13.9M
G&A Expenses	$14.1M	$5.7M
Loss from Operations	$24.9M	$13.3M

* Pro forma estimate: $175.7M on balance sheet (6/30/14) plus $109.8M raised during July financing, net of expenses and discounts

bluebird Core Values

We Strive To Become Legendary In The Eyes Of Patients