bluebirdbio®

Ready to RECODE

May 2019

NASDAQ: BLUE

Forward-Looking Statements

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.

Potential 2019 Catalysts

By Mid Year

LentiGlobin TDT

EU Approval

Northstar-2 (HGB-207) & Northstar-3 (HGB-212) Data Update

LentiGlobin SCD

HGB-206 Group C Data Update

bb2121 MM

KarMMa-2 & KarMMa-3 Study Start*

Pipeline

Analyst Day

By End of Year

LentiGlobin TDT

EU First Launch

Potential U.S. Filing

Northstar-2 and Northstar-3 Data Update

LentiGlobin SCD

HGB-210 Study Start

HGB-206 Group C Data Update

bb2121 MM

CRB-401 Data Update*

KarMMa-1 Data*

bb21217 MM

CRB-402 Data Update

Cash Position as of December 31, 2018: $1.9B

CASH RUNWAY INTO 2022

*Driven by Celgene/BMS

WE **RECODE** FOR LIFE

RADICAL CARE

We care in a way that's intense and truly sets us apart.

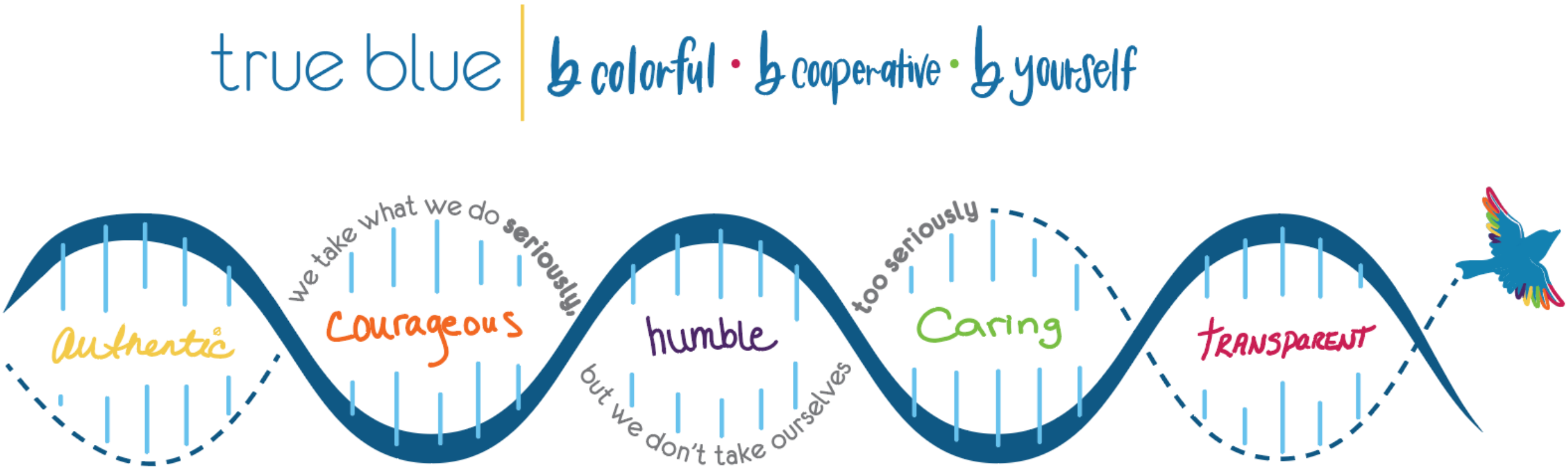
THIS IS PERSONAL

Gene therapy is about saving lives one person at a time. And we are, each of us, personally all in.

PIONEERS WITH PURPOSE

We're exploring new frontiers for the sake of patients.

We **LIVE** By Our **Non-negotiables**



Our 2022 Vision -- Just Got BOLDER

LentiGlobin TDT
2019 EU Potential Approval
2020 U.S. Potential Approval

Lenti-D CALD
2021 Potential Approval

LentiGlobin SCD
2022 Potential Filing/Approval

bb2121 Multiple Myeloma
2020 Potential Approval

4 Products on the Market

5+ Clinical Programs

1-2 INDs Per Year Beginning 2020

UNPRECEDENTED OPPORTUNITY

Anticipated research, development, regulatory and commercial milestones

Gene Therapy Necessitates Commercialization That's Fit-for-Purpose

GENE THERAPY IS THE ULTIMATE PERSONALIZED MEDICINE

MANUFACTURING PROCESS IS START OF THE PATIENT EXPERIENCE

1X INTERVENTION: INTENDED LIFELONG BENEFIT

FILING BASED ON SMALL, SINGLE-ARM DATA SETS

STEPWISE LAUNCH BEGINNING IN EUROPE

Keys to Success for TDT Launch

1. Identifying and Understanding Patients and Physicians
2. Care Delivery Network: Qualified Treatment Centers (QTCs) and Supply Chain
3. Successful Implementation of Value-Based Payment Model

Laying the Foundation for Future Launches

Living with Transfusion-Dependent β-Thalassemia (TDT)

Potentially fatal genetic disease caused by mutations in the β-globin gene that result in reduced or absent hemoglobin

Despite advances in iron management, TDT patients suffer from serious complications and organ damage caused by excess iron

Laurice's experience:

- Hemoglobin of 6.9 g/dL growing up [normal range for females: 12.1-15.1 g/dL][1]
- Congestive heart failure at 9 and 25
- Splenectomy at 10, tonsillectomy at 13, gall bladder removal at 22
- Severe osteoporosis
- Chronic pain
- Under care of PCP, cardiologist, hematologist, endocrinologist, and a pain specialist
- Lost many friends with TDT

1. National Institutes of Health (NIH). *Hemoglobin*. https://medlineplus.gov/ency/article/003645.htm.

Clinical Data Supports Patient and Physician Desired Outcomes in TDT

Normal Levels of Hemoglobin

- Northstar-2: Median total Hb at 12 months was 12.3g/dL (n=5)

Intended Lifelong Benefit

- All patients in Northstar and Northstar-2 who achieved TI, maintained TI
- Northstar (HGB-204): TI maintained up to 45 months

Transfusion Independence (TI)

- The majority of evaluable non-β^0/β^0 patients achieved TI
  - Northstar: 8/10 patients achieved TI
  - Northstar-2: 10/11 patients free of transfusions

Evidence of Response at 6 Months

- Gene therapy derived Hb (HbA^{T87Q}) supports total hemoglobin production soon after infusion
  - Northstar-2: Median total hemoglobin at 6 months: 11.9g/dL
  - Northstar: Median 6 month Hb in non-β^0/β^0 patients was 9.7 g/dL; HbA^{T87Q} was 4.7 g/dL

TDT – Initial Launch Focus

	EU Anticipated 1st Indication Patients* non-β^0/β^0; age ≥12; no matched related donor	Estimated total TDT Patients	Trial Site in Country?	Patient concentration
Germany	80-100	200-350	Yes	6 centers see ~50% of patients
Italy	2,000-2,200	6,500-7,500	Yes	73 centers see ~80% of patients
UK	200-300	500-600	Yes	15 centers see ~75% of patients
France	100-150	400-500	Yes	6 centers see ~50% of patients

EST TOTAL TDT:
3,500-4,000

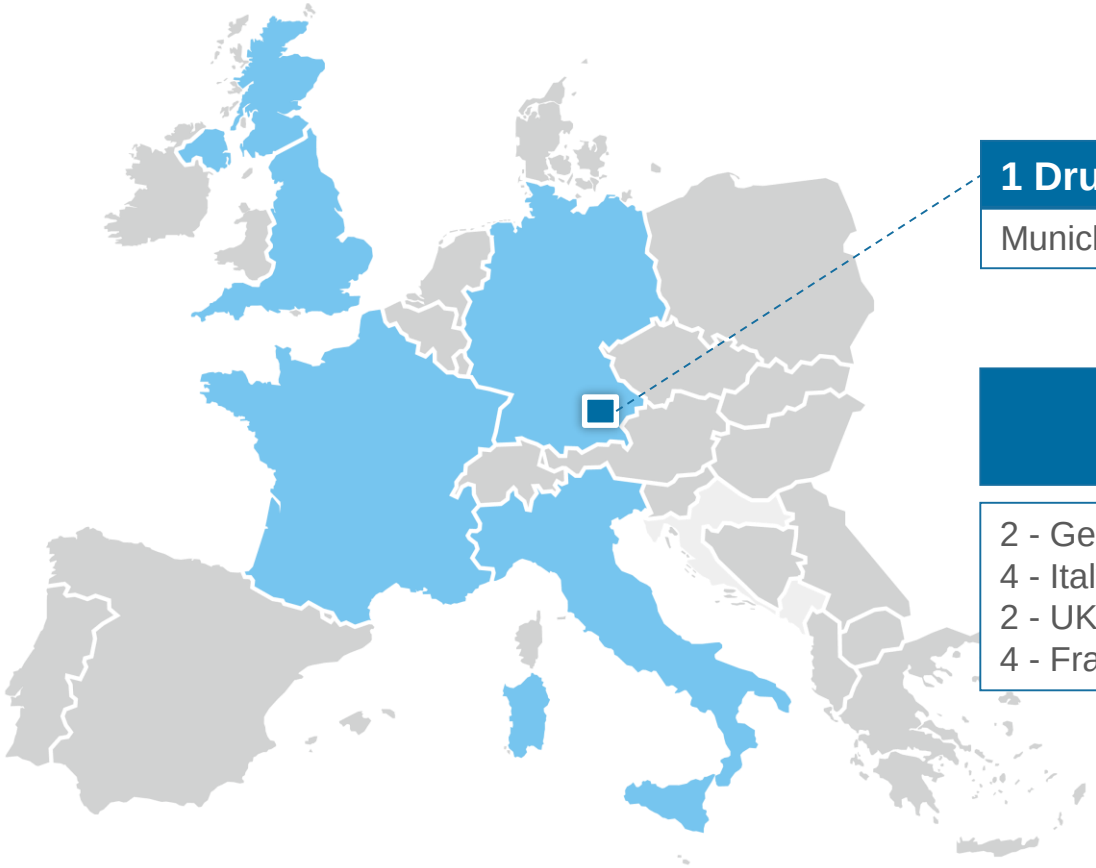
EST TOTAL TDT:
1,400-1,500

*Numbers represent addressable patient population

Preparing to Serve Patients in Europe in 2019

Key Considerations to Onboarding QTCs

- **Identification:** patient outreach, disease expertise
- **Qualification:** transplant accreditation, skills, capacities
- **Process alignment:** IT, data protection, and logistics
- **Training:** processes, systems and interfaces (e.g. enrollment, scheduling, ordering, storing, handling and infusing)
- **Contracting:** commercial, quality and registry agreements



1 Drug Product Manufacturing

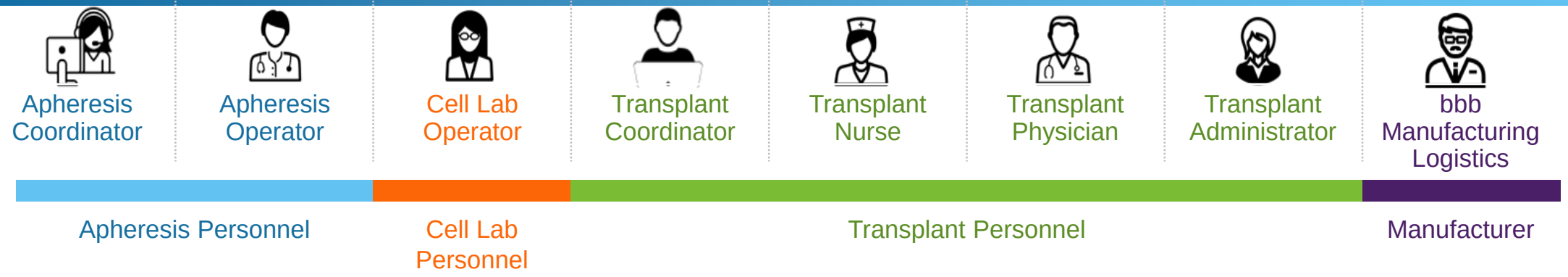
Munich, Germany

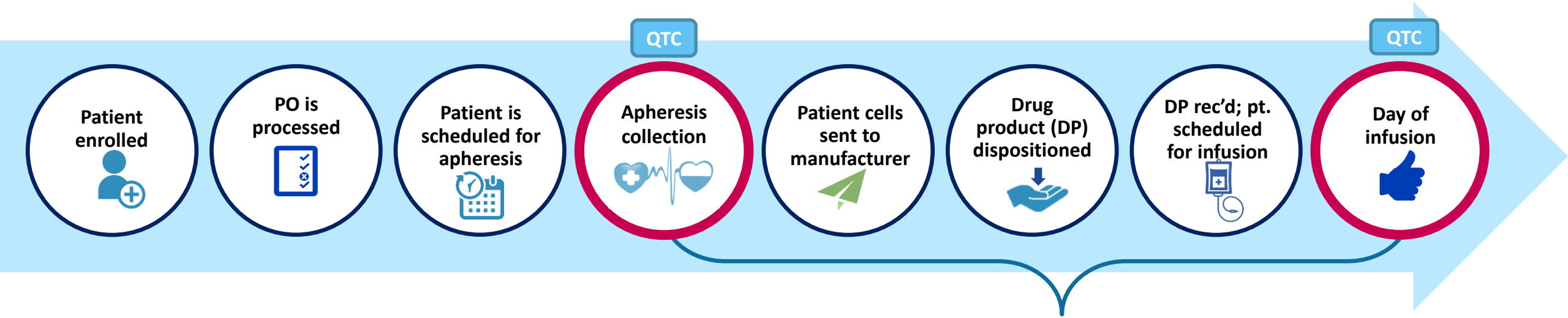
&

Anticipated QTCs at Country Launch

2 - Germany (+1 in early 2020)
4 - Italy
2 - UK
4 - France

The Patient Journey is an Organizing Framework for bluebird QTC Support





bluebird bio system in place to support steps in patient treatment pathway

6-8 weeks from apheresis to infusion in TDT

Product Supply Through Internal Capacity & Contract Partners

Prepared to Deliver

- Robust supply chain for vector and drug product through internal capacity and contract partners to meet demand across products
- Drug product hub-and-spoke model in Europe
- Building towards redundancy to support US and European commercial operations for all products
- bRT to have clinical and commercial scale vector production
- Additional space available for non-vector manufacturing

An Iterative Process: Continued Learning and Advancement

People

- ✓ 75 people in place across Europe – scaling medical and commercial teams
- ✓ CMLs in place across EU4
- ✓ Financial infrastructure

Partners & Supply Chain

- QTC network – overlapping for TDT & SCD
- ✓ Provider and patient referral networks
- ✓ Establishing registry partnerships

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System

- Payment model
- ✓ Patient support system
- ✓ IT System

Processes

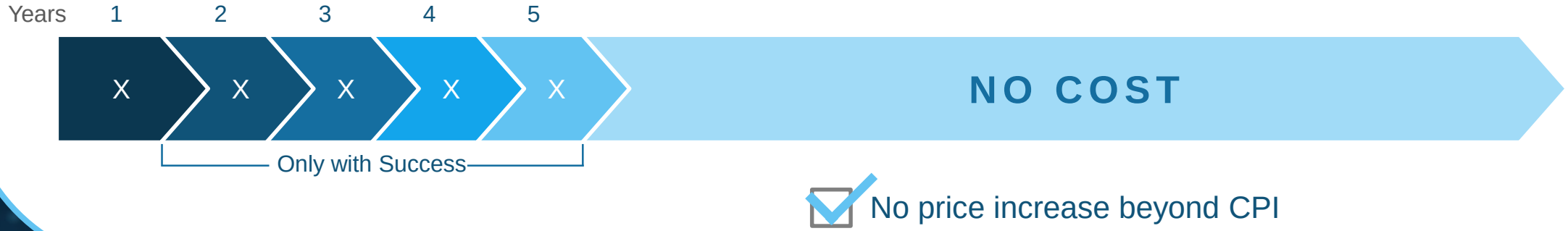
- Operational processes
- ✓ TRUE BLUE patient experience
- ✓ Training processes

Approach – VALUE-BASED PAYMENT Over Time Based on OUTCOME

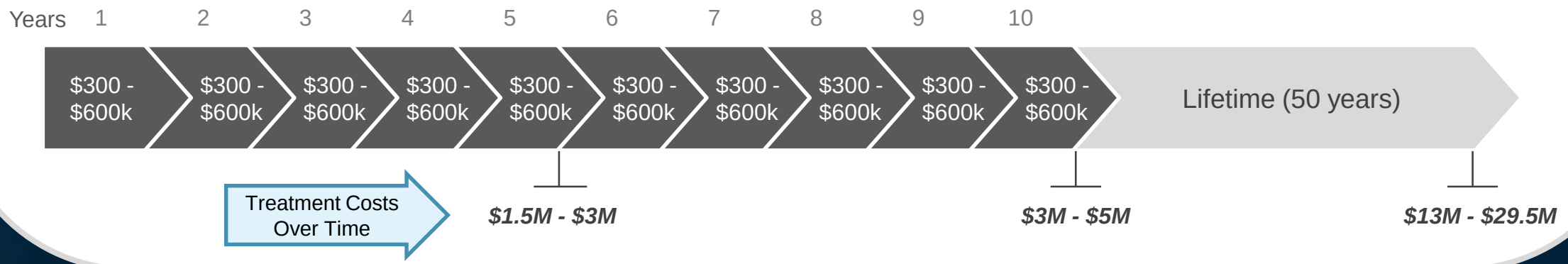
OBJECTIVE	STRATEGIC APPROACH
1 FAIR VALUE RECOGNITION	✓ *Lifetime cost-time effectiveness timeframe* ✓ *Base value only on patient QOL and Life Extension*
2 SHARED RISK	✓ *Pay ONLY IF the treatment works* ✓ *Put UP TO 80% of the price at risk based on success*
3 PER PATIENT AFFORDABILITY	✓ *Spread payments over UP TO A FIVE YEAR period* ✓ *NO PRICE INCREASES above CPI*
4 HEALTH SYSTEM AFFORDABILITY	✓ *NO COST after payment period (vs. for life)*

Payment Model – Patient **and** System Friendly

INTENDED BLUEBIRD APPROACH



TRADITIONAL FOR LIFE MODEL*

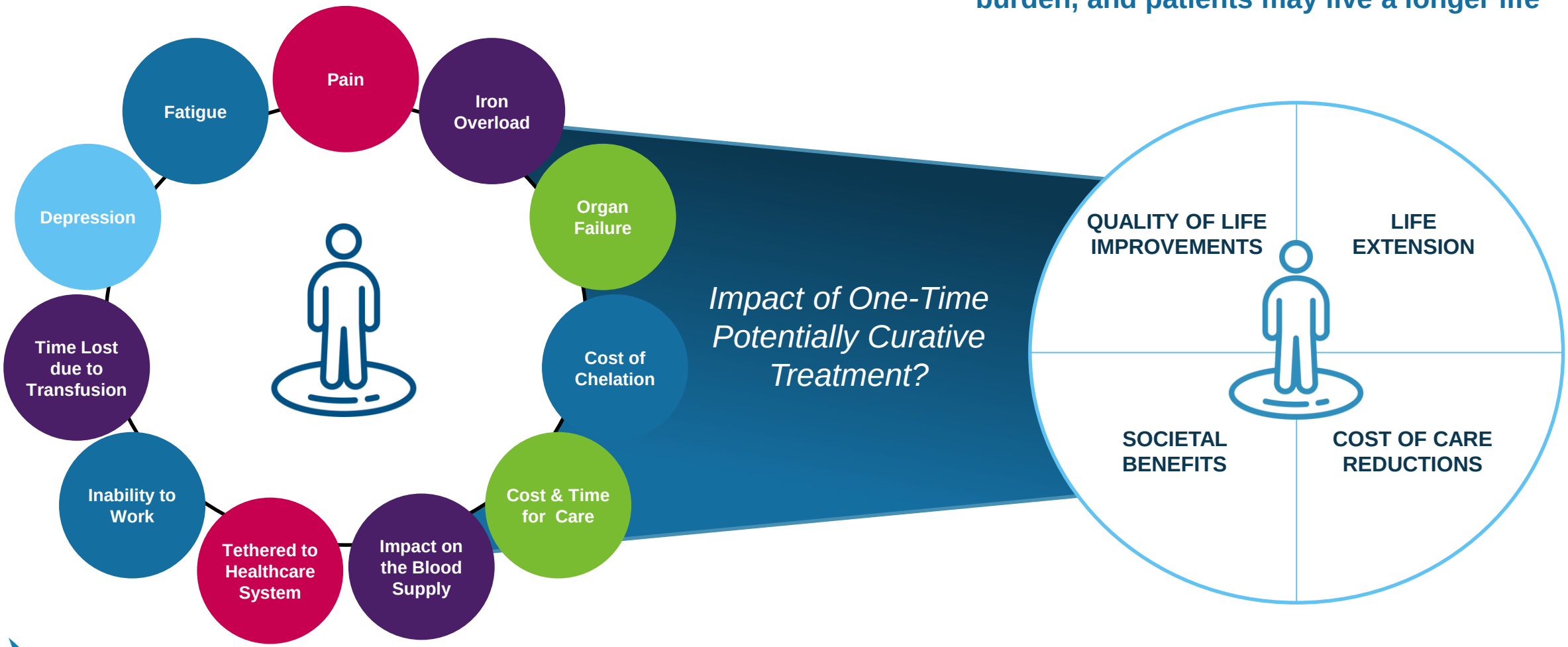


*Ranges based on 2018 U.S. list prices from a sampling of seven chronic rare disease therapies.

What Value Can LentiGlobin Bring to TDT Patients, Payers and System?

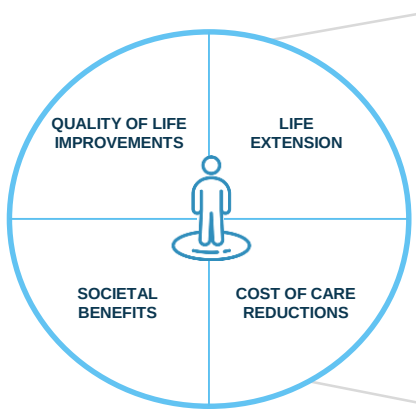
Disease and treatment-related burden builds up over time and can even lead to early death

LentiGlobin, if successful, has the potential to relieve patients of their daily disease and treatment-related burden, and patients may live a longer life



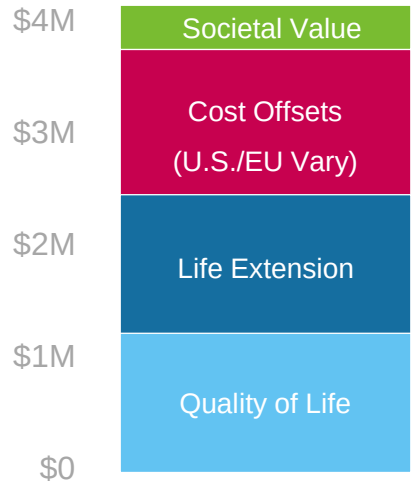
Cost Effective Analysis Focused on Actual Patient Value:
QOL and Life Extension

THE VALUE AT WHICH TREATMENT IS COST EFFECTIVE* *(NOT PRICE)*

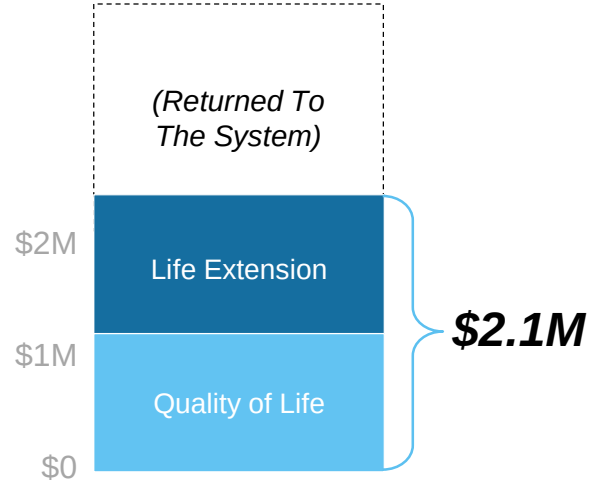


- Clinical Trial Data
- Outcomes Research
- Real World Evidence
- Economic Modeling

Traditional
All Inclusive Calculation



LentiGlobin
Intrinsic Value

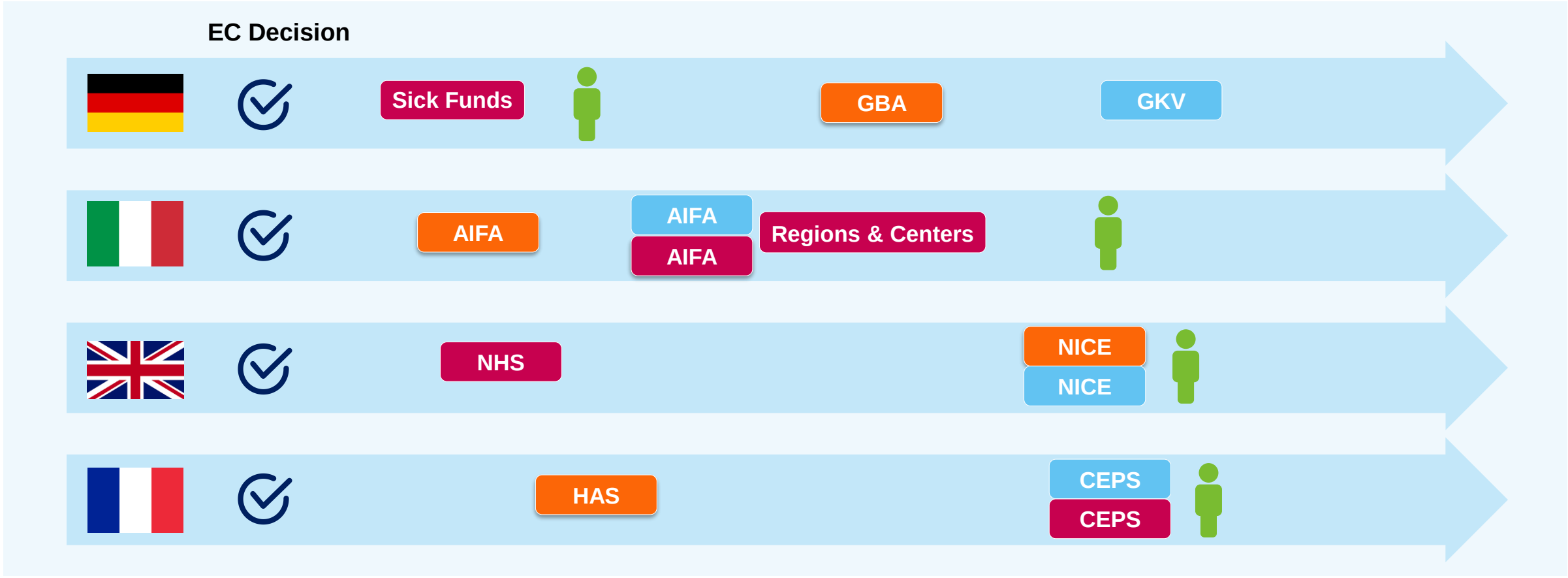


The actual LentiGlobin price is TBD, but will not exceed the intrinsic value (total value minus cost offsets).

*We have quantified the impact on patient quality of life, survival, treatment cost and society using established modeling techniques

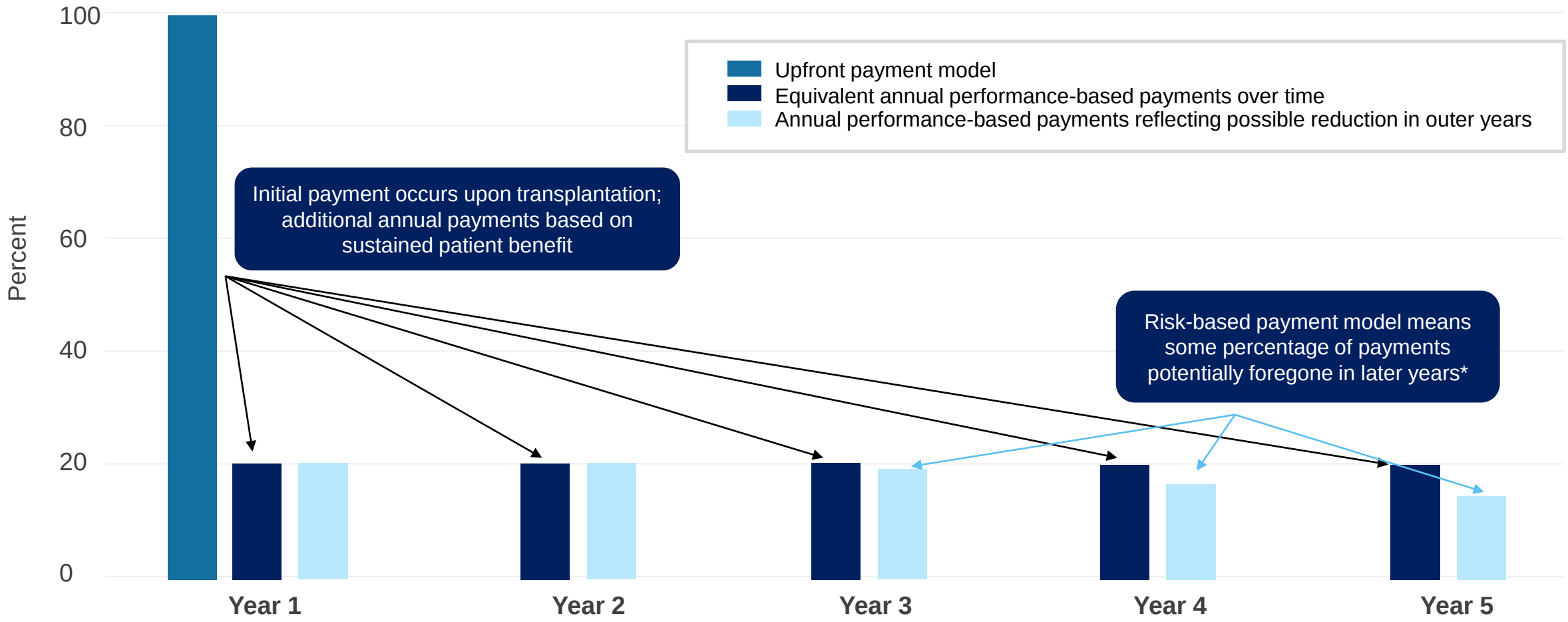
Country-by-Country Recoding Will Play Out Over Time

Each Journey is Different



Recoding the Payment Model

Payment Modeling Scenarios



*Illustrative reduction in payments

Commercial and Revenue Models for TDT in Europe: Anything but Traditional

	JPM 2019	MAY 2019
Target Payment Model	5 year value-based payment over time (VBPOT) based on outcomes	• 5 year VBPOT based on outcomes
Value	$2.1M lifetime intrinsic value to patients for expected reduction in morbidity and mortality	• Value dossiers in progress • Targeting narrow band for per patient total realized price • European price post-EC adoption
Estimated Launch Timing	TBD	• Germany – 2H 2019 • Italy, France, UK – 2020 • EU expansion starting in 2020
Revenue Recognition	TBD	• May be more than 20% upfront based on GAAP revenue recognition

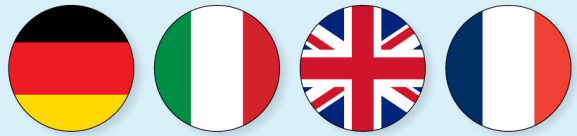
BLUE Style Commercial Success Factors

In the near-term, product revenue is not the most telling indicator on European TDT launch progress

- Payment models may vary by country
- Stub period for 2019 (~3-4 months of potential commercial infusions) in Germany only
- Focus on establishing the commercial model and operations for the long-term

Performance metrics that we will be tracking and sharing externally

Commercial patient infusions



Pricing approval by country

QTC contracts in place

Learnings and local market insights to inform continuous innovation

US Preview – Recoding the System for TDT, Expanding to Sickle Cell Disease (SCD)

TDT

Prevalence ~1,400 - 1,500

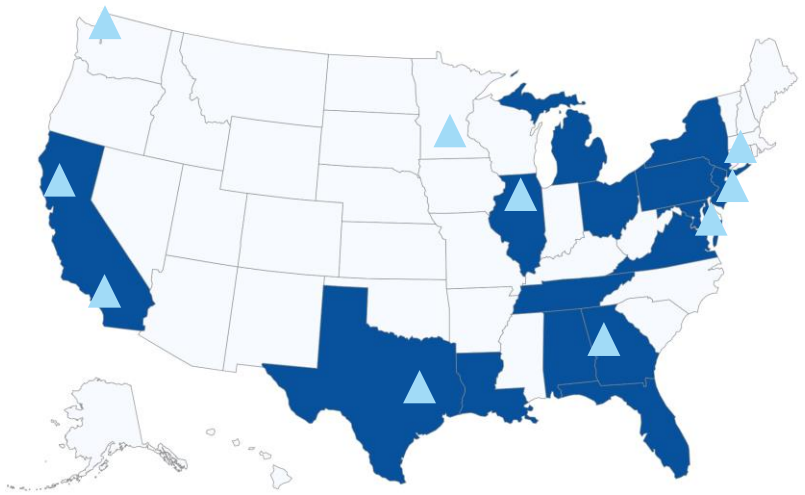
2020 Potential approval

SCD

Prevalence ~110,000

2022 Potential filing/approval

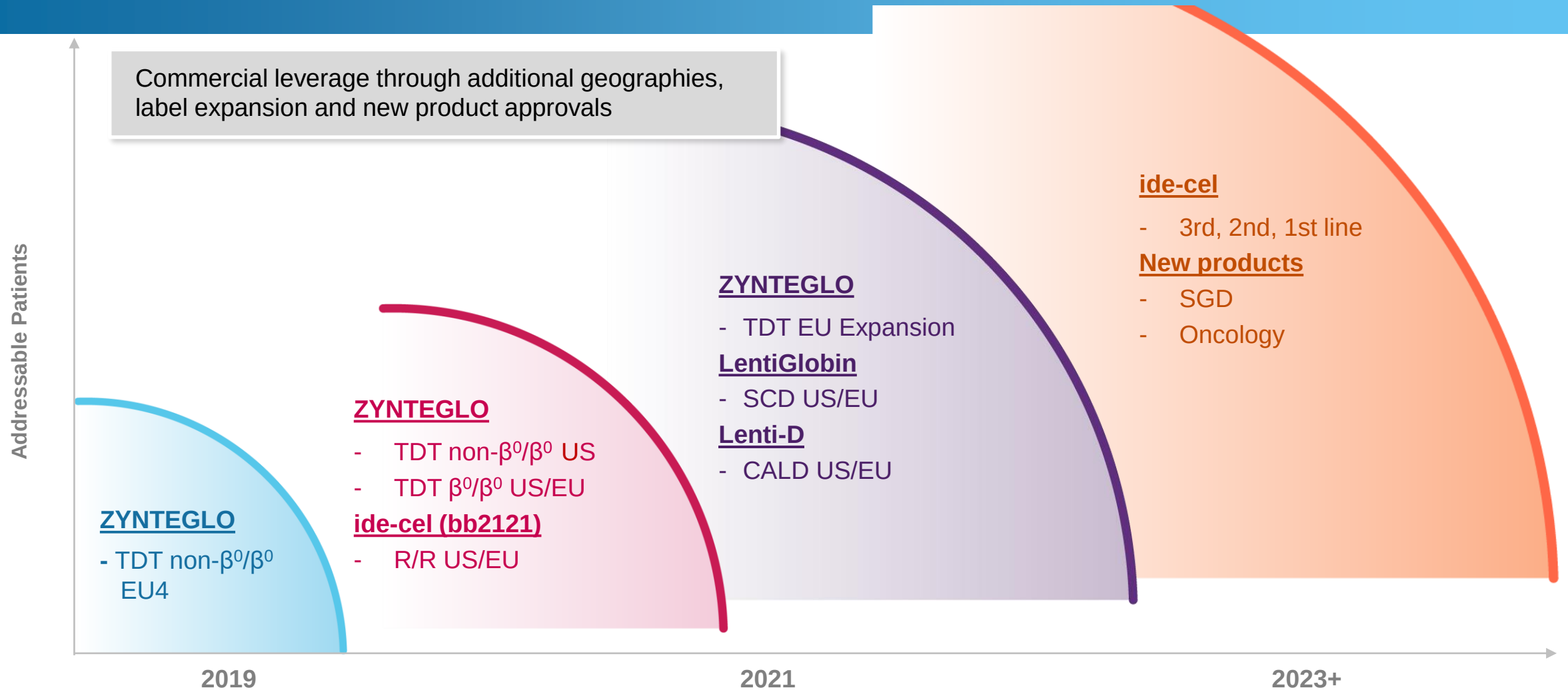
- Majority of TDT & SCD patients in 15 States
- ~80% overlap of top healthcare providers
- Key payers are the same



▲ Planned first wave bluebird bio QTCs

Market Opportunity

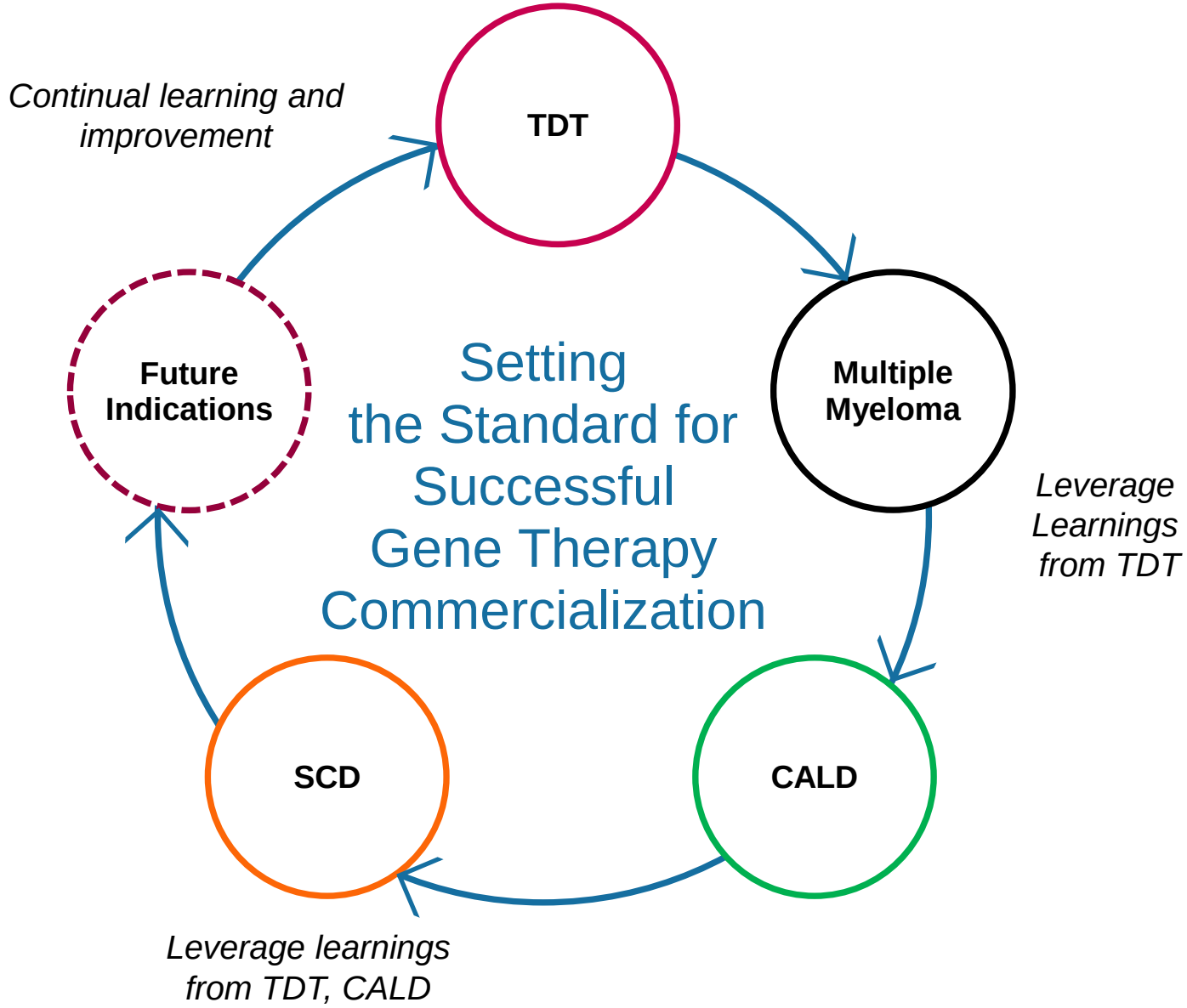
Commercial leverage through additional geographies, label expansion and new product approvals



ZYNTEGLO™ is not approved

Highly Leverageable Commercial Model

Ability to learn and improve over time through experiences with TDT and subsequent indications



Transfusion Dependent β-Thalassemia

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Transfusion-Dependent β-Thalassemia (TDT)

- Inherited blood disease that requires lifelong, frequent blood transfusions and iron reduction therapy

PROGRAM OVERVIEW

- CHMP positive opinion granted on March 29
- General regulatory agreement with FDA for BLA filing
- Studies ongoing:
  - Northstar-2 (HGB-207)
  - Northstar-3 (HGB-212)
  - HGB-205
- Long-term follow-up: LTF-303

Transfusion-Dependent β-Thalassemia

NORTHSTAR STUDY — HGB-204	• Basis of EU filing • Original manufacturing process • All genotypes
HGB-205 — HGB-205	• Basis of EU filing (with Northstar) • Original manufacturing process
NORTHSTAR-2 STUDY — HGB-207	• Basis of EU and U.S. filings • Refined manufacturing process • Non-β^0/β^0 genotypes
NORTHSTAR-3 STUDY — HGB-212	• β^0/β^0 genotypes • Refined manufacturing process

TDT Registration Strategy

General agreement with EU & US regulators on the registration path for LentiGlobin for the treatment of transfusion-dependent β-thalassemia

EU

CHMP positive opinion granted for **CONDITIONAL APPROVAL** in patients with non-β^0/β^0 genotypes on the basis of data from ongoing Northstar (HGB-204) & HGB-205 studies, as well as available data from Northstar-2 (HGB-207) study

ADAPTIVE PATHWAYS

PRIME

US

Pursue **approval** in adults and adolescents with non-**β^0/β^0** genotypes based on data from ongoing pivotal Northstar-2 (HGB-207) trial

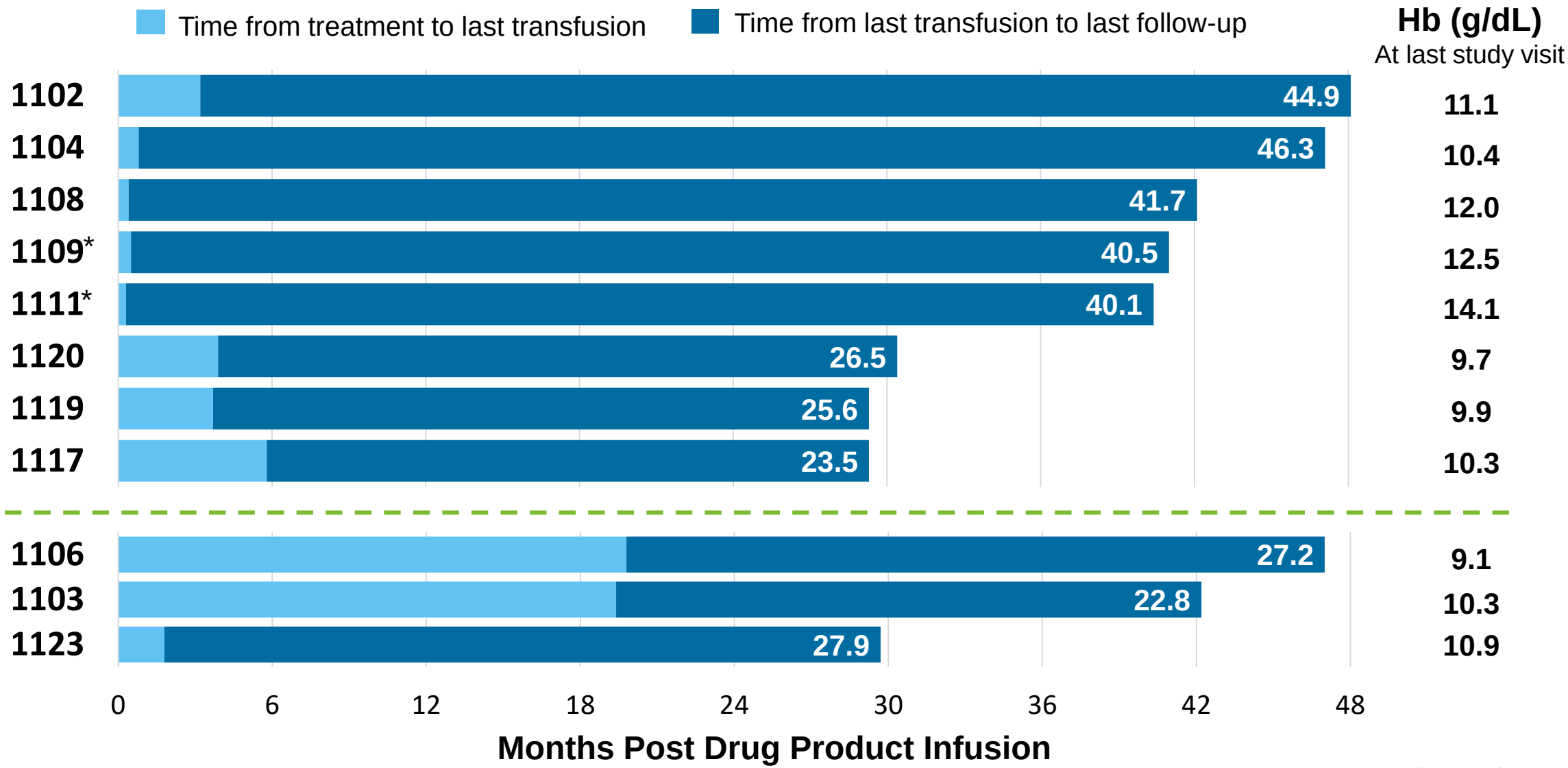
Pediatric population to be included as a cohort of HGB-207, rather than separate study

Submission for approval in **β^0/β^0** patients to be based on ongoing Northstar-3 (HGB-212) study

BREAKTHROUGH THERAPY DESIGNATION

ORPHAN DRUG DESIGNATION

8/10 Patients with Non-β^0/β^0 Genotypes and 3/8 Patients with β^0/β^0 Genotypes are Free from Chronic RBC Transfusions

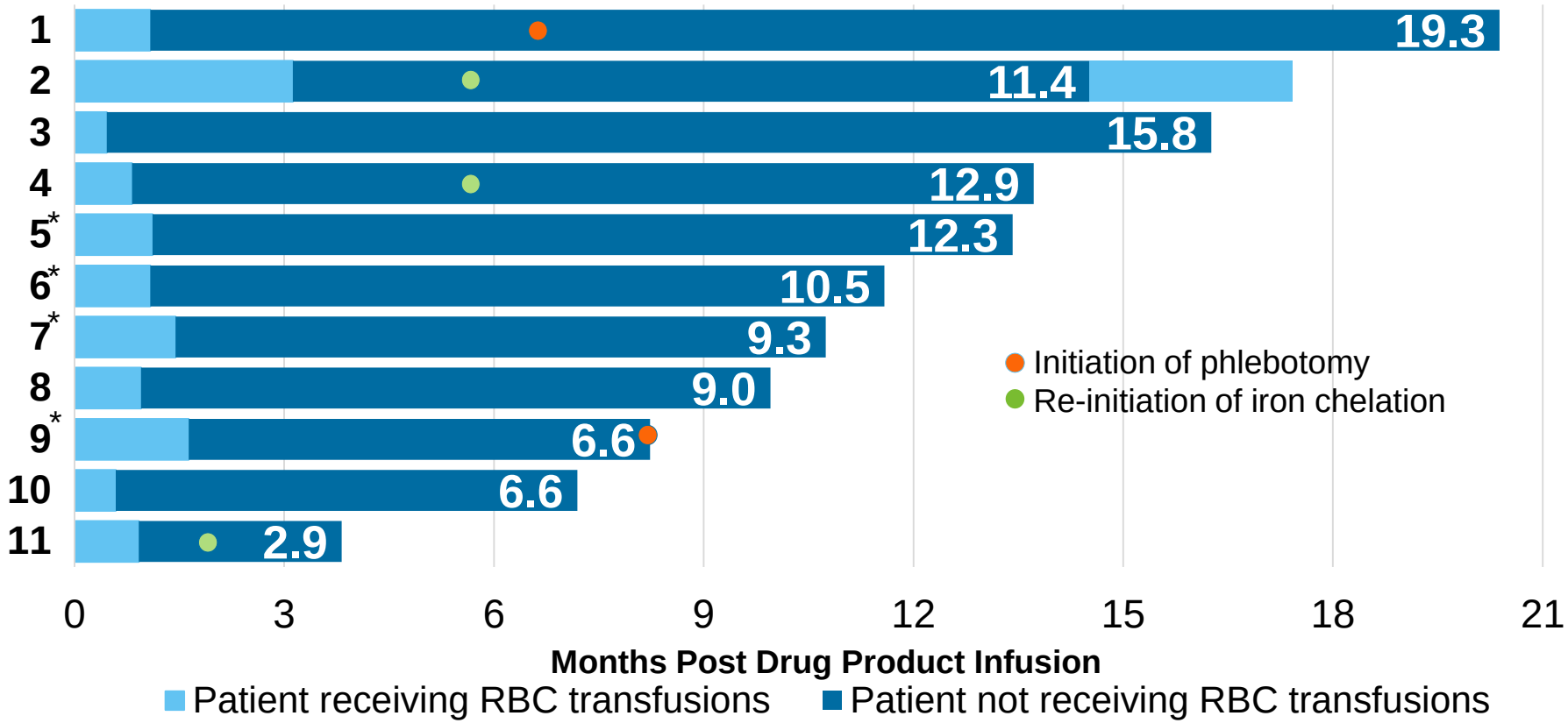


*Indicates male patients. Hb, hemoglobin; TI, transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months)

Data as of September 14, 2018

10/11 Patients Are Transfusion Free with Hemoglobin >11g/dL

Time free from chronic transfusions in patients with ≥3 months follow-up



	Hb (g/dL) At last study visit	Peripheral VCN At last study visit
1	13.3	3.2
2	11.3‡	0.4
3	11.1	2.2
4	12.1	1.7
5*	12.3	1.7
6*	12.5	2.9
7*	11.6	5.6
8	12.4	1.1
9*	11.9	4.9
10	11.6	5.4
11	11.2	5.6

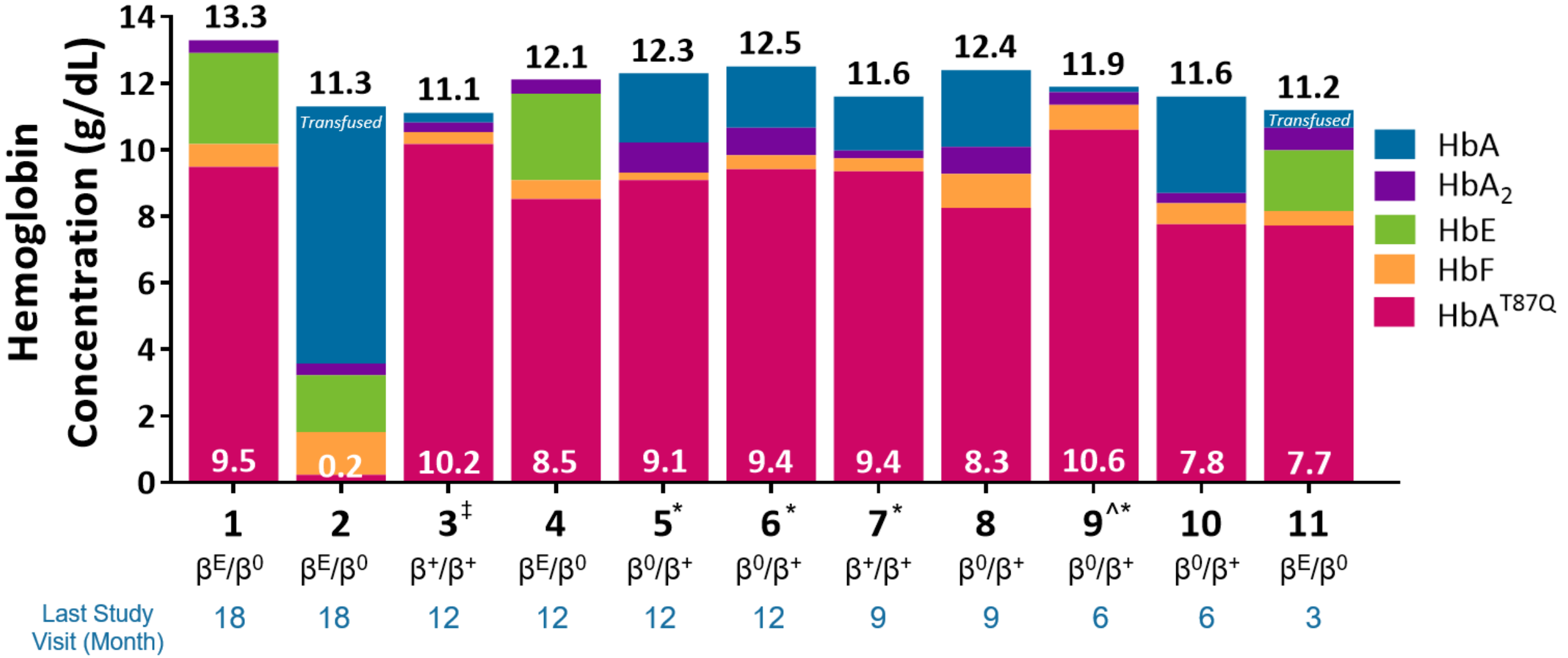
Safety profile post DP infusion remains consistent with myeloablative conditioning

Patients 1 and 3 have achieved the protocol definition of transfusion independence†

*Male patients; ‡Hb supported by transfusions; †Weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

Data as of September 14, 2018

High Levels of Gene Therapy Derived HbA^{T87Q} in 10/11 Patients



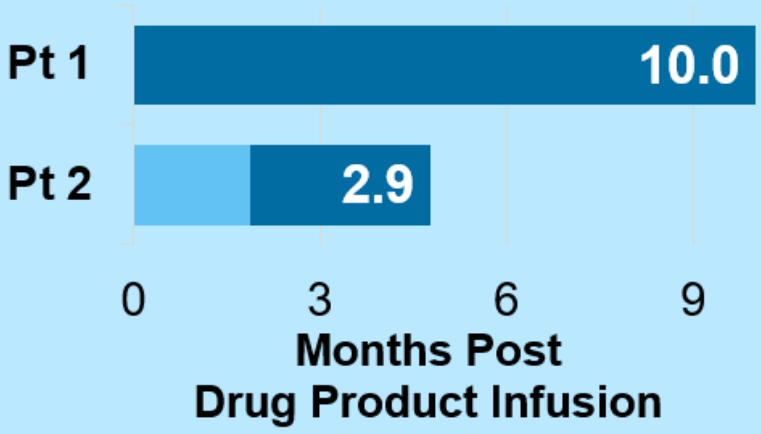
*Male patients; ‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, hemoglobin.

Data as of September 14, 2018

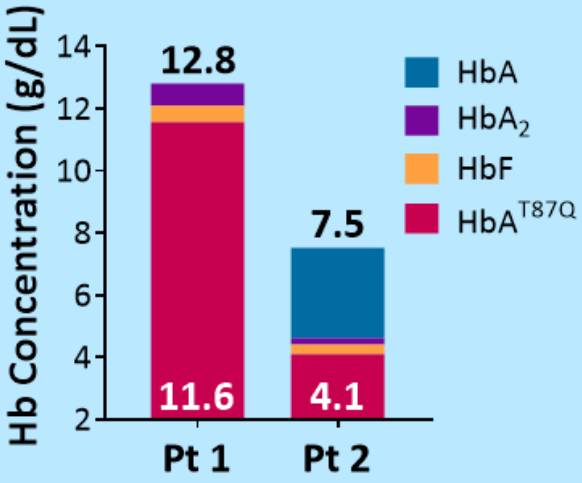
Normal Total Hemoglobin in First Northstar-3 β^0/β^0 Patient

NORTHSTAR-3 STUDY

Time free from transfusions in patients with ≥3 months follow-up

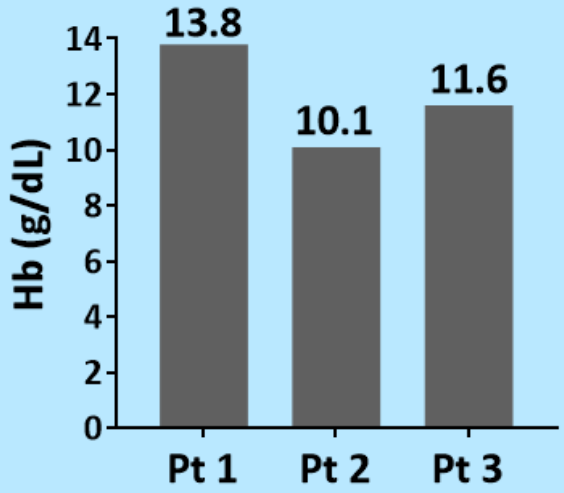


Hb fractions in patients with ≥3 months follow-up



	Pt 1	Pt 2
Peripheral VCN	3.4	2.2
Study Visit	M9	M3

Investigator reported Hb at last visit*



	Pt 1	Pt 2	Pt 3
Last RBC transfusion	M0	M1.9	M1.4
Study Visit	M12	M6	M3

Safety profile post-drug product infusion remains consistent with myeloablative conditioning

*Includes investigator reported data as of November 19, 2018, not from programmed statistical outputs

AEs, adverse events; DP, drug product; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

Data as of September 14, 2018 unless otherwise noted

Sickle Cell Disease

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Sickle Cell Disease (SCD)

- Severe blood disorder that causes anemia, frequent pain crises and shortened lifespan
- Global annual birth incidence ~ 300,000 – 400,000
- Mean age of death in the U.S. is 44 years[1]

PROGRAM OVERVIEW

- Plan to pursue accelerated development path based on hematological primary endpoint
  - Phase 3 study to begin in 2019
- HGB-206 amended and Group C expanded

[1]Paulukonis et al, California's Sickle Cell Data Collection Cohort, 2005-2015* ASH 2017*

Increasing Momentum to #ConquerSCD

2017

- March 2017, bluebird SCD case study published in *NEJM*
- July 2017, the FDA approved Endari (L-glutamine oral powder) to address acute complications of SCD

2018

- February 2018, Admiral Brett Giroir, M.D., appointed as Assistant Secretary for Health, HHS, is shining a spotlight on the toll of SCD and the need for improved treatment options
- March 2018, NHLBI launched "Cure SCD Initiative" spearheaded by Dr. Francis Collins
- October 2018, FDA-ASH Sickle Cell Disease Clinical Endpoints Workshop

"Unfortunately, some treated [SCD] patients will have no reduction of their symptoms and the disease will continue to progress," says Ann T. Farrell, M.D., director of the FDA's Division of Hematology Products, CDER. "***Better therapies are desperately needed***," Farrell explains. "We will continue to work with sponsors as much as possible to help remove roadblocks to new product development. ***It's important for the FDA to help as much as we can***."

FDA

Accelerated Development Plan Using Novel Composite Primary Endpoint Based on Hemoglobin

EXPANDED

Updated Primary Endpoint

Up to add'l 21 patients

Expanded age range

HGB-206 Group C

(Sickle Cell Disease, history of VOEs over 24 months)

Ongoing Phase 1/2, single arm, multi-center, U.S. study
N=41 (Group C)

- Primary Endpoint: HbA^{T87Q} and Total Hb
- Key Secondary Endpoint:
  - Reduction in severe VOEs
- ≥12 years of age - ≤50 years of age

HGB-210

(Sickle Cell Disease, history of VOEs over 24 months)

Phase 3, single arm, multi-center, global study

- Primary Endpoint: HbA^{T87Q} and Total Hb
- Key Secondary Endpoint:
  - Reduction in severe VOEs

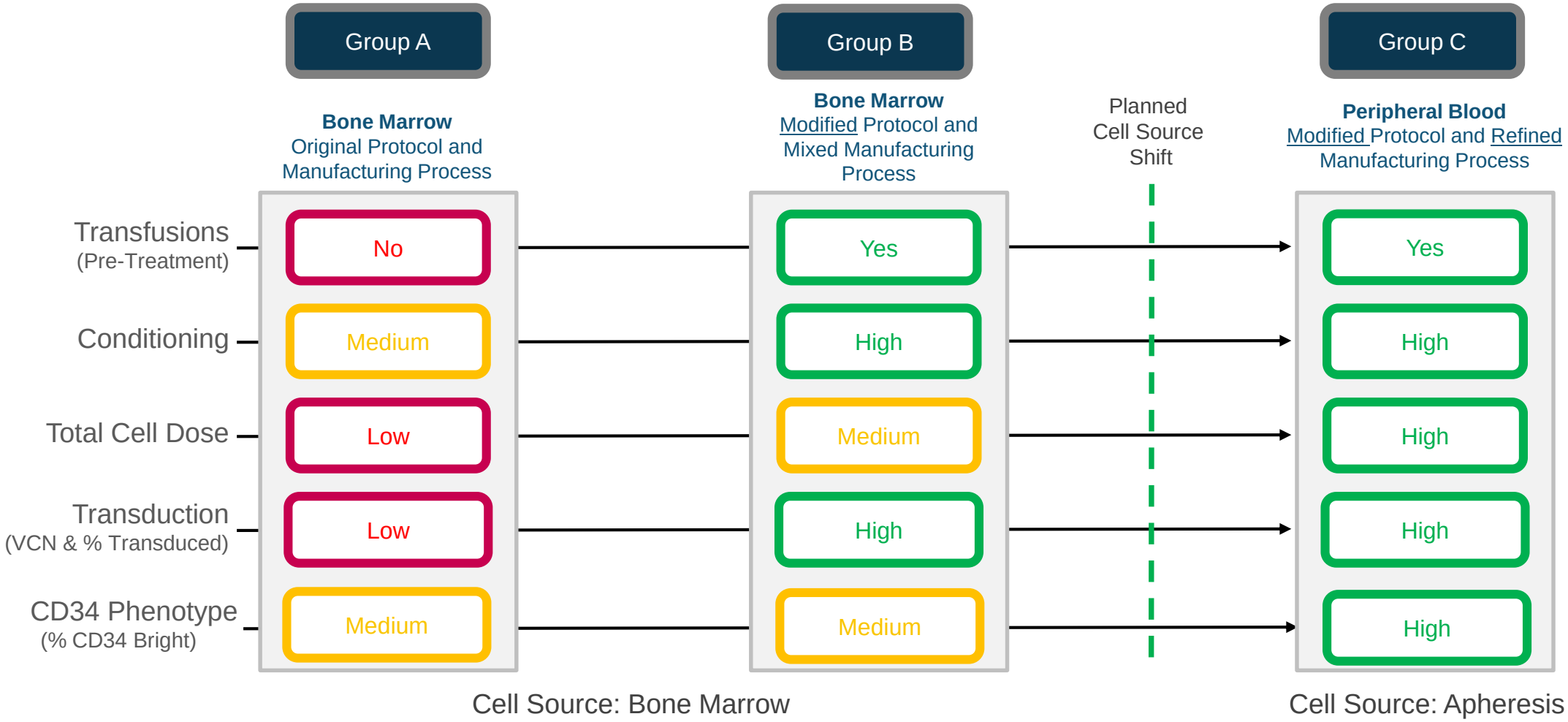
NEW

Planned for 2019

Additional Clinical Investigation in Other Patient Types and Ages Planned

Plans Based on Ongoing Engagement with Regulators

HGB-206: Evolution of LentiGlobin in SCD



Group C: Patient Characteristics

N=14 Patients Who Started Cell Collection

HGB-206

Parameter	Group C N=14
Age at consent median (min – max), years	**25.5** (18 – 36)
Gender	**6 F 8 M**
Genotype β^S/β^S	**14**
Prior SCD History	
Hydroxyurea use, n	**8**
Recurrent VOCs*, n Annualized no. of events, median (min – max)	**9** **6.5** (3.5 – 14.0)
ACS†, n Annualized no. of events, median (min – max)	**2** **1** (1 – 1)
Any history of stroke, n	**3**
TRJV >2.5 m/s, n	**0**

* ≥2 events/year in preceding 2 years; † ≥2 episodes in preceding 2 years, with at least one episode in the past year or in the year prior to the initiation of a regular transfusion program

ACS, acute chest syndrome; F, female; M, male; VOC, vaso-occlusive crisis; pRBC, packed red blood cell; TRJV, tricuspid regurgitant jet velocity

Data as of September 14, 2018

Group C: Safety Profile Generally Consistent with Myeloablative Busulfan Conditioning

HGB-206

Non-hematologic* grade ≥ 3 AEs Post-DP infusion in ≥2 patient	**n (%)** **N=9**
Febrile neutropenia	6 (67)
Stomatitis	6 (67)
Serious AEs* Post-DP infusion in ≥1 patient	**n (%)** **N=9**
Abdominal pain	1 (11)
Depression	1 (11)
Drug withdrawal syndrome	1 (11)
Hallucination	1 (11)
Mucosal inflammation	1 (11)
Nausea	1 (11)
Non-cardiac chest pain	1 (11)
Splenic hematoma	1 (11)
Vomiting	1 (11)

*Hematologic AEs commonly observed post-transplant have been excluded

- **No VOEs post-DP infusion in 9 patients**
- SAEs were reported in 4 patients
  - No AE considered related to DP
  - No cases of VOD observed to date
- No vector-mediated RCL detected to date
- Integration site (IS) analysis data available for two patients at 6 month visit
  - Total IS: Showed consistent polyclonality
- One patient in Group A: MDS diagnosed 36 months post-DP infusion: no evidence of LVV integration in dysplastic cells; monosomy 7 mutation identified (associated with sporadic and chemotherapy-related MDS)

AE, adverse event; DP, drug product; RCL, replication competent lentivirus; SAE, serious adverse event; VOD, veno occlusive liver disease; VOE, vaso-occlusive event; LVV, lentiviral vector

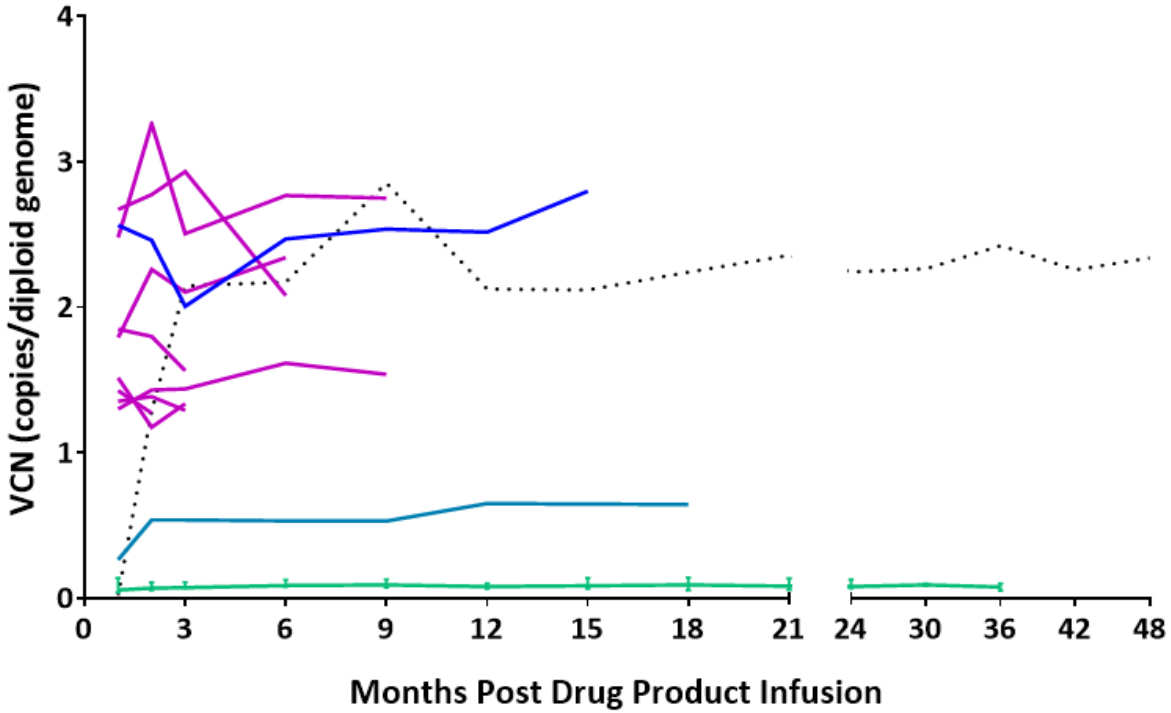
Data as of September 14, 2018

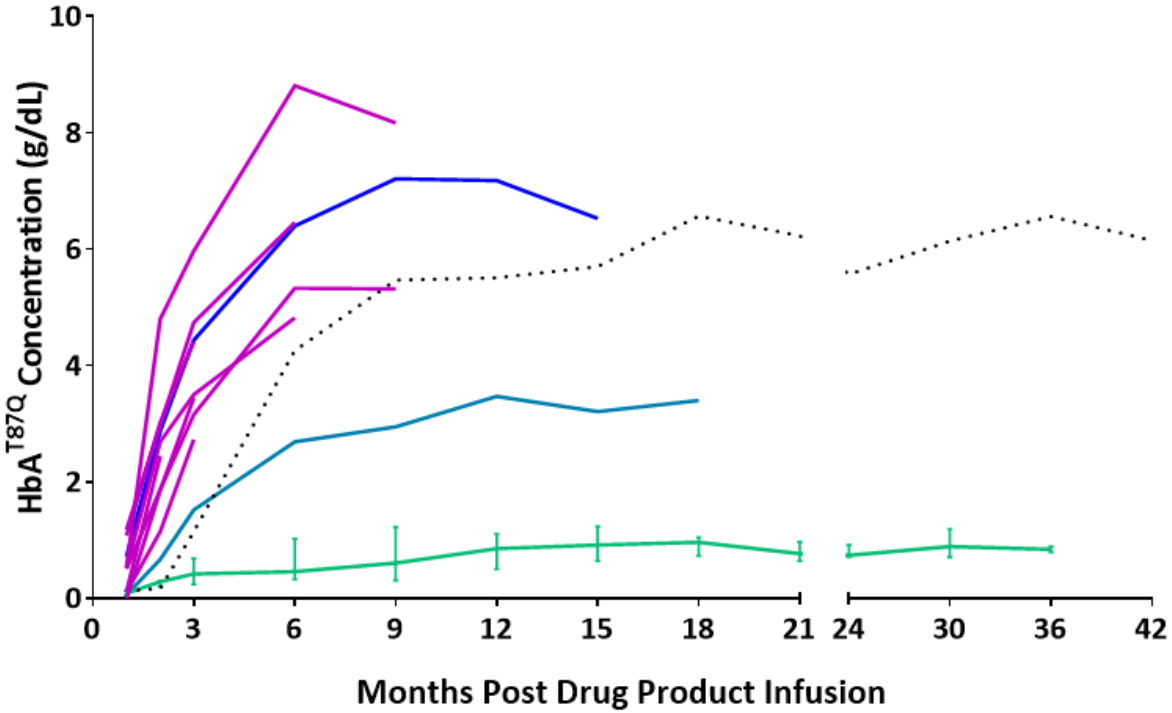
Critical Elements of LentiGlobin Success in SCD
Fundamentally Improving Red Blood Cell Physiology

GOAL	GROUP C RESULTS
High & Stable Levels of HbA^{T87Q} Derived Hemoglobin & Total Hemoglobin	• 4 out of 4 patients with ≥47% anti-sickling Hb (range: 47% - 62%) at 6 months • Sustained expression of HbA^{T87Q} levels through 9 months follow-up
Correction of Hemolysis	• Normalization of reticulocyte counts, lactate dehydrogenase and bilirubin levels
Pancellular Expression of HbA^{T87Q} Resulting in Reduction of Sickling	• Pancellular expression shown in two independent assays of patient cells • Reduction of sickling of patient RBCs at levels consistent with sickle trait cells
Improvement of Clinical Outcomes	• Increased total hemoglobin and robust HbA^{T87Q} production • No VOEs in early clinical follow up

Group C: Stable Peripheral Blood VCN, HbA^{T87Q} Trajectory Robust and Consistent

HGB-206





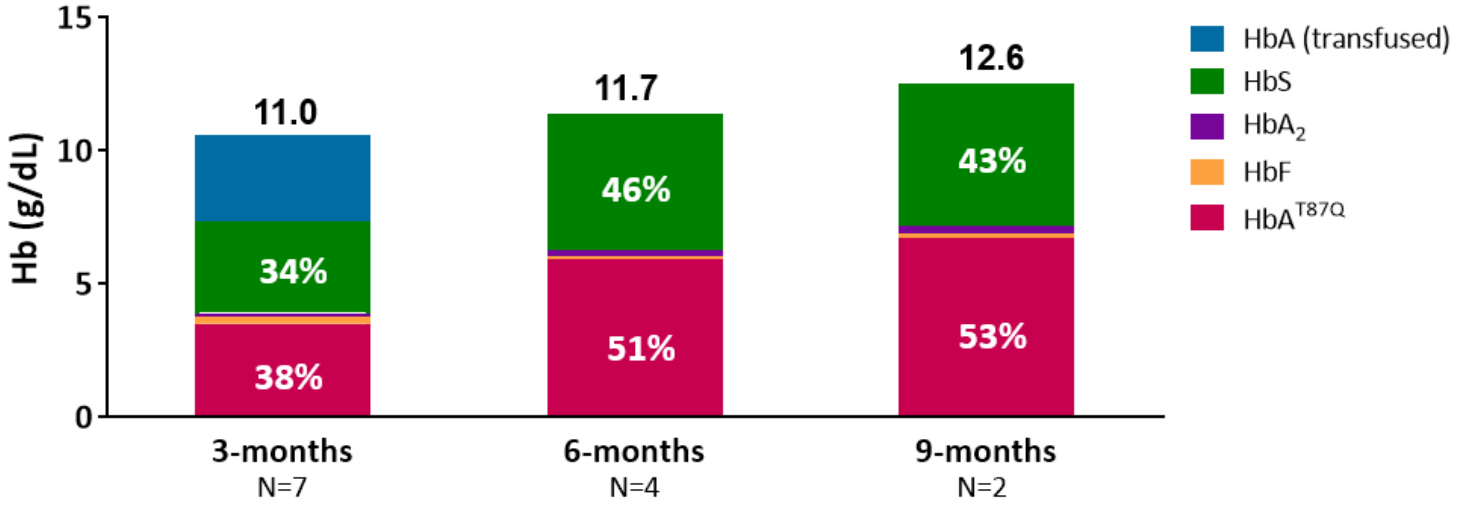
Group A — Group B: 1312 — Group B: 1313 — Group C ··· 1204

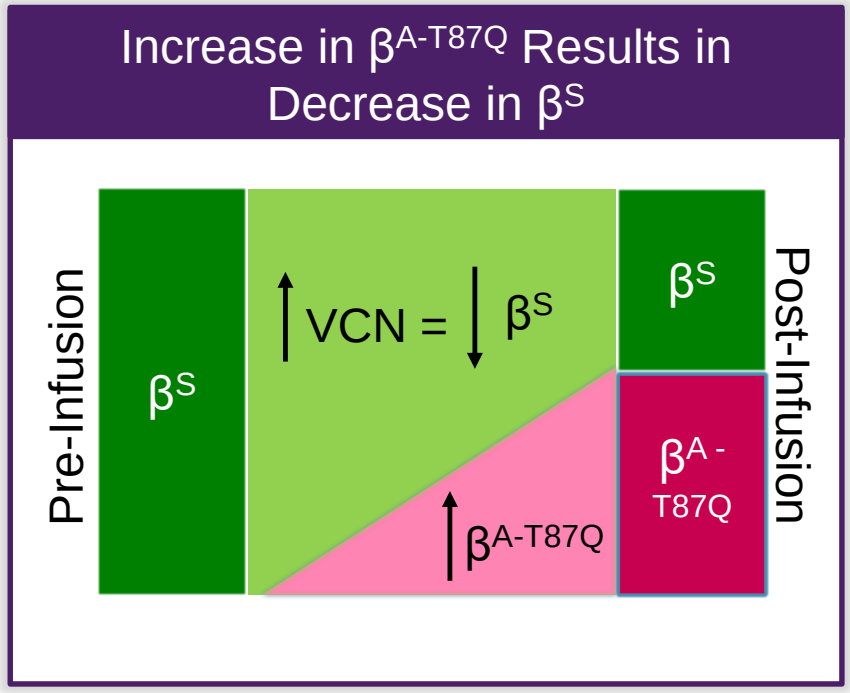
For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 36 study visit (N=2)

Data as of September 14, 2018

Group C Patients Achieving Sickle Trait-like Hemoglobin Distribution

HGB-206





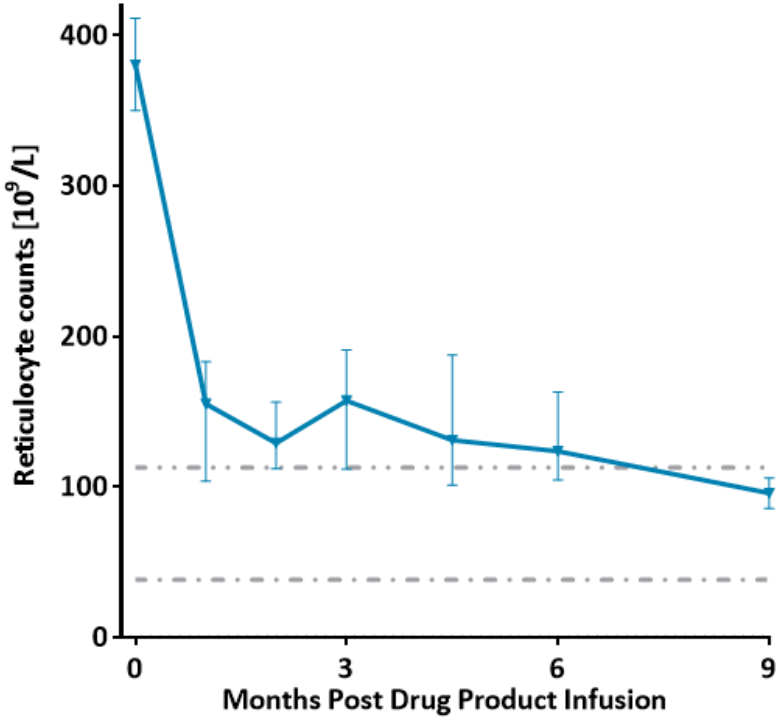
βS-globin decreasing with increasing HbAT87Q
(average concentration of hemoglobin per cell has not changed post-treatment)

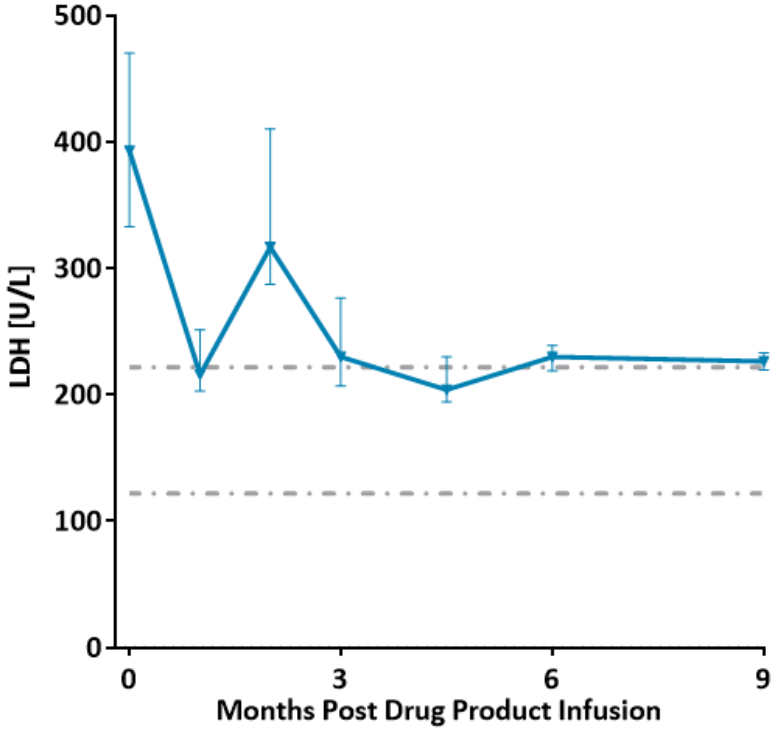
Data as of September 14, 2018

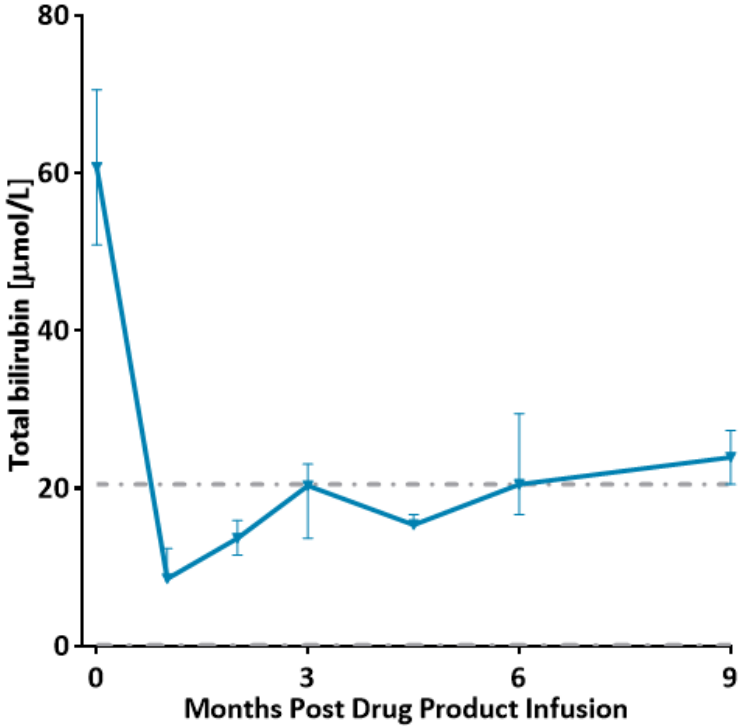
Impact on Clinical Outcomes of SCD in Group C
Normalization of Key Biomarkers of Hemolysis Over Time

HGB-206

Reticulocyte Counts	Lactate Dehydrogenase	Total Bilirubin







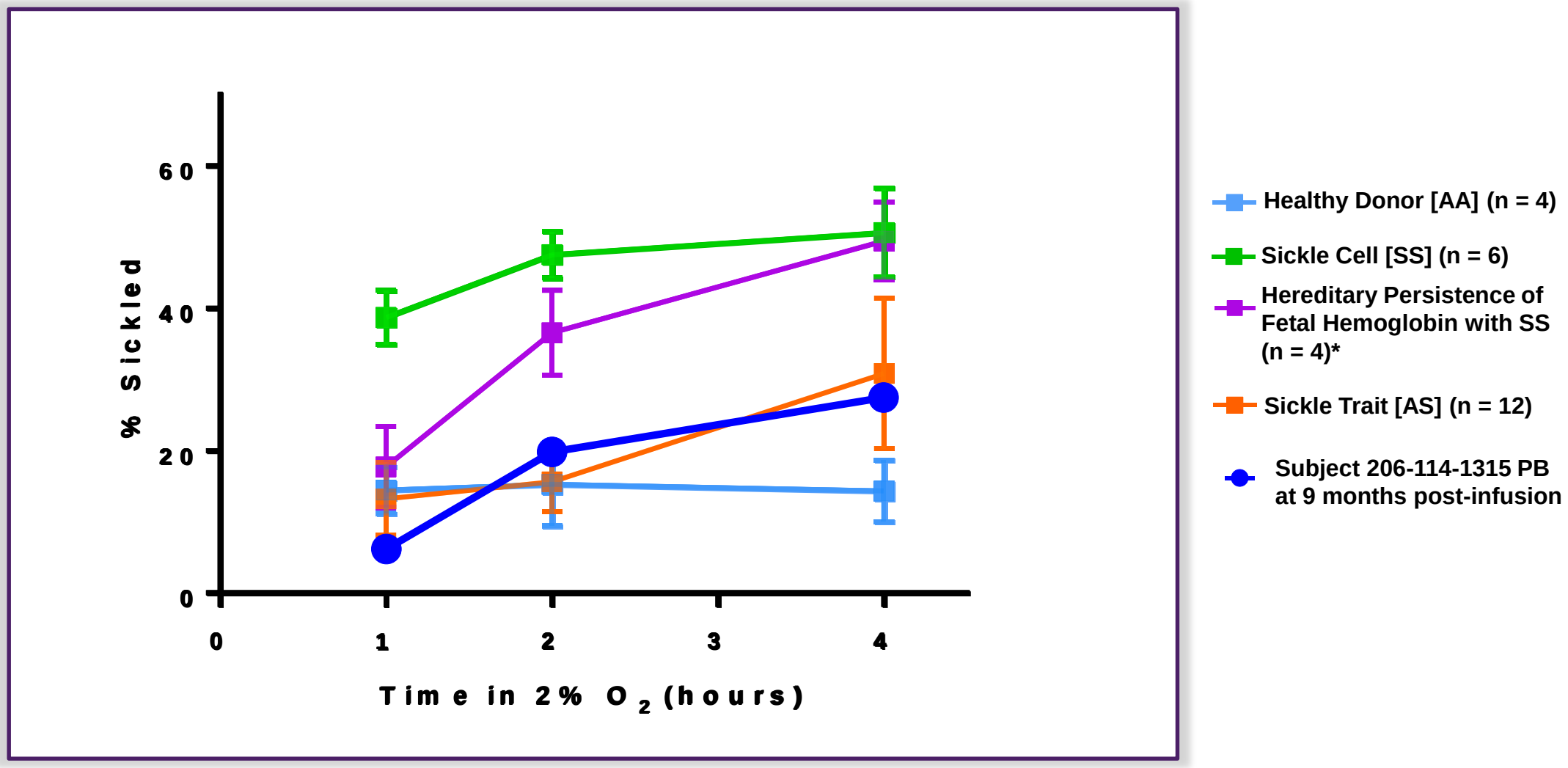
Dot-dash lines denote lower and upper limits of normal values

Median (Q1, Q3) depicted

Data as of September 14, 2018

LentiGlobin has Anti-Sickling Activity Comparable to Sickle Trait

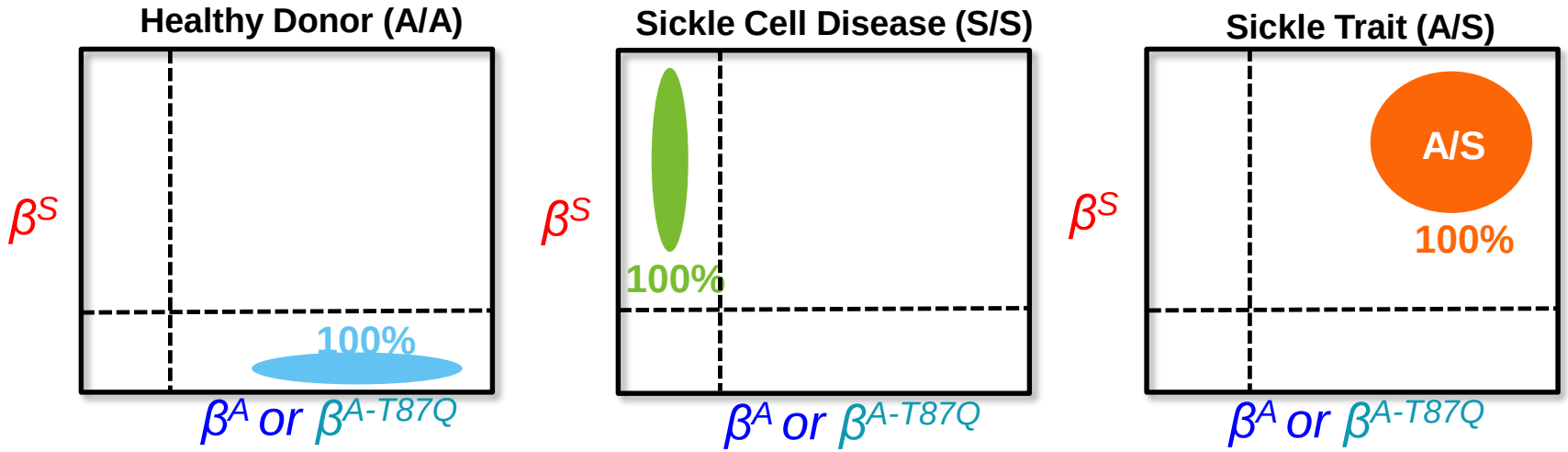
Reduction in % Sickled and Time to Sickling in Patient RBCs Post-Treatment

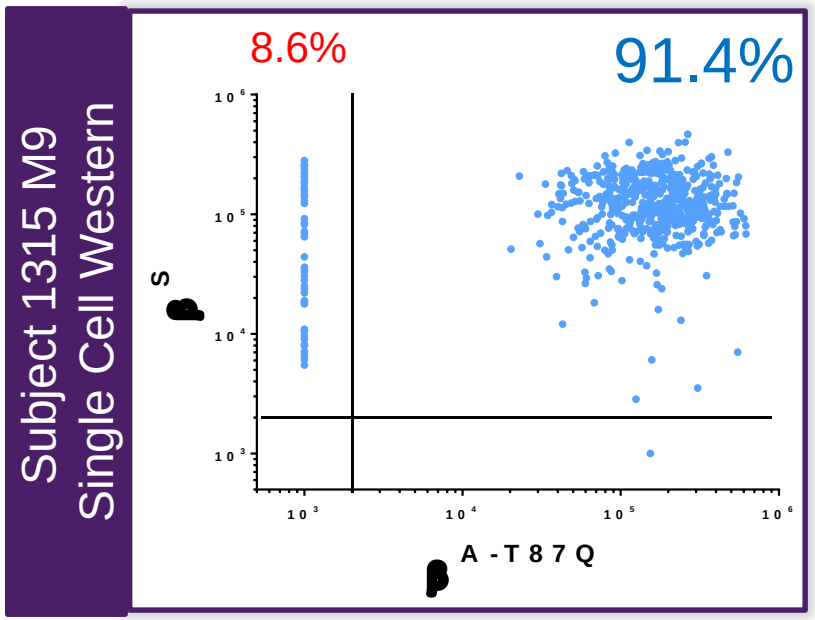


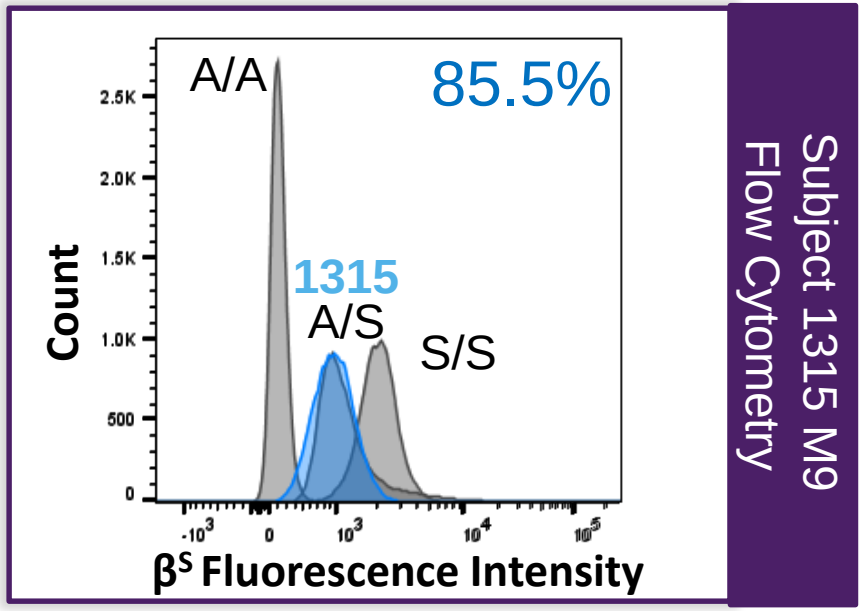
*HbF levels in HPFH donors ranged from 28.1 to 42.3%

Two Independent Assays Reveal Near Pancellular $\beta^{A\text{-}T87Q}$ Distribution

Majority of Patient RBCs are Positive for Anti-Sickling Globin



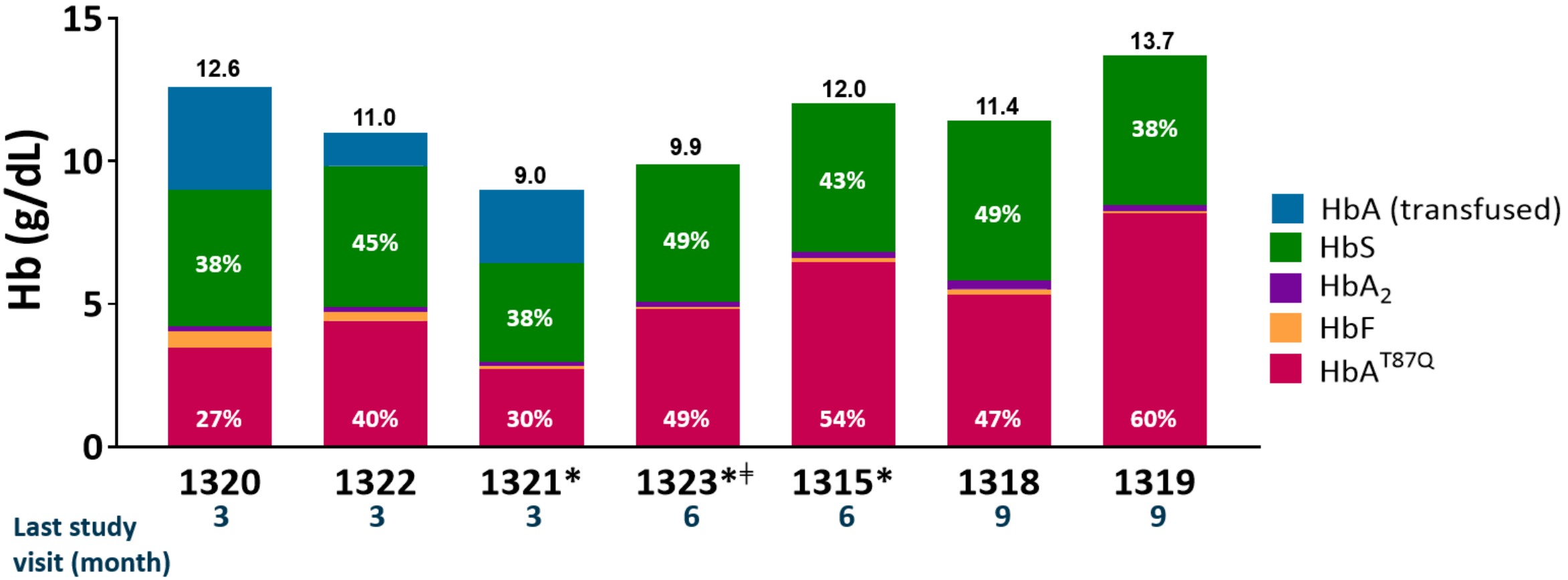




Impact on Clinical Outcomes of SCD

Resolution of Anemia (and Robust HbA^{T87Q} Levels) in All Patients by 6 Months; No VOEs Since DP Infusion

HGB-206



Group C: All patients free of VOEs as of data cut-off

* Denotes female patients; ‡ Patient current receiving phlebotomy

Data as of September 14, 2018

A Case of Myelodysplastic Syndrome with Excess Blasts

Patient and treatment characteristics

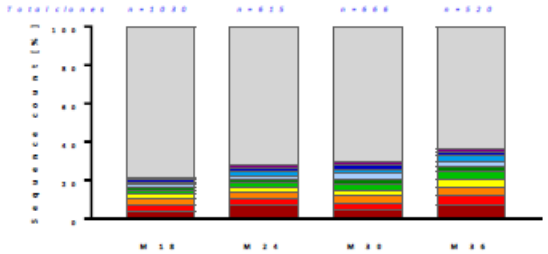
- >40 years old at LentiGlobin infusion
- Continuous hydroxyurea (HU) for 8 years before enrollment; restarted post-LentiGlobin treatment
- Received 3.3 mg/kg (200 mg) daily IV busulfan conditioning over 4 days
- LentiGlobin DP characteristics:
  - DP VCN = 1.3 copies/diploid genome
  - % LVV positive cells = 29%
  - CD34+ cell dose = 2.8 x 106 CD34+ cells/kg

A grade 4 SAE of MDS in a Group A patient ~36 months post LentiGlobin GT

- BM biopsy showed 15% myeloblasts and dysplasia
- Cytogenetics showed monosomy 7 and abnormal chromosome 19p in 8 of 20 metaphases

No evidence of clonal dominance by insertion site (IS) analysis

Frequencies of top 10 integration sites



- No single IS represents >30% of total
- Top 5 clones consistently transitory over last 18 months of follow-up

Blast cells (CD34+) had low VCN consistent with the absence of LVV integration

Cell populations from BM aspirate collected ~3 weeks post MDS diagnosis	Purity (%)	VCN (c/dg)
Unsorted	N/A	0.14
CD34-	98	0.21
CD34+, with myeloblasts as major contributors	93	0.02

Conclusions

- Given that there is no evidence of LVV-mediated oncogenesis, the MDS SAE is considered unlikely related to LentiGlobin GT*
- MDS has been reported in adults post autologous HSCT with use of alkylating agents such as busulfan (Rege KP et al., BMT 1998; Howe R et al., BMT 2003; McNerney ME et al., Nat Rev Cancer 2017)

*Per safety database

BM, bone marrow; c/dg, copies per diploid genome; DP, drug product; GT, gene therapy; HSCT, hematopoietic stem cell transplant; IV, intravenous; LVV, lentiviral vector; N/A, not applicable; VCN, vector copy number

Multiple Myeloma

bluebirdbio®

Multiple Myeloma

- A lethal blood cancer that often infiltrates the bone marrow causing anemia, kidney failure, immune problems and bone fractures

BCMA PROGRAM OVERVIEW

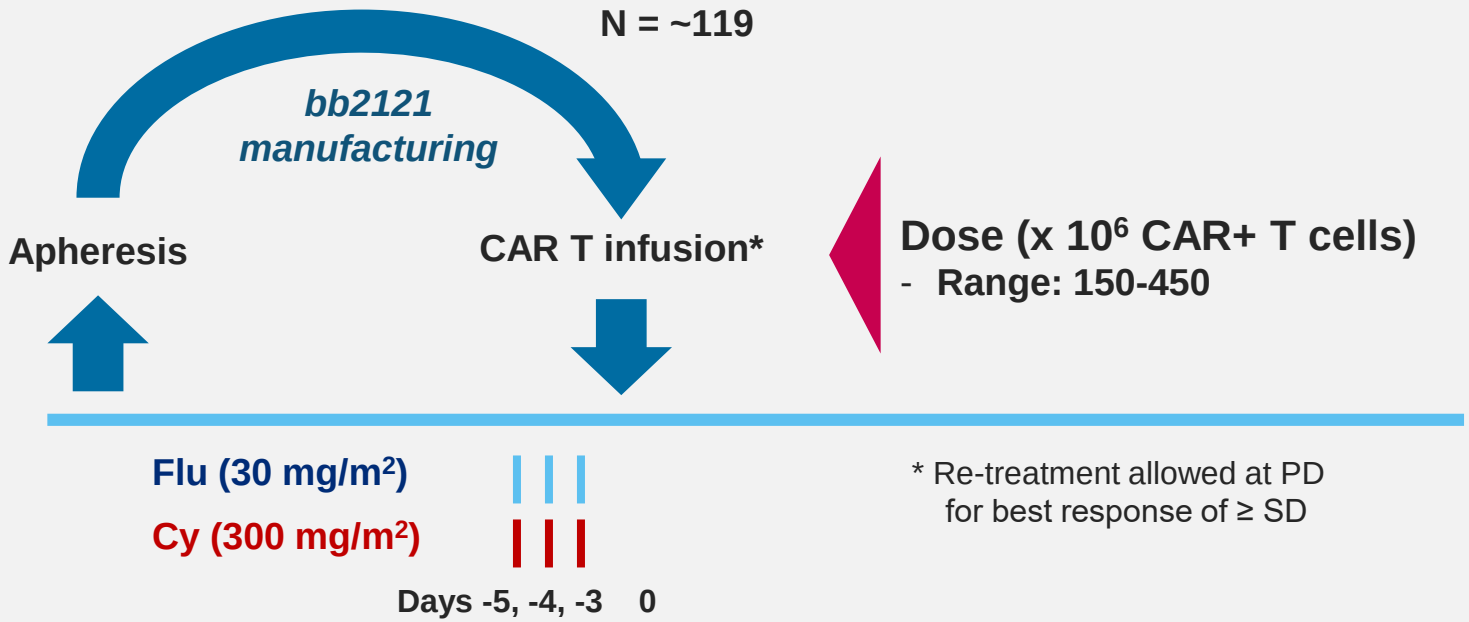
- bb2121: Enrollment in KarMMa registration-enabling study complete (N=140)
- Additional studies advancing:
  - KarMMa-2 in 2nd line Phase 2 study enrolling soon
  - KarMMa-3 in 3rd line+ Phase 3 study enrolling soon
  - Opportunities for bb2121 in newly diagnosed MM including high risk, transplant ineligible and transplant eligible vs. transplant under evaluation

bb2121-MM-001: bb2121 Registration-Enabling Trial (KarMMa)

KarMMa

Relapsed and refractory MM

- ≥3 prior treatment regimens with ≥ 2 consecutive cycles each (unless PD was best response)
- Received prior IMiD®, PI and anti-CD38
- Refractory (per IMWG) to last treatment regimen



Endpoints

Primary: ORR

Key Secondary: CR, TTR, DOR, PFS, TTP, OS, Safety, bb2121 expansion and persistence, MRD (genomic and flow assays)

Exploratory: BCMA expression/loss, T cell immunophenotype, GEP in BM, HEOR

CRB-401 Data at ASCO 2018 - Baseline Demographics and Clinical Characteristics

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) follow-up, d	345 (46, 638)	87 (29, 184)
Median (min, max) age, y	58 (37, 74)	65 (44, 75)
Male, n (%)	13 (62)	16 (73)
Median (min, max) time since diagnosis, y	4 (1, 16)	6 (1, 36)
ECOG PS,[1] n (%)		
0	10 (48)	6 (27)
1	11 (52)	16 (72)
High-risk cytogenetics, n (%)		
del(17p), t(4;14), t(14;16)	8 (38)	9 (41)

ECOG, Eastern Cooperative Oncology Groups performance status; ISS, international staging system; NA, not available. [1]Data at screening presented.
Data cutoff: March 29, 2019

CRB-401 Data at ASCO 2018 - Heavily Pretreated Patient Population

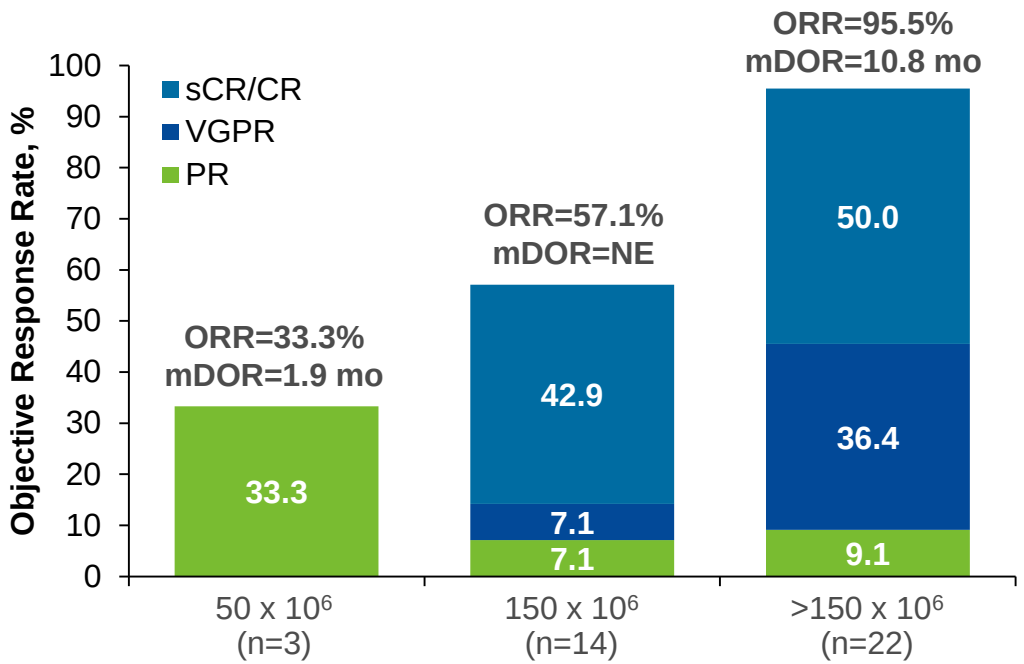
Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

	Escalation (N=21)		Expansion (N=22)	
Parameter	**Exposed**	**Refractory**	**Exposed**	**Refractory**
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Cumulative exposure, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

SCT, stem cell transplant. Data cut-off: March 29, 2018.

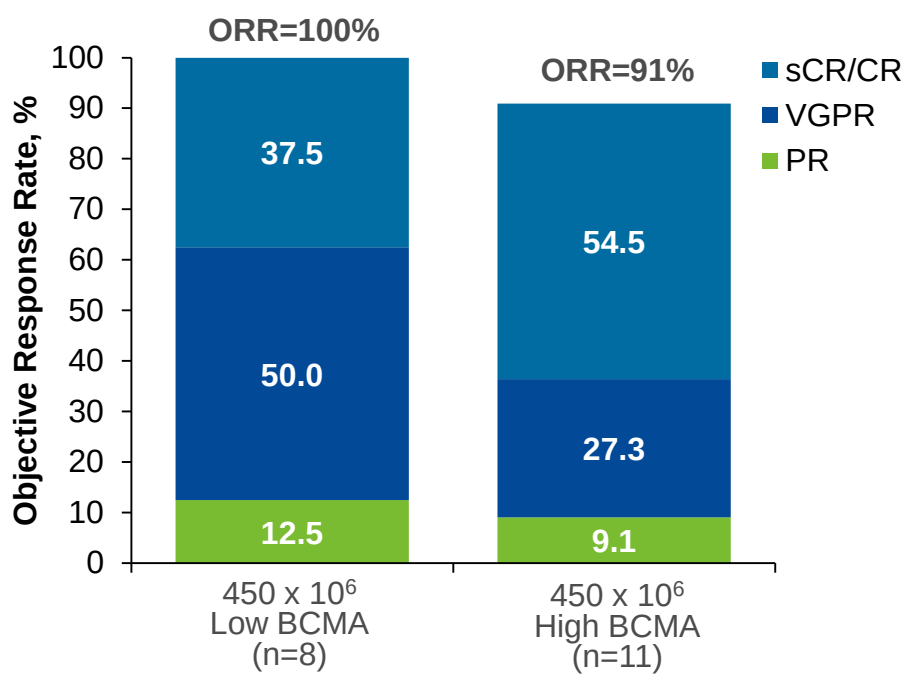
CRB-401 Data at ASCO 2018 - Tumor Response: Dose-related and Independent of Myeloma BCMA Expression Levels

Tumor Response By Dose[1]



	50 x 10^6 (n=3)	150 x 10^6 (n=14)	>150 x 10^6 (n=22)
Median follow-up (min, max), d	84 (59, 94)	87 (36, 638)	194 (46, 556)

Tumor Response By BCMA Expression[1]



	450 x 10^6 Low BCMA (n=8)	450 x 10^6 High BCMA (n=11)
Median follow-up (min, max), d	168 (121, 184)	311 (46, 556)

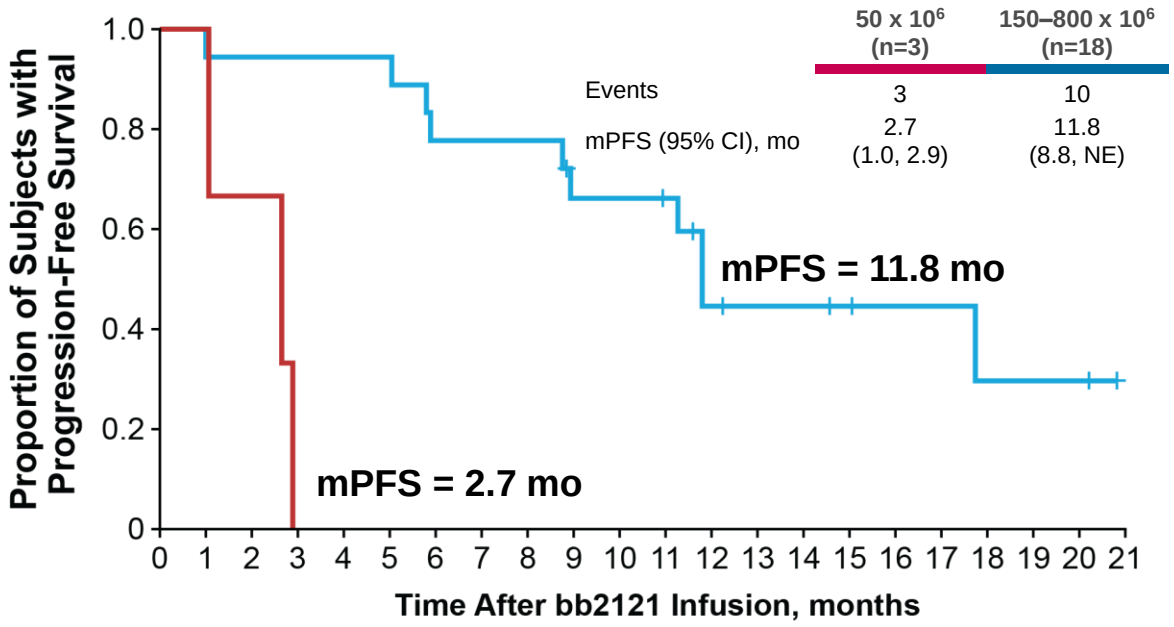
- 80.6% ORR across active dose cohorts (150-800 x 10^6)

CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. Data cut-off: March 29, 2018. [1]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

CRB-401 Data at ASCO 2018 - Hitting the Mark for Progression Free Survival

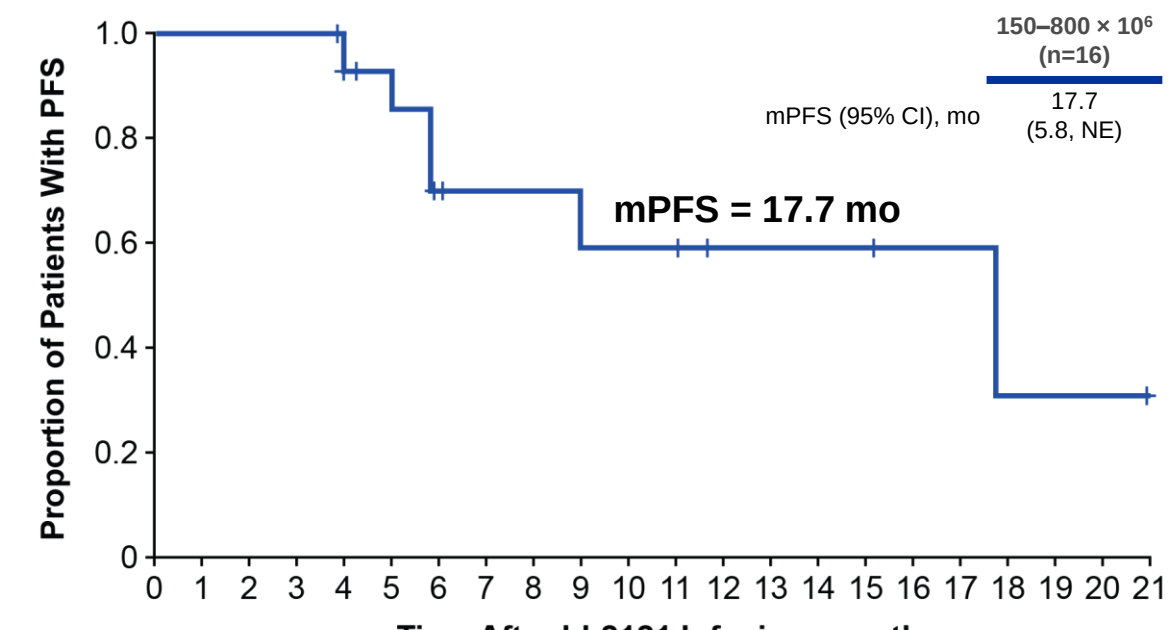
- mPFS of 11.8 months at active doses (≥150 x 10^6 CAR+ T cells) in 18 subjects in dose escalation
- mPFS of 17.7 months in 16 responding subjects from all study cohorts who are MRD-negative

PFS at Inactive (50 x 10^6) and Active (150–800 x 10^6) Dose Levels[1]



Data cut-off: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable.
[1]PFS in dose escalation cohort.

PFS in MRD-Negative Responders
Escalation and Expansion Cohorts



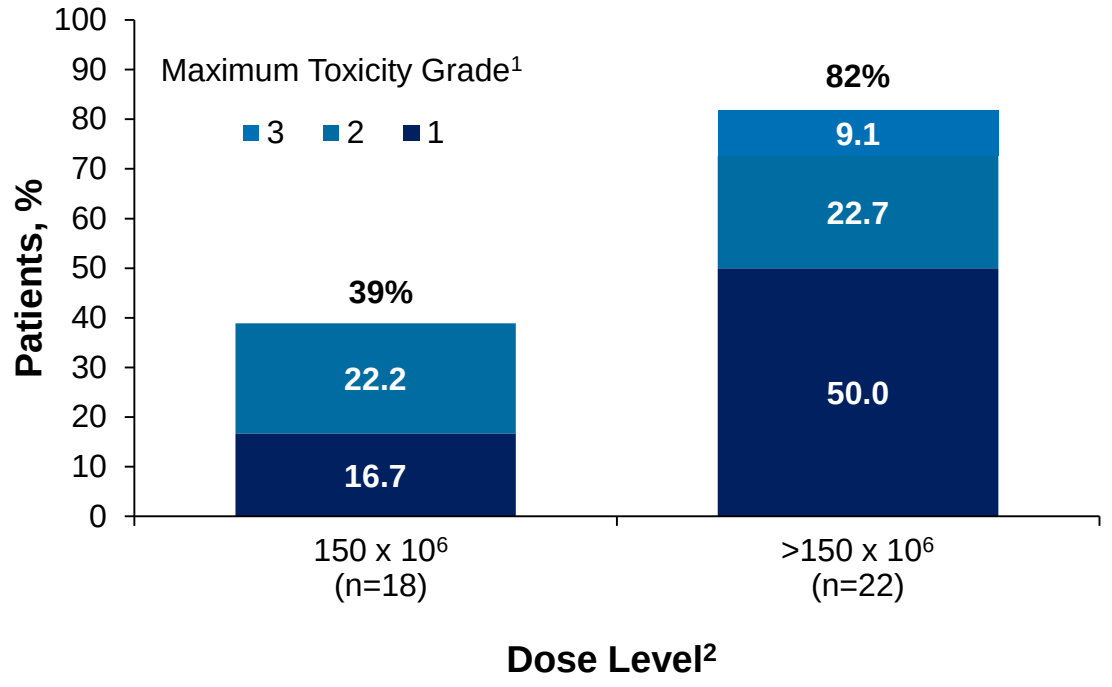
PFS progression-free survival; MRD, minimal residual disease.
Includes patients treated with <50 x 10^6 CAR T cells who were MRD-negative at >1 postbaseline time point

CRB-401 Data at ASCO 2018 - bb2121 Continues to be Generally Well-Tolerated; No New Safety Signals

CAR T Treatment-Emergent Adverse Events
All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥3
Cytokine release syndrome[1]	27 (63)	2 (5)
Neurotoxicity[2]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection[3]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Cytokine Release Syndrome By Dose Level



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events
- Patients with a CRS event, 63%

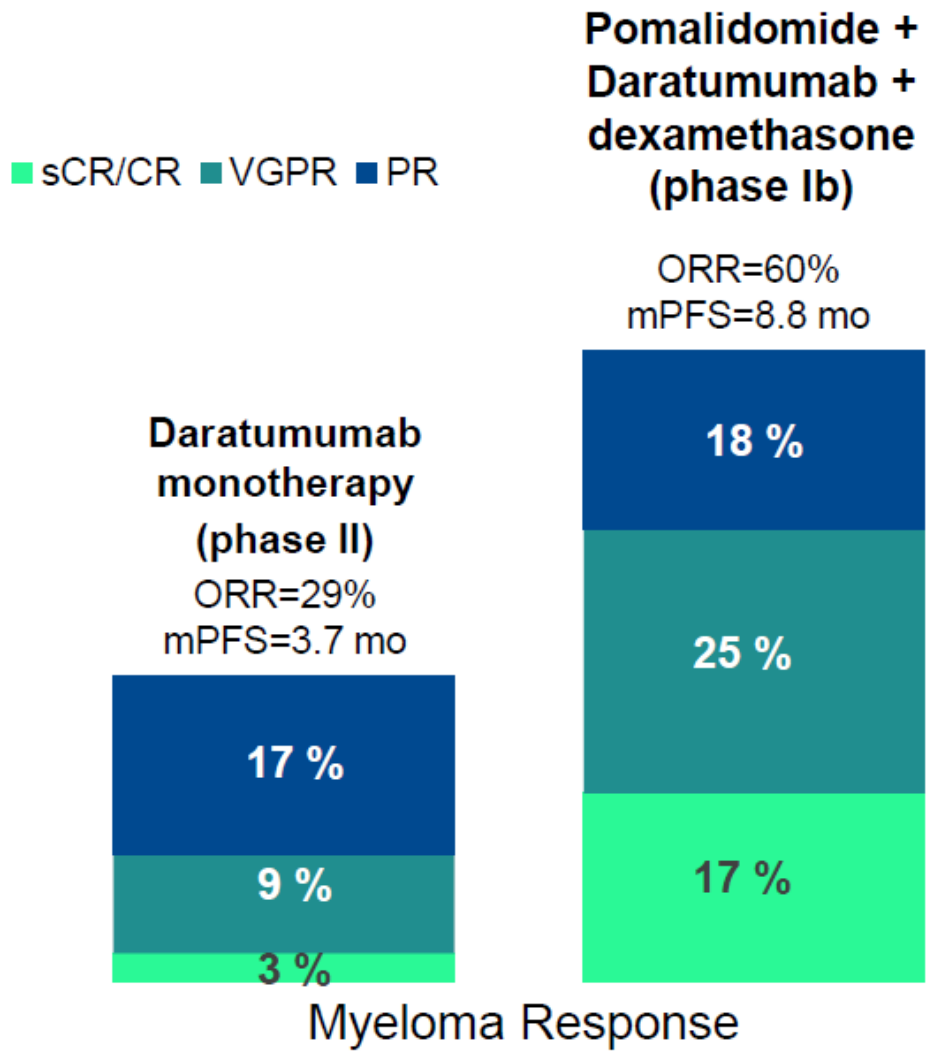
Data cut-off: March 29, 2018. NE, not estimable.[1]CRS uniformly graded per Lee et al., *Blood* 2014;124:188-195. [2]Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagnmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. [3]Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. [4]Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. [5]Time from first bb2121 infusion to the first grade ≤2 event after day 32.

Response to Current Standard of Care in Late Line RRMM

Current standard of care in RRMM after two or more lines of therapy:

	Dara	PDd	bb2121
Phase	II	I	I
N	106	103	43
Eligibility	≥ 3 prior lines Pom allowed Dara-naive	≥ 2 prior lines Pom-naïve Dara-naive	≥ 3 prior lines Pom allowed Dara allowed
Median prior lines	5	4	7

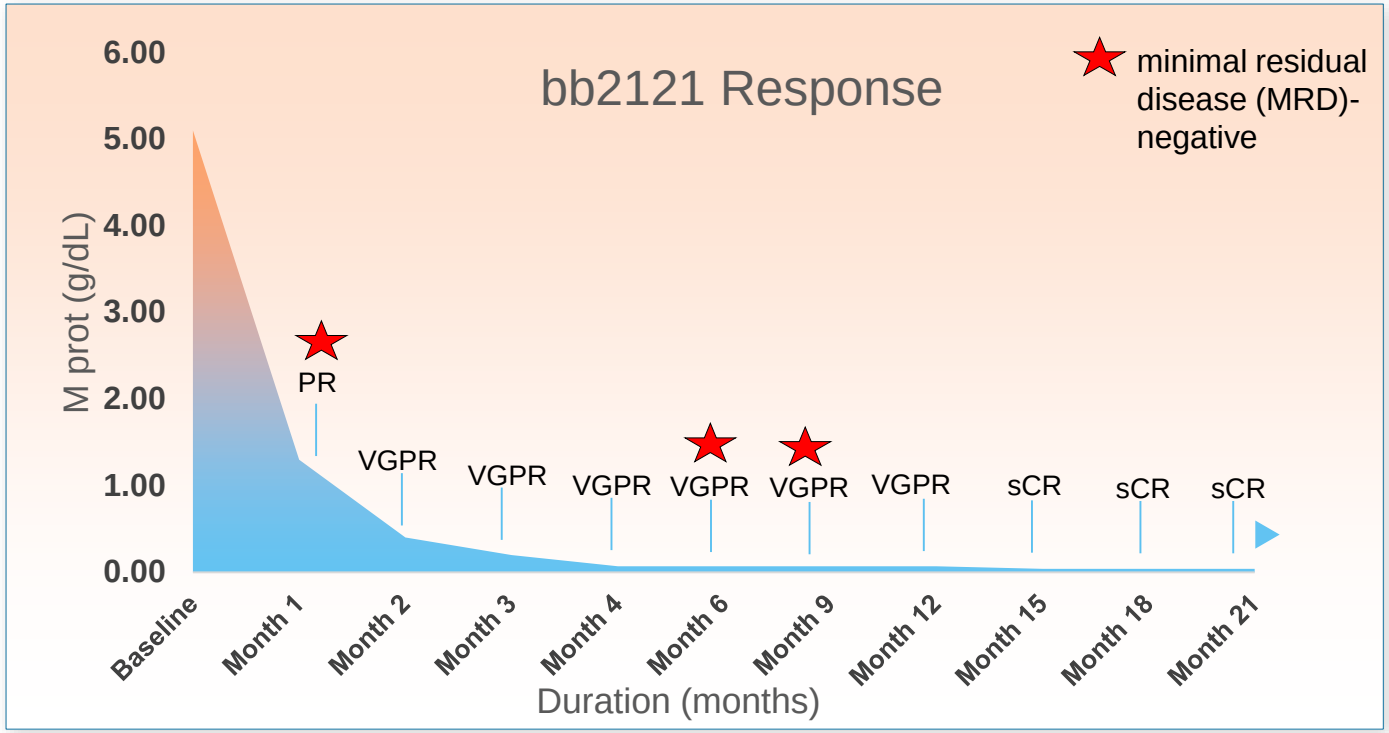
PDd=Pomalidomide + Daratumumab +dexamethasone.
Pom=Pomalidomide; Dara=Daratumumab



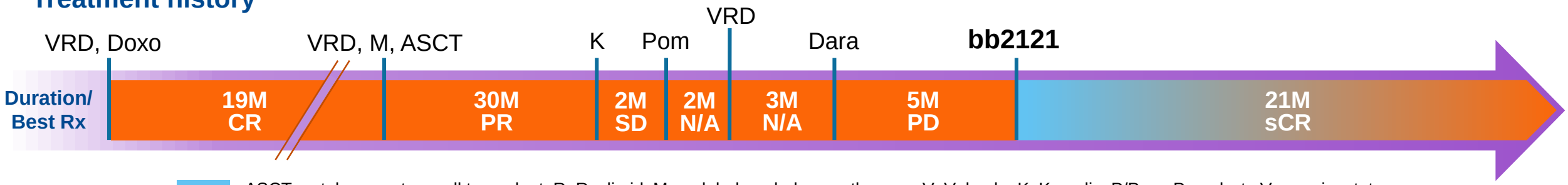
Chari, A. Blood 2017

bb2121 Patient Case: 21 Months in sCR

General Information	
Age & Gender	52 year old Male
Dose group	150x10^6
Tumor Burden	High
High Risk Cytogenetics (based on FISH)	No
Number of prior regimens	6
Initial diagnosis	May, 2010
BCMA% (prescreen, baseline)	60, 75

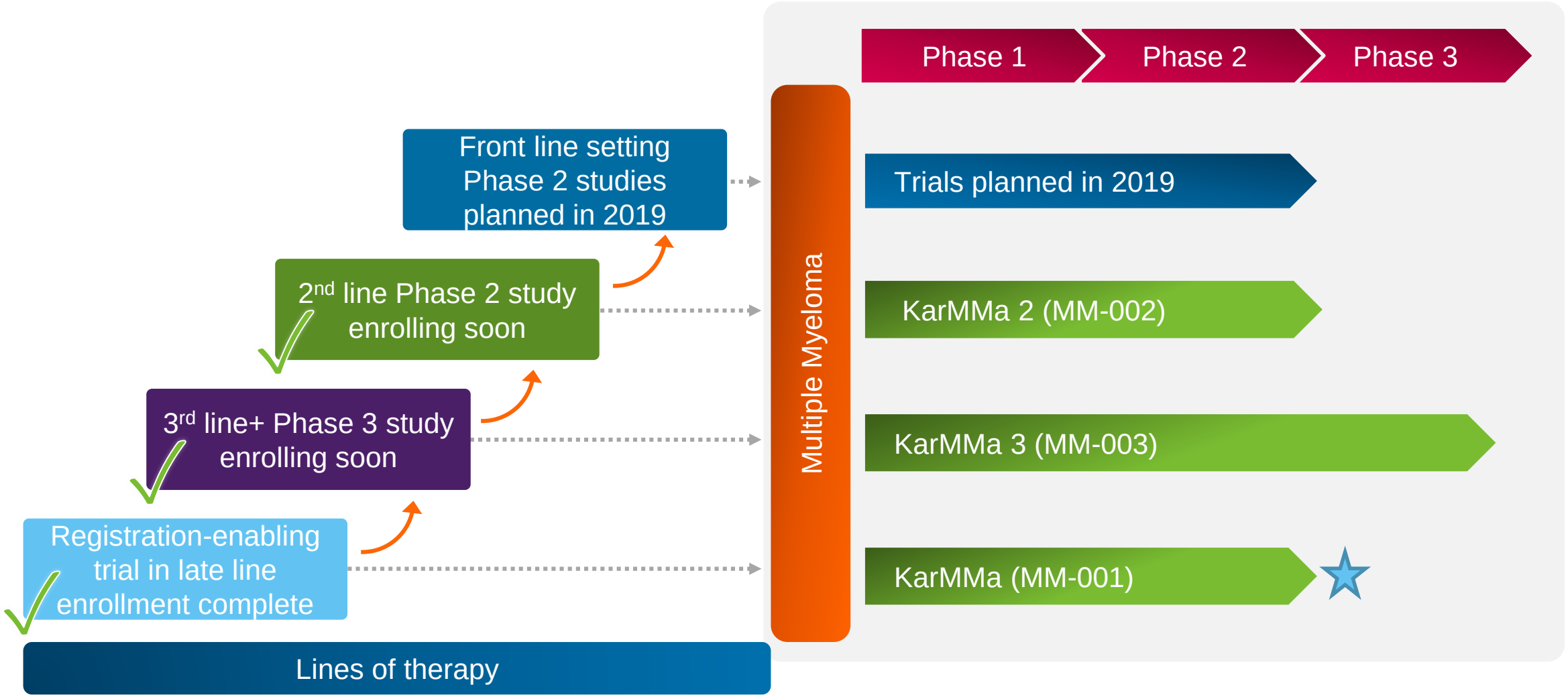


Treatment history



KEY ASCT: autologous stem cell transplant, R: Revlimid, M: melphalan, d: dexamethasone, V: Velcade, K: Kyprolis, P/Pom: Pomalyst, Vor: vorinostat, Dara: daratumumab, Doxo:Doxorubicin

Advancing bb2121 into Earlier Lines of Multiple Myeloma



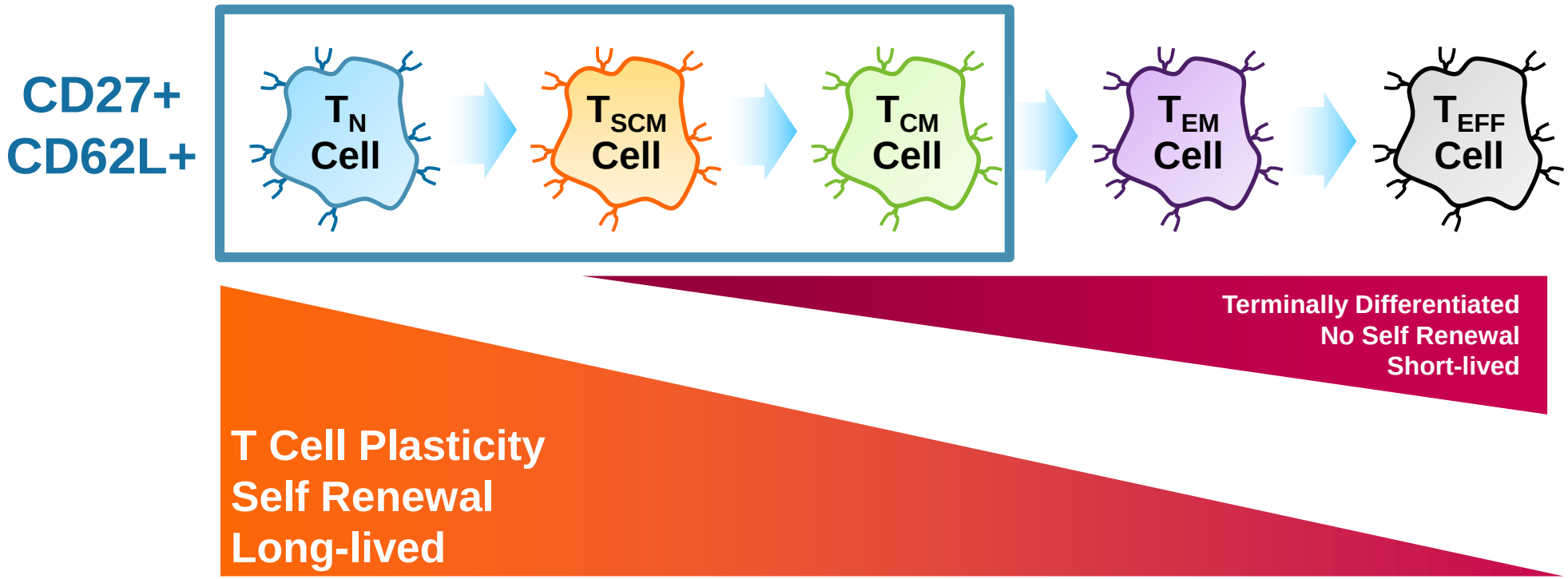
Anticipated Approval in 2020

Key Takeaways from CRB-401 Presented at ASCO

Efficacy?	• 95.5% ORR in doses above 150M cells. • 50% CR rate at doses above 150M cells.
Durability?	• 11.8 months median PFS in dose-escalation active doses. • 17.7 months median PFS in MRD(-) patients with response (escalation and expansion).
BCMA? MRD?	• Consistent responses across BCMA expression levels. • 16/16 responding, MRD-evaluable patients were MRD negative.
Safety?	• No new safety signals (G3/G4 CRS or Neurotox).
Path forward?	• KarMMa amendment raised high end of dose range to 450 based on observed dose-response and acceptable safety profile. Potential approval on track for 2020. Earlier line development plan advancing.

bb21217: PI3K Inhibition During Manufacturing Drives Increase in Long-lived, Memory-like T Cells

CRB-402

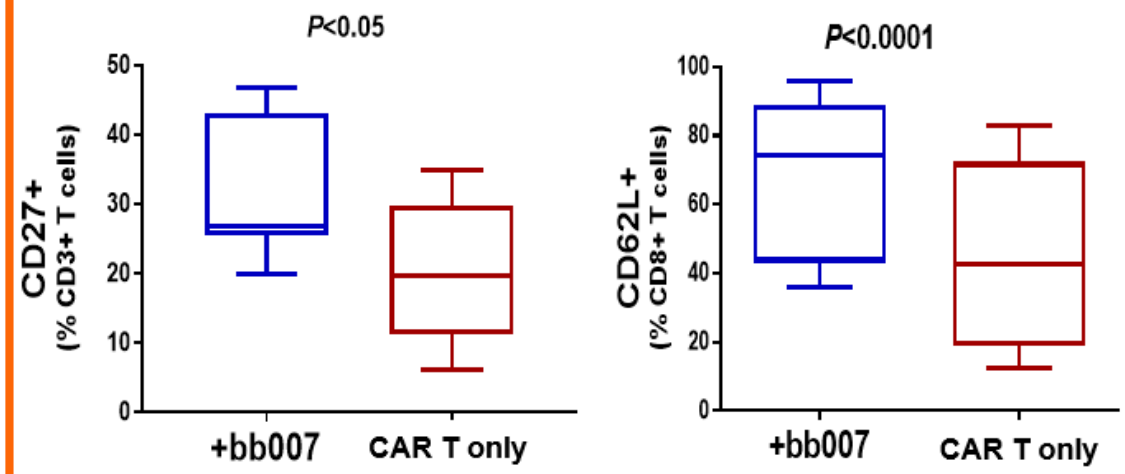


Hypothesis: Increasing long-lived, memory-like T Cell subsets in the drug product may result in enhanced persistence of functional anti-BCMA CAR T cells *in vivo*

Preclinical Models: bb21217 is Enriched for Memory-like T Cells Exhibits; Enhanced Persistence of Anti-tumor Effect

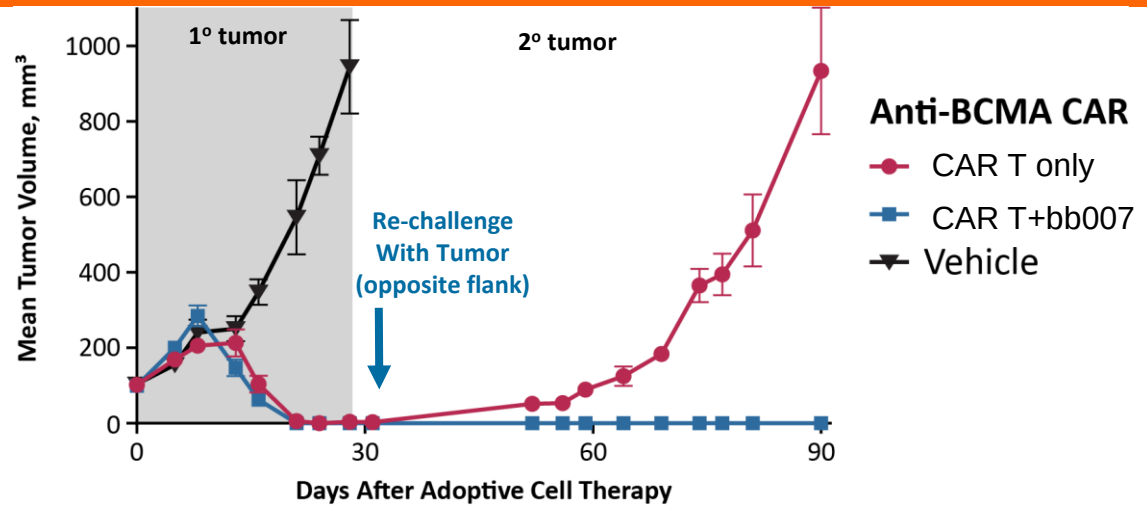
CRB-402

bb007 enriches for memory-like T Cell phenotype



- CD62L and CD27 are markers of memory-like T cells
- bb21217 is significantly enriched for T cells with this memory-like phenotype

bb007 enhances anti-tumor effect in mouse models



- ONLY CAR T cells cultured with PI3K inhibitor bb007 (i.e. bb21217) clear a second tumor challenge
- Data are consistent with improved persistence of functional CAR T cells leading to sustained anti-tumor effect

CRB-402 Phase 1 Study Design and Status

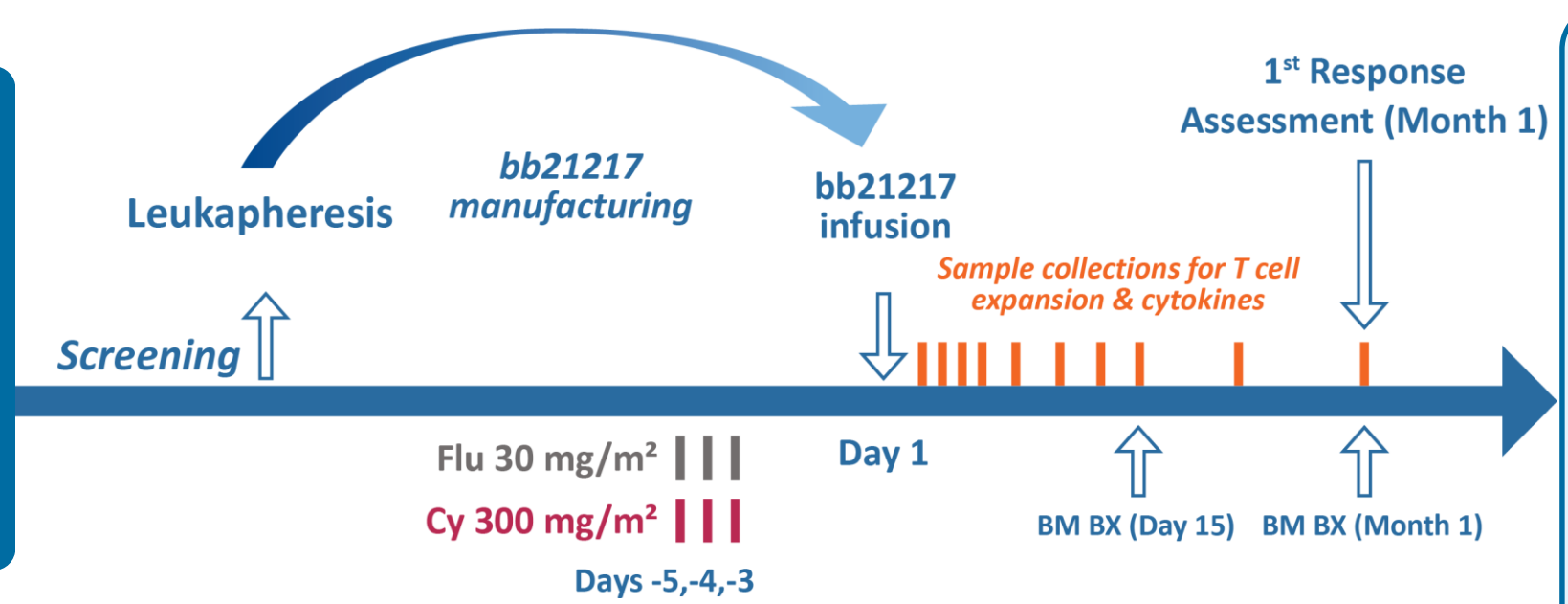
CRB-402

3 + 3 dose escalation[a]

CAR+ T cell dose

150 × 10^6 → 300 × 10^6 → 450 × 10^6 → 800 × 10^6

N ≈ 50
- R/R MM
- ≥3 prior regimens
  - IMiDs and
  - Proteasome inhibitors
  - Or double-refractory
- ≥50% BCMA expression (dose escalation only)



Study Status as of Oct 18, 2018

Collected N=13

Dosed N=12 (150 × 10^6 dose)

HTB[b] n=6 LTB[b] n=6

Median (min, max) follow-up

26 wk (4, 51)

Primary endpoints: AEs, DLTs
Other endpoints: Response[c], PFS, OS, MRD, CAR+ T cell expansion and persistence

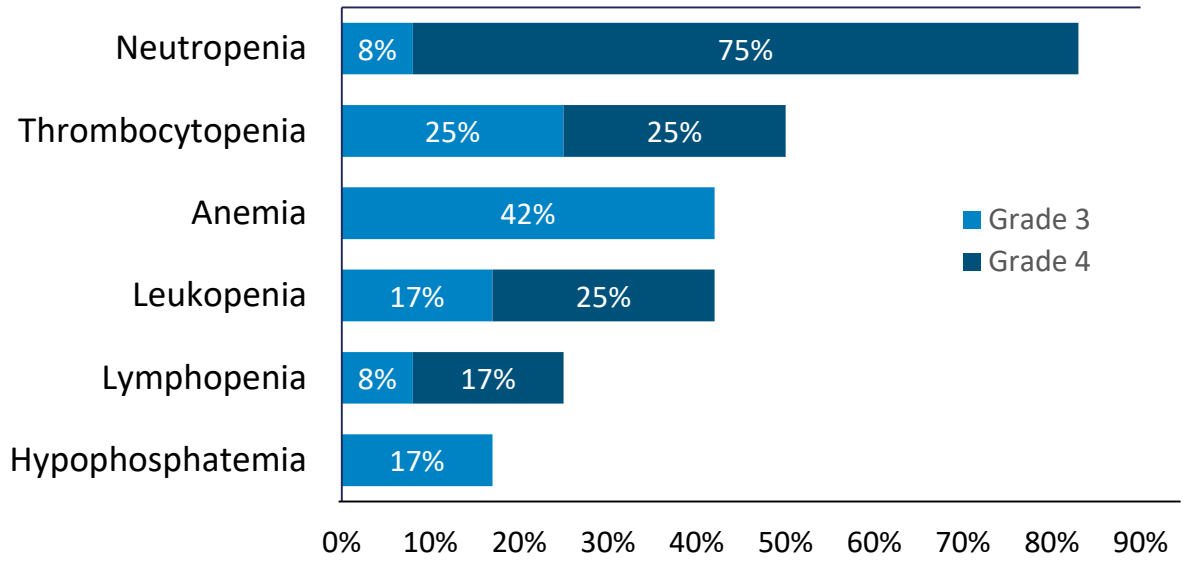
NCT03274219

AE, adverse events; BCMA, B-cell maturation antigen; DLT, dose-limiting toxicity; HTB, high tumor burden; IMiD, immunomodulatory imide drugs; LTB, low tumor burden; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed/refractory multiple myeloma. [a]All patients to date received 150 × 10^6 CAR+ T cells; an intermediate dose of 300 × 10^6 CAR+ T cells will be the next dose level. [b]HTB defined as ≥50% bone marrow plasma cells pre-infusion; LTB <50%. [c]Per International Myeloma Working Group criteria.

Early Clinical Safety and Tolerability Consistent with CAR T Experience

CRB-402

Grade ≥3 AEs in >1 Patient[a]



AEs of Special Interest[a]

	Grade, n (%)			
	1	2	3	4
CRS[b]	4 (33)	3 (25)	1 (8)	–
Neurotoxicity[c]	1 (8)	1 (8)	–	1 (8)

- CRS occurred in 67% of patients
  - Mostly grade 1/2, 1 grade 3, no grade 4
  - Median time to onset of CRS 4.5 days (2,11)
  - Manageable with or without tocilizumab
- 1 patient experienced DLT (grade 4 encephalopathy and grade 3 CRS)
  - Patient had high tumor burden and rapidly accelerating disease at baseline
  - No other DLTs occurred
- 1 grade 3 catheter-related infection; no other severe infections reported to date
- 4 patients experienced 1 or more SAEs
- No deaths on study to date

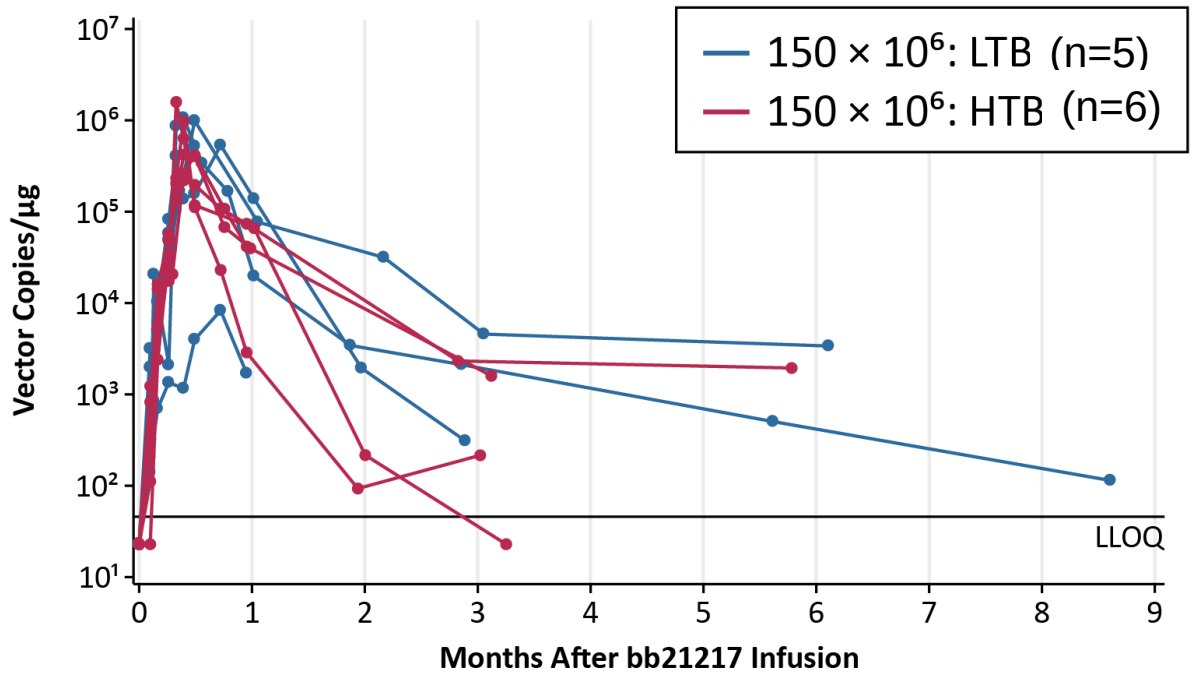
AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event. [a]AEs occurring between bb21217 infusion and disease progression. [b]Cytokine release syndrome (CRS) uniformly graded according to Lee et al., *Blood* 2014;124:188-195. [c]Events selected as CAR T neurotoxicity on the case report form occurring within 90 days after bb21217 infusion.

Data as of October 18, 2018

Clinical Data is Early But Consistent with Goal of Enhanced Persistence

CRB-402

Vector Copy Number Over Time by Baseline Tumor Burden



	Month 1	Month 3	Month 6	Month 9
At risk, n	9	7	3	1
With detectable vector, n (%)	9 (100)	6 (**86**)[a]	3 (100)	1 (100)

- Robust and reliable bb21217 CAR T cell expansion post-infusion observed at first dose
- Early bb21217 clinical data is consistent with robust functional CAR T cell persistence
  - Enrichment for memory-like CAR T cells observed in preclinical studies, and in patients post-infusion
  - Vector detectable up to 9 months post-infusion, and in 3/3 patients at 6-month time point
  - Sustained sBCMA suppression observed, reflecting ongoing plasma cell aplasia

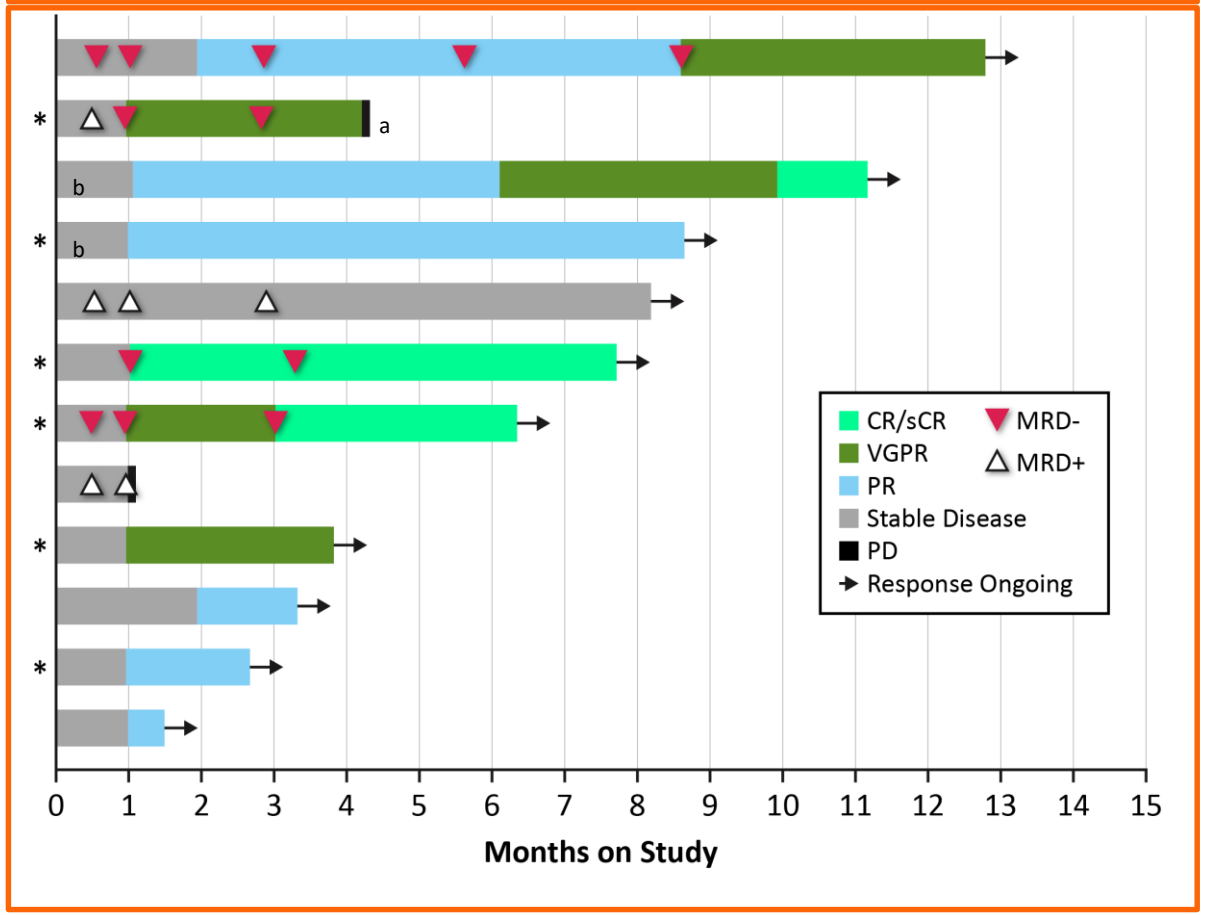
HTB, high tumor burden; LLOQ, lower limit of quantitation; LTB, low tumor burden. [a]One patient with undetectable vector received cyclophosphamide on day 15 for grade 4 encephalopathy.

Data as of October 18, 2018

Clinical Responses Observed in 10/12 Patients (83%) at First Dose Level Tested (150 x 10^6 CAR+ T cells)

CRB-402

Clinical Responses Over Time



- 10/12 patients (83%) achieved an objective response at the first tested dose (150 × 10^6 CAR+ T cells)
- Deepening responses over time; CR achieved as late as month 10
- 100% MRD negativity in 4/4 responders evaluable for MRD status
- Responses are ongoing in all but 1 responder; the first patient dosed continues response >1 year after treatment

CR, complete response; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden.
[a]Progression based exclusively on appearance of new bone lesions. [b]MRD status not available.

Data as of October 18, 2018

High Clinical Response Rate Observed at First Dose Level (150 x 10^6 CAR+ T cells)

CRB-402

Clinical Response	
	bb21217-Treated (N=12)
ORR,[a] n (%) [95% CI]	10 (83.3) [51.6, 97.9]
sCR/CR	3 (25)
≥VGPR	6 (50)
MRD status in bone marrow, n	
MRD-evaluable responders[b]	4
MRD-neg	4[c]
Median time to first response (min, max), [a,d] mo	1 (1, 2)
Median time to best response (min, max), [a,d] mo	1 (1, 10)
Median follow-up duration (min, max), mo	5.9 (1.0, 11.8)

CR, complete response; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden. [a]Includes unconfirmed responses. [b]Patients with ≥PR and valid MRD assessments. [c]Two MRD-neg. responses at 10^{-6} and 2 at 10^{-5} sensitivity level by Adaptive next-generation sequencing. [d]Among 10 responders with ≥PR.

Data as of October 18, 2018

Promising Early Data with Next-Generation Anti-BCMA CAR T

- bb21217 demonstrated promising early clinical activity in heavily pretreated patients with relapsed/refractory multiple myeloma at first dose level tested
  - 83% ORR with 90% of responses ongoing
  - Elimination of MRD in the bone marrow of all 4 evaluable responders
- Early indications of increased persistence using enriched CAR T cells
- Safety profile appears consistent with known toxicities of CAR T cell therapies
- Dose escalation is ongoing

CALD

bluebirdbio®

Ethan's family spent nearly two years trying different medications and meeting with specialists to try and resolve his symptoms. Tragically, during this period, the ravaging effects of ALD were continuing to damage Ethan's brain and adrenal glands.

Ethan Zakes 2000 - 2011

Source: Ethan Zakes Foundation

Cerebral Adrenoleukodystrophy

- Severe, often fatal neurological disease in boys

UNMET NEED

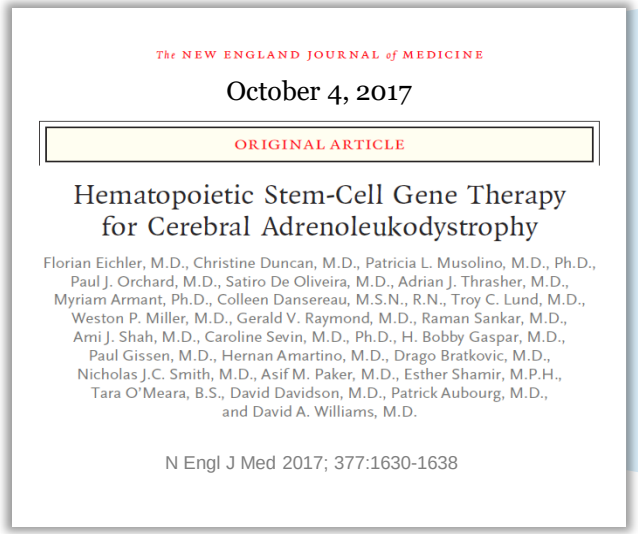
- Treatment limited to allo-HSCT
- Sometimes severe treatment-related risks and complications, especially when donor is not a matched sibling

EPIDEMIOLOGY

- Global incidence of ALD: 1 in ~21,000 newborns
- Cerebral form develops in ~40% of affected boys

[1]Salzman, R., Kemp, S. (2017, December 06) Newborn Screening. Retrieved from http://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening

Lenti-D Treatment Halts CALD Disease Progression


The NEW ENGLAND JOURNAL of MEDICINE

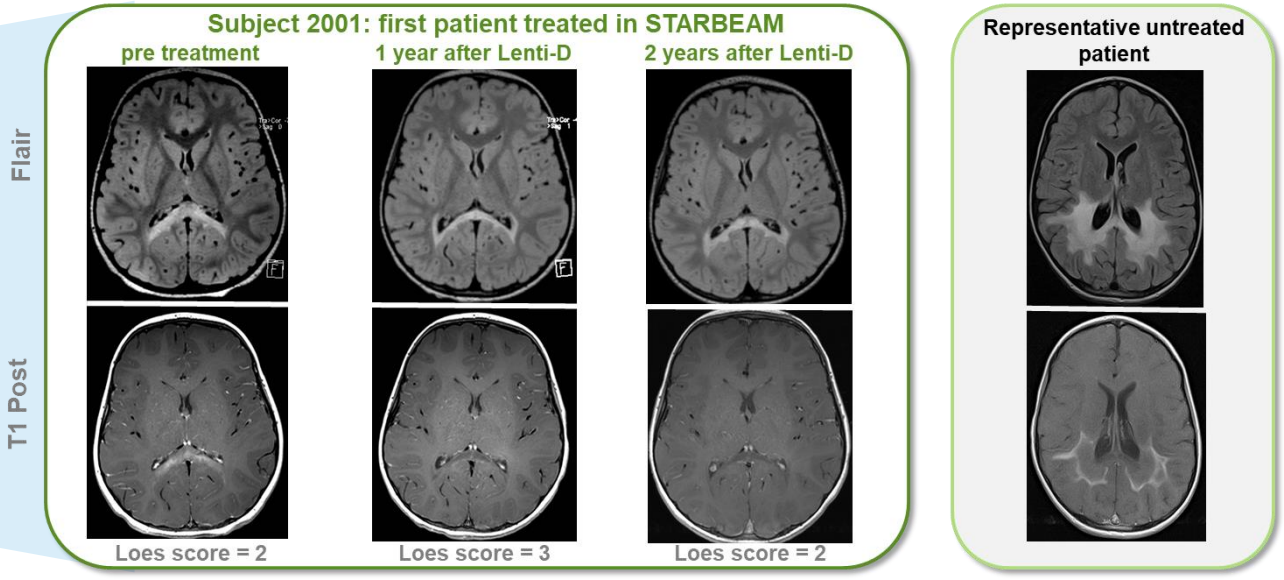
October 4, 2017

ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.

N Engl J Med 2017; 377:1630-1638



15/17 patients (88%) alive and MFD-free at 24 months follow-up; all patients continue to be MFD-free as of April 25, 2018

- Exceeds pre-determined efficacy benchmark for the study MFD-free survival in 13/15 (76%)

12 additional patients treated in Starbeam study

- No MFDs reported as of April 25, 2018; median follow-up for this additional cohort of patients is 4.2 months (0.4 – 11.7 months)

Safety profile consistent with autologous transplantation

- No GvHD, no graft rejection

Two patients did not meet primary endpoint:

- Patient 2016: Withdrew
- Patient 2018: Rapid disease progression early in the study

Data as of April 25, 2018

Research Pipeline

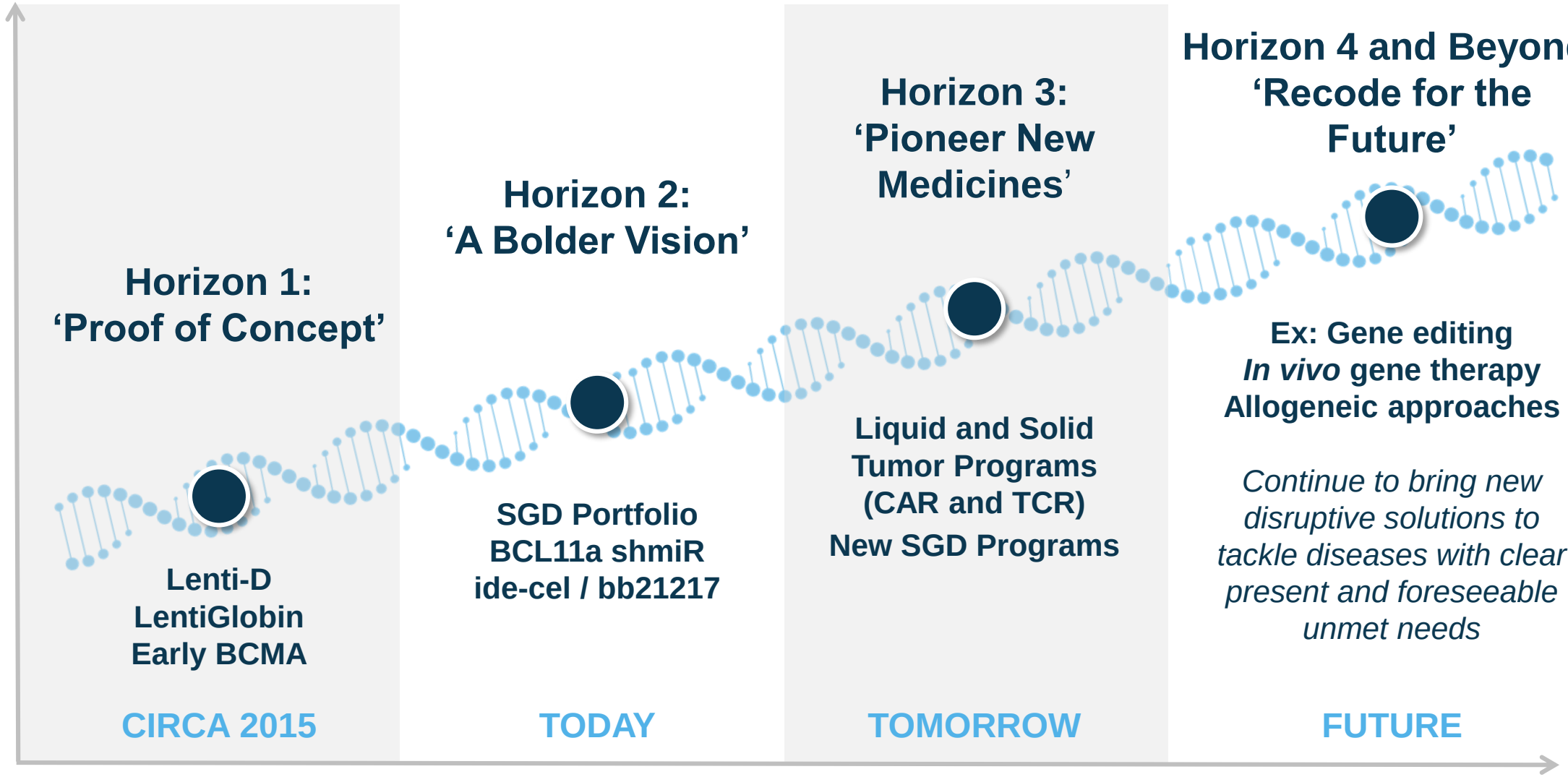
bluebirdbio®

R&D BLUE Style: What Do We Work On?

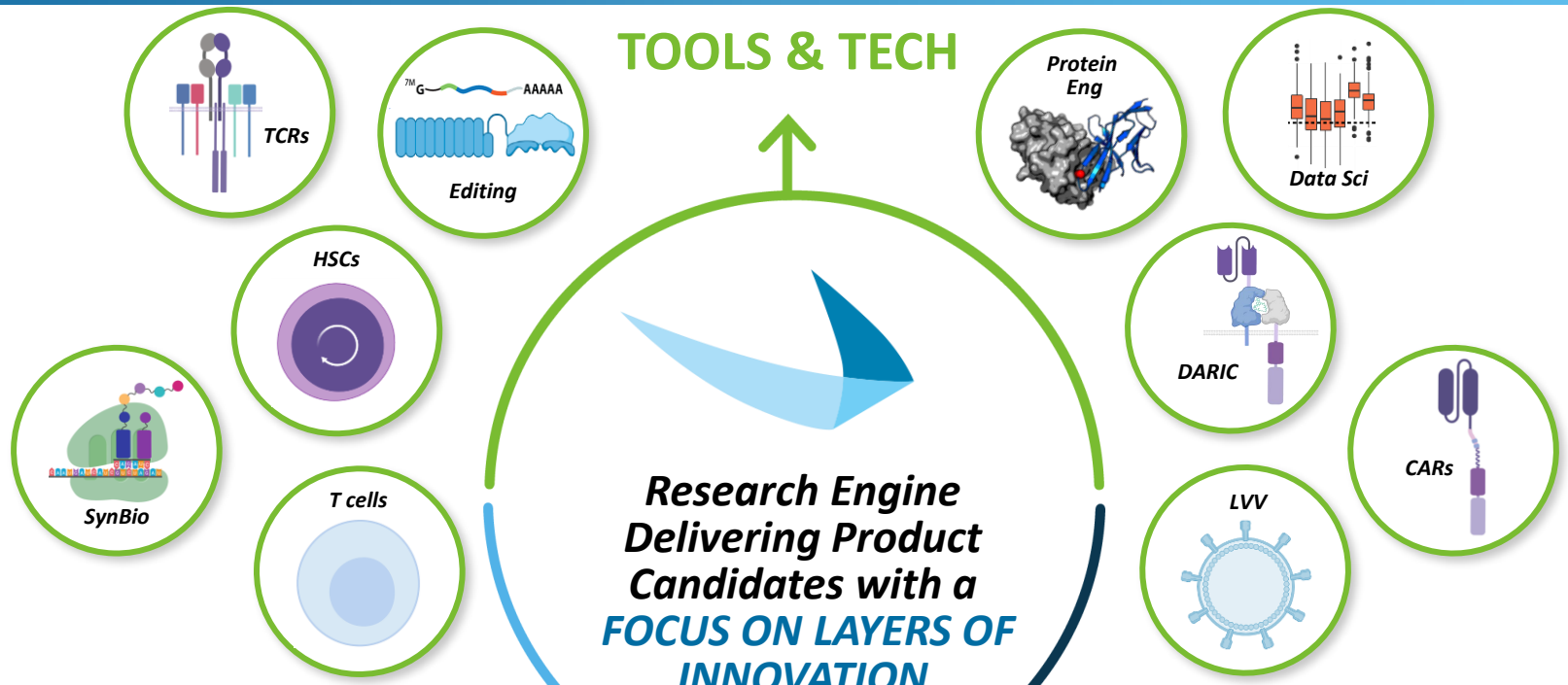
Core Research Principles

Programs with the Potential to Transform Patient Lives	Diseases with Definitive Endpoints of Clinical Success	Targets with Human Genetic and/or Functional Validation	Disruptive Solutions to the Problems that Need to be Solved
We tackle diseases with a clear unmet medical need based on the magnitude of impact and not necessarily the number of patients	Clinical success should be objective, measurable, un-incremental, and rapid	Biology may be complex but the role of the target in the disease must be definitive	We don't do incremental science. We take on the big problems that, if successful, will disrupt our field

Continuous Innovation is in Our DNA



We Believe the Winning Strategy Will Require: The Right Tools, Leading Partnerships, Stellar Collaborators



ACADEMIC COLLABORATORS

INDUSTRY PARTNERSHIPS

Anti-Pure Play: 1 to Many Strategy
What Do We Mean?

RECODING TRADITIONAL R&D

RESEARCH INNOVATION ENGINE

CLINICAL EXPERIENCE

PLATFORM TOOLS & TECH

ACADEMIC COLLABORATORS

INDUSTRY LEADING PARTNERS

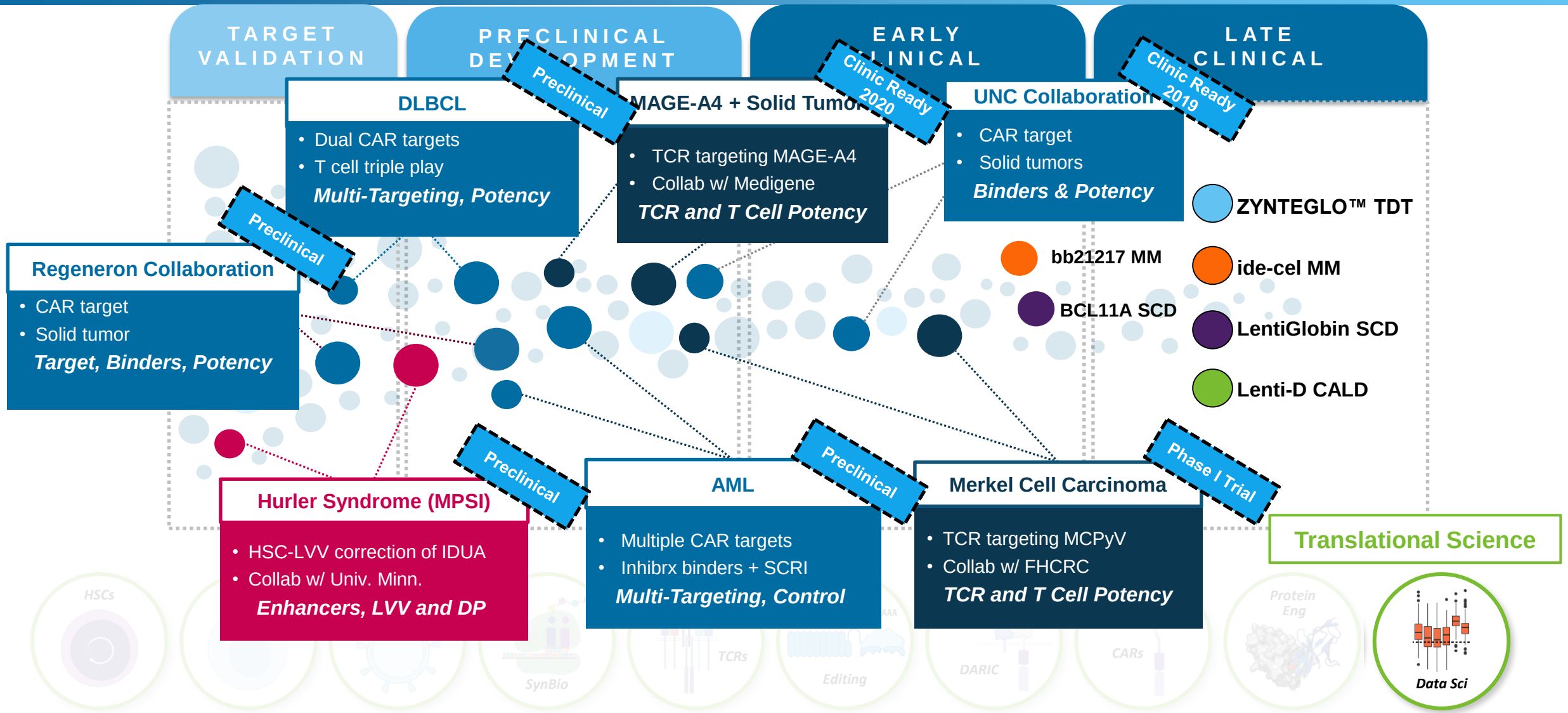
NEXT GEN PRODUCT CANDIDATES

- MM – bb21217
- SCD – BCL11a
- MCC – MCC1 TCR

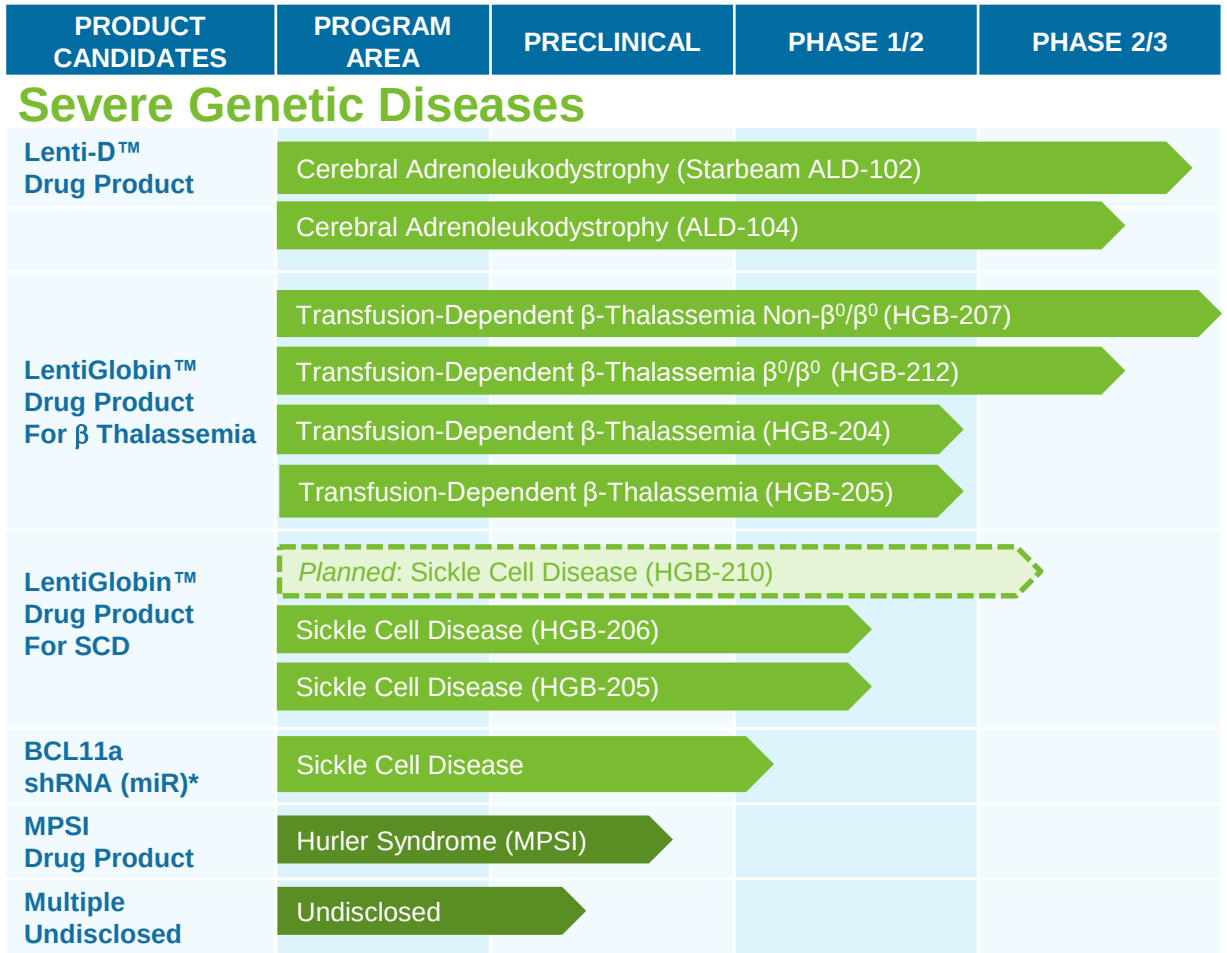
- TDT – ZYNTEGLO™
- MM – ide-cel
- SCD – LentiGlobin
- CALD – Lenti-D

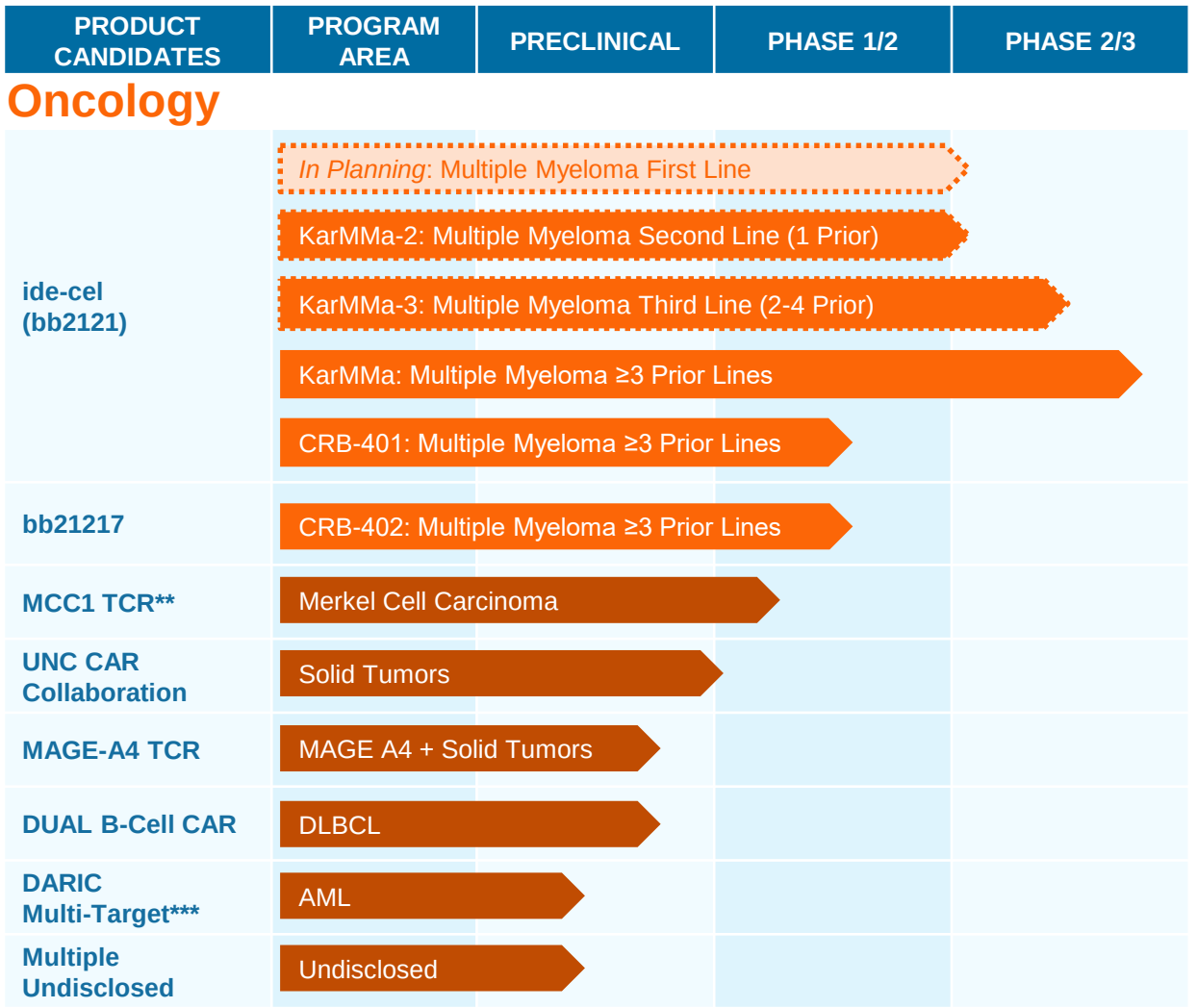
RAPID CLINICAL TRANSLATION

Our Research Strategy in Action:
Emerging Pipeline of NextGen Products



RECODE THE SCIENCE: Pipeline Overview





*Development is led by Dana-Farber/Boston Children's Cancer and Blood Disorders Center
**Development is led by Fred Hutch Cancer Research Institute
***Development is led by Seattle Children's Research Institute

ide-cel (bb2121) and bb21217 development in collaboration with Celgene

1:Many Strategy Applied to Our Research Portfolio

	First Generation Product		NextGen Product		1: MANY
MERKEL CELL CARCINOMA	MCC1 TCR Combo w/ PD-L1 Inhibitor	Phase I Trial	Built-in Checkpoint Inhibition w/ MegaTAL	Preclinical	PD-1/L1 BOOST to Any CAR or TCR Product
DLBCL	Prior CD19 Experience from Others	Clinic Ready 2020	Triple Play: Dual Targeting Signal Extension and Amplification	Preclinical	Apply to Any CAR or TCR Product
MAGE-A4 and Solid Tumors	Co-receptor Independent TCR T cell	Preclinical	2-for-1 Co-stimulation + TME Evasion; New binders	Preclinical	Apply Learnings Across TCR & CAR Products
AML	Multiplex-targeted, Drug-Regulated CAR-T		Allo Platform + Potency Enhancements		Apply Multiplex / Regulation Learnings Across Portfolio
Hurler Syndrome (MPSI)	LVV Transduction Enhancement		Optimized HSC LVV Drug Product		Apply Platform to Other HSC-based SGD Programs

Data Sciences – Iterating from the Clinic

bluebirdbio®

Our Research Strategy in Action:
Data Science – Iterating from the Clinic

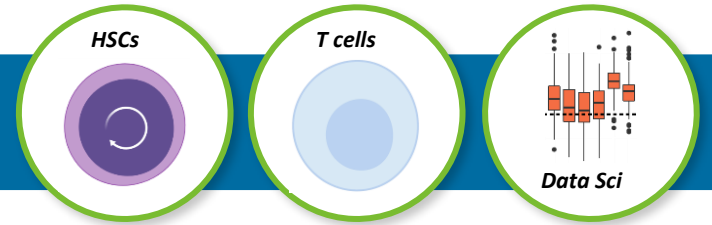
The Problem That Needs to be Solved

Our products start with each patient's cells and thus to leverage our clinical experience requires characterizing our therapies and patients on a molecular, single-cell level.

Why It Matters

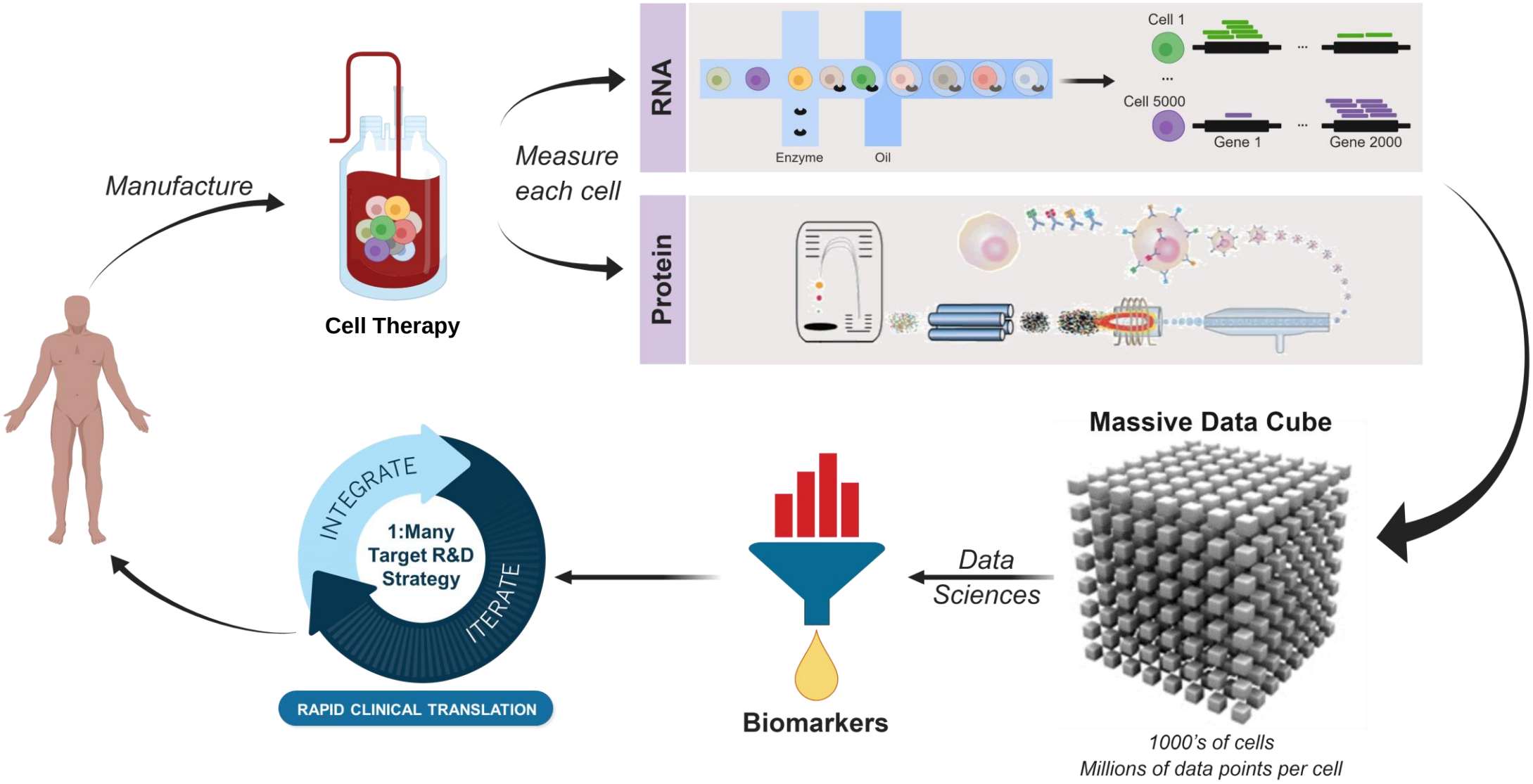
Translational research has the potential to lead to better therapies for patients, faster.

Our Un-incremental Approach



Employ cutting-edge technologies and deep analytics to study ZYNTEGLO™, ide-cel, and our pipeline programs at an ultra-high resolution to pinpoint the key factors driving safety and efficacy.

We Study Our Therapies at Ultra-High Resolution to Maximize the Benefit Patients Receive and Accelerate R&D



Answering Disruptive Questions Requires Clinical Insights and Data Science

Is there a gene expression signature predictive of depth of response in MM?

Which cell type in ZYNTEGLO™ correlates with speed of engraftment in patients?

Which cells need to be transduced to achieve robust clinical responses in SCD?

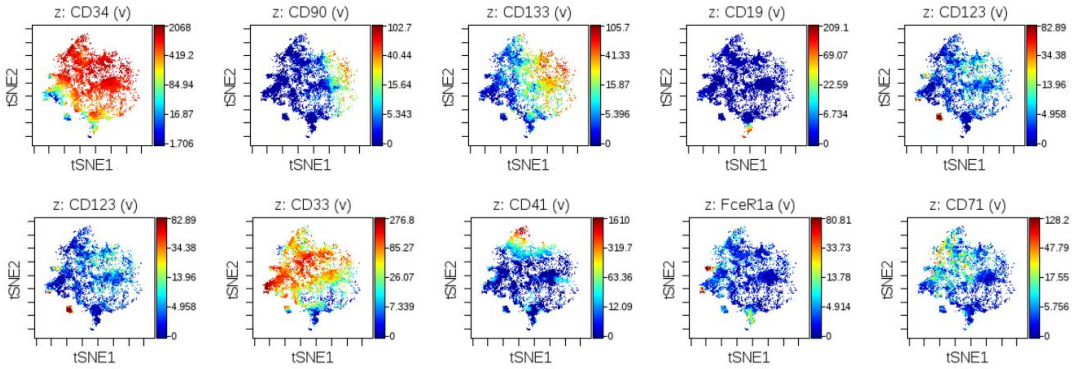
Are there cell populations in the drug product that predict CRS or neurotoxicity?

What are the determinants of resistance?

Are levels of memory-like T cells in the drug product correlated with T cell persistence in patients?

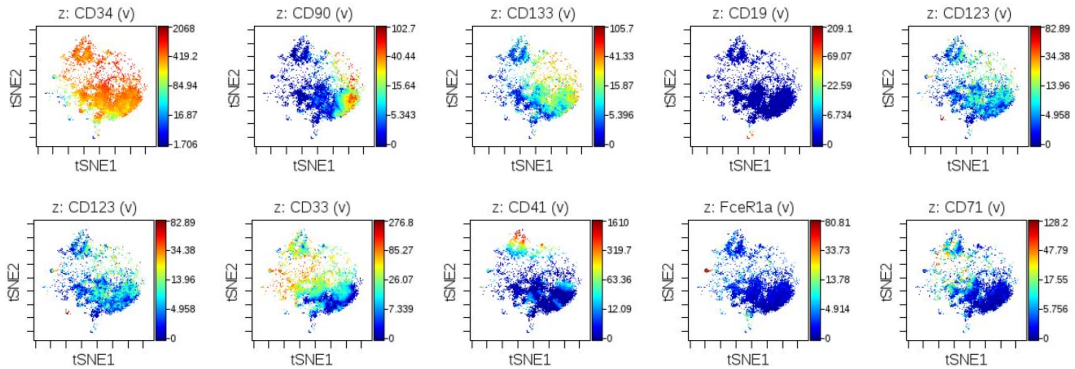
Using Advanced Technologies and Analytics, We Can Measure Proteins in Each Cell to Determine Cell Type and Correlate to Safety and Efficacy

Patient 1: Shorter Engraftment Time



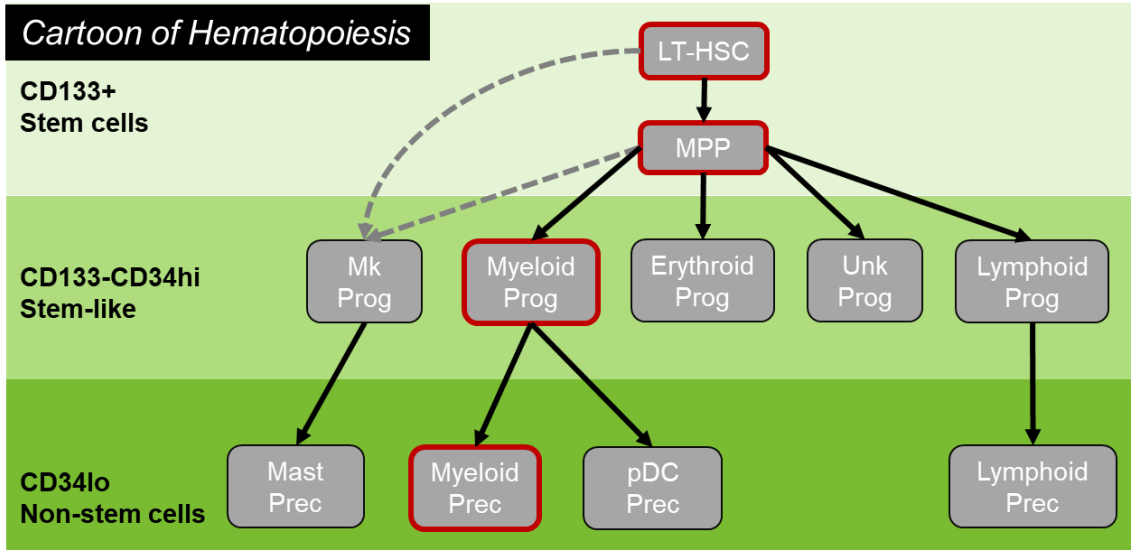
Mass Cytometry of Patient 1 Drug Product

Patient 2: Longer Engraftment Time



Mass Cytometry of Patient 2 Drug Product

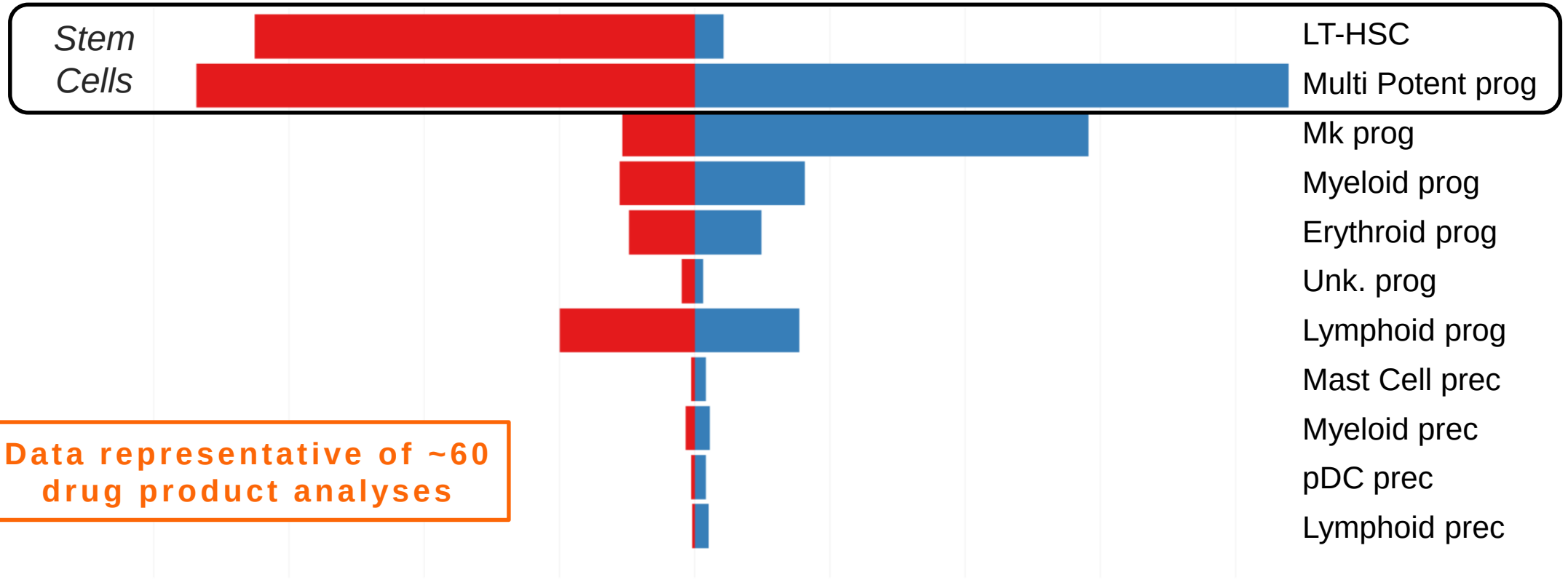
Each of these cell populations is present in the drug product <u>but which predicts engraftment</u>?



Translational Analyses Pinpoint: Higher Dose of Stem Cells Results in Shorter Neutrophil Engraftment Times

Patient 1: Shorter Engraftment Times *Higher proportion of LT-HSCs*

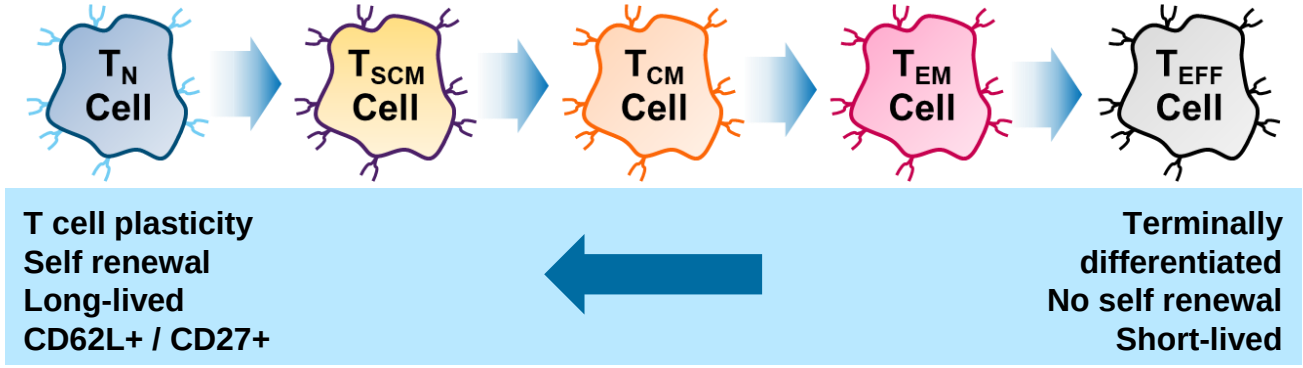
Patient 2: Longer Engraftment Times *Lower proportion of LT-HSCs*



Data representative of ~60 drug product analyses

Optimizing for stem cells is broadly applicable to all HSC therapies

bb21217: Next-generation anti-BCMA CAR T Cell Therapy for Multiple Myeloma



bb21217 is enriched for T_{CM} and T_{SCM} cells

- CAR T cells enriched for memory-like cells **may persist and function longer than non-enriched CAR T cells[1] – potentially leading to more durable tumor regressions**
- bb21217 uses **the same CAR construct design** as ide-cel[2] (bb2121)
- bb21217 is cultured with PI3 kinase inhibitor, bb007, to **enrich for T cells displaying a memory-like phenotype**

BCMA, B-cell maturation antigen; PI3K, phosphoinositide 3 kinase.

1. Fraietta JA, et al. *Nat Med*. 2018 May;24:563-571 2. Friedman et al. *Hum Gene Ther* 2018;29:585-601.

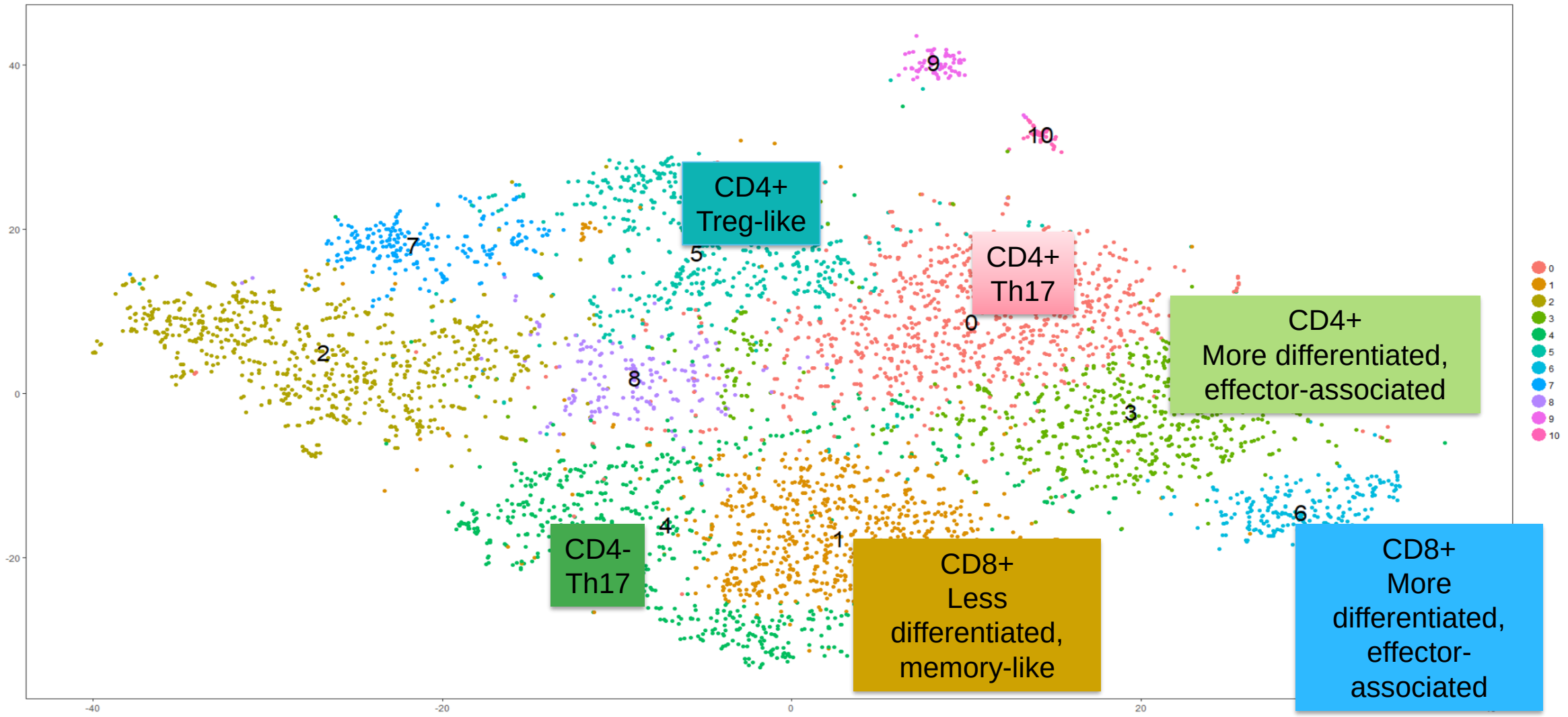
Single-cell RNAseq Allows Ultra-fine Resolution of the Biology of Cells

Bulk RNAseq

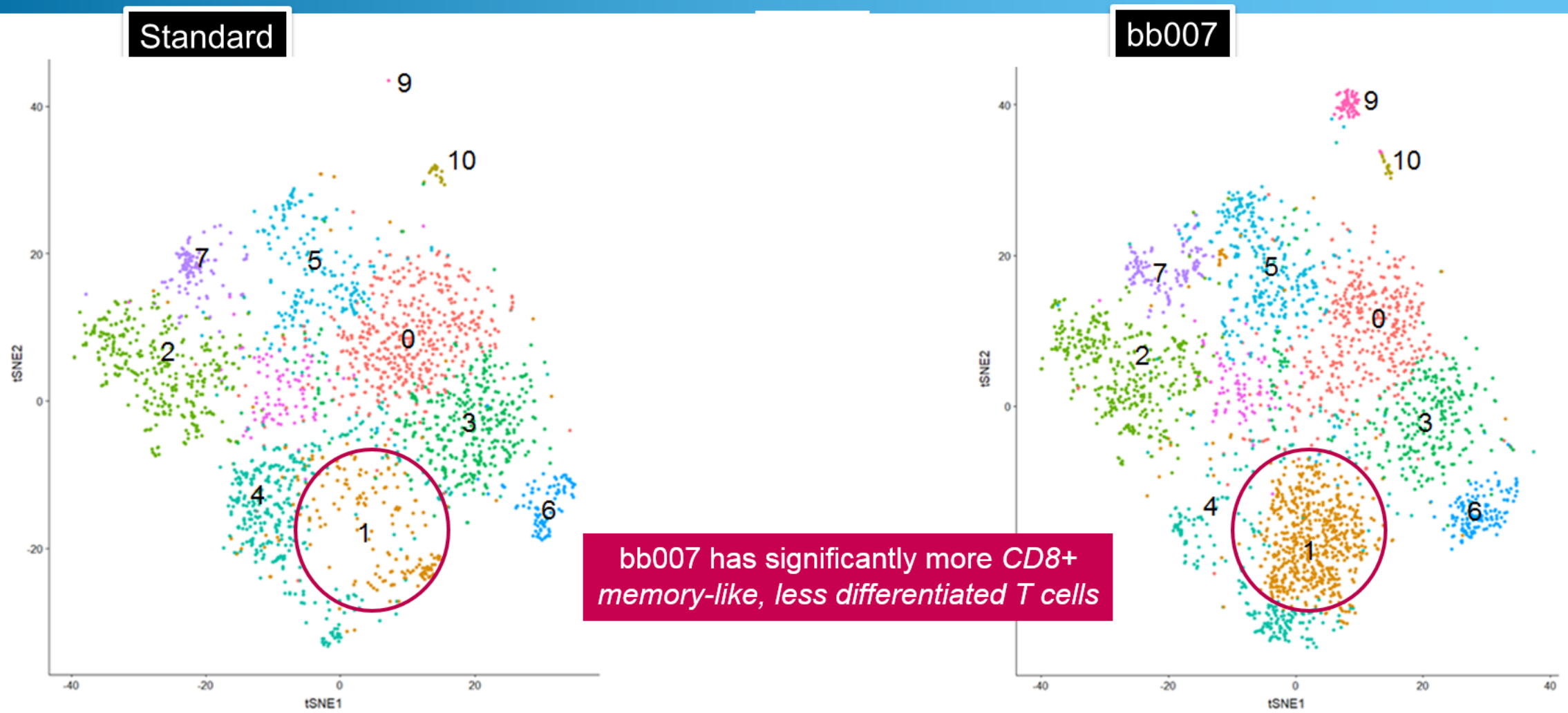
Single-cell RNAseq

Cellular therapies are uniquely suited to be studied with single-cell RNAseq

Single-cell RNAseq Identifies Diverse T Cell Populations



Single-cell RNAseq Shows Differences Between Standard vs. bb007

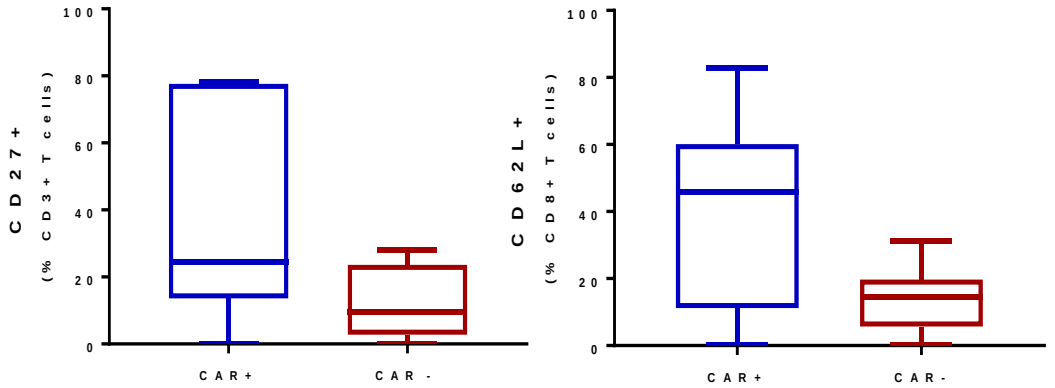


bb007 has significantly more *CD8+ memory-like, less differentiated T cells*

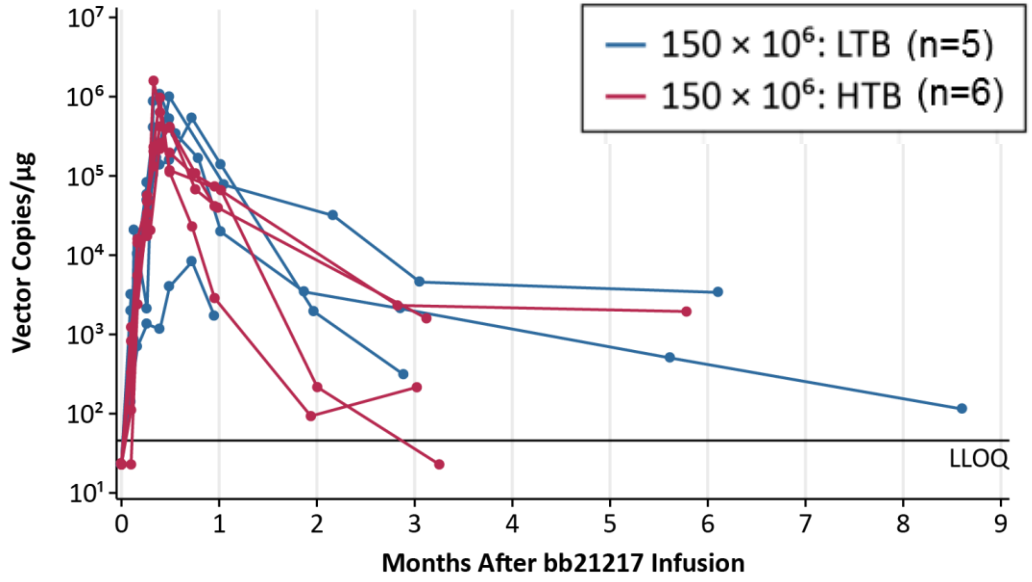
Enriching for memory-like T cells with bb007 is broadly applicable to T cell-based therapies

Infusion of bb21217: CAR+ Memory-like T Cells Show Robust Expansion and Persistence in the Clinic (CRB-402)

Memory-like T cells enriched in CAR+ (CD27+ or CD62L+ CD45RA– CD8+ Cells[a])



Persistence of CAR+ T cells (bb21217)



	Month 1	Month 3	Month 6	Month 9
At risk, n	9	7	3	1
With detectable vector, n (%)	9 (100)	6 (**86**)[b]	3 (100)	1 (100)

HTB, high tumor burden; LLOQ, lower limit of quantitation; LTB, low tumor burden. [a]Immunophenotyping occurred at time of peak CAR T expansion. [b]One patient with undetectable vector received cyclophosphamide on day 15 for grade 4 encephalopathy.

Merkel Cell Carcinoma TCR Program

bluebirdbio®

Our Research Strategy in Action: Planned Merkel Cell Carcinoma TCR Program at Fred Hutchinson Cancer Research Center

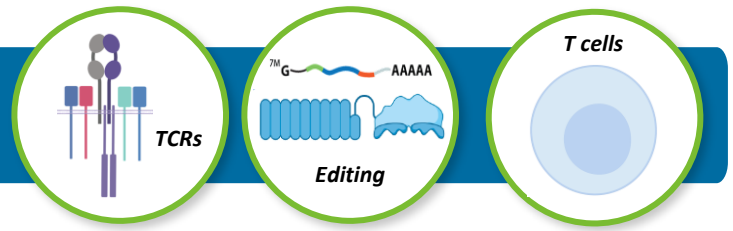
The Problem that Needs to be Solved

Realizing the full potential of adoptive T cell therapies requires targets that have a suitable tumor / normal tissue therapeutic window

Why it Matters

Viral antigens (e.g., MCPyV) provide a tumor-specific target ideal for testing with TCR-based cell therapies and potency enhancement strategies

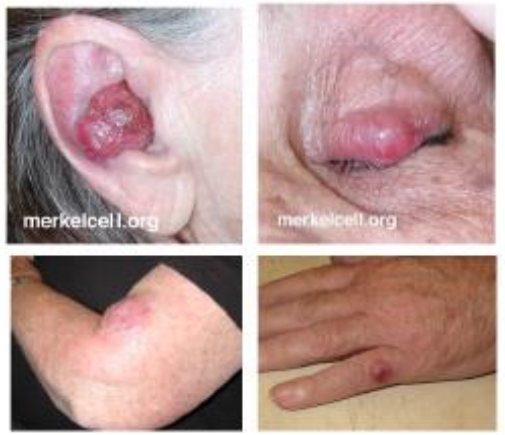
Our Un-Incremental Approach



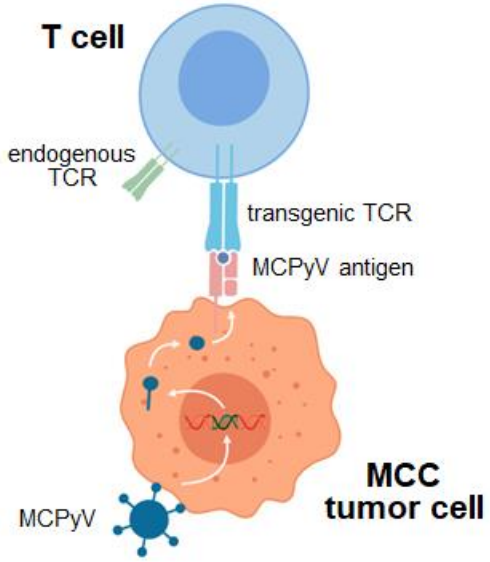
Build on PoC with cellular therapies targeting MCC and bring forward next generation T cell approaches including TCR engineering and checkpoint inhibition

Merkel Cell Carcinoma (MCC) and Merkel Cell Polyomavirus (MCPyV)

Overview and Rationale



Images Nghiem P et al, merkelcell.org

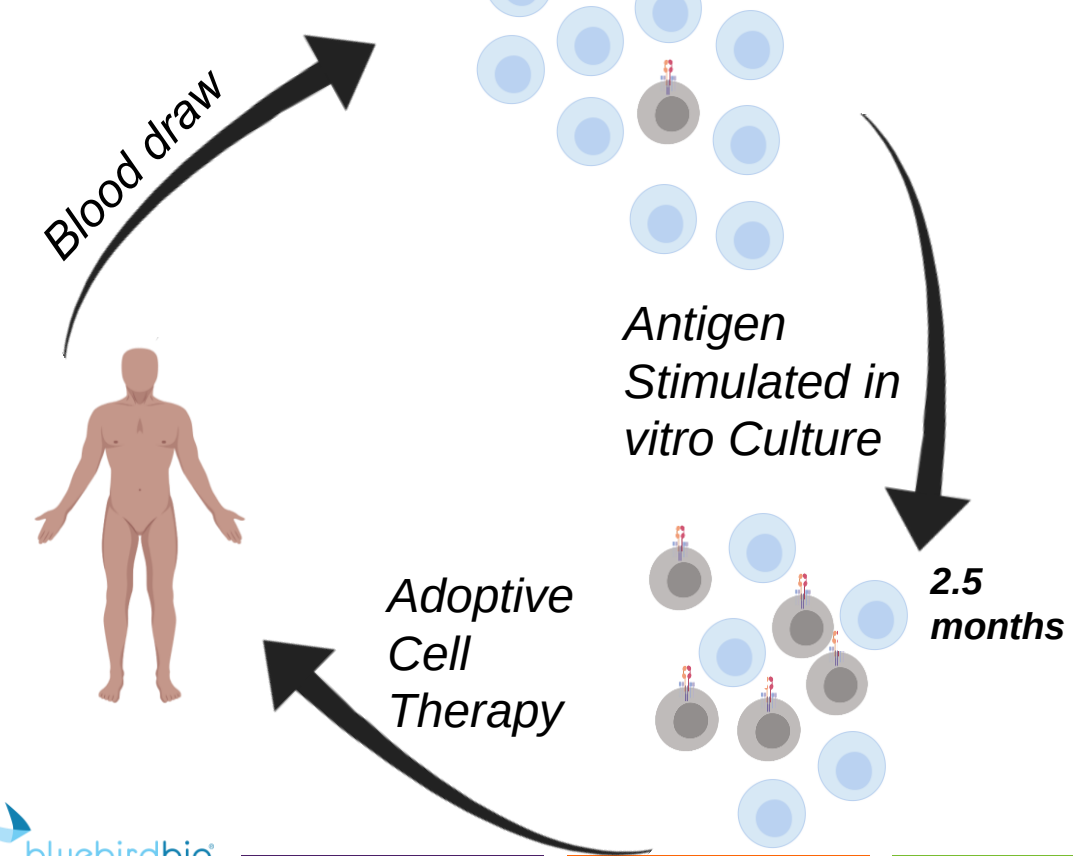


- MCPyV **not expressed in normal tissues** therefore **relatively de-risked target for T cell approaches**
- **~80% of MCC** cases are caused by MCPyV
- **Many patients** treated with checkpoint inhibitors do not respond or relapse
- Incidence of MCC **increasing disproportionally to other solid tumors** (estimated >3000 cases by 2025)

Feng et al. Science. 2008 Feb;319(5866); D'Angelo et al. JAMA Oncol. 2018 Sep;4(9); Kaufman et al. J Immunother Cancer. 2018 Jan;6(1); Paulson et al. J Am Acad Dermatol. 2017 Mar;78(3):457-463.

Initial Proof of Concept for MCPyV-specific T Cell Therapy Approach
Treatment with MCPyV-Enriched T Cells Results in Clinical Regressions

Proof of Concept



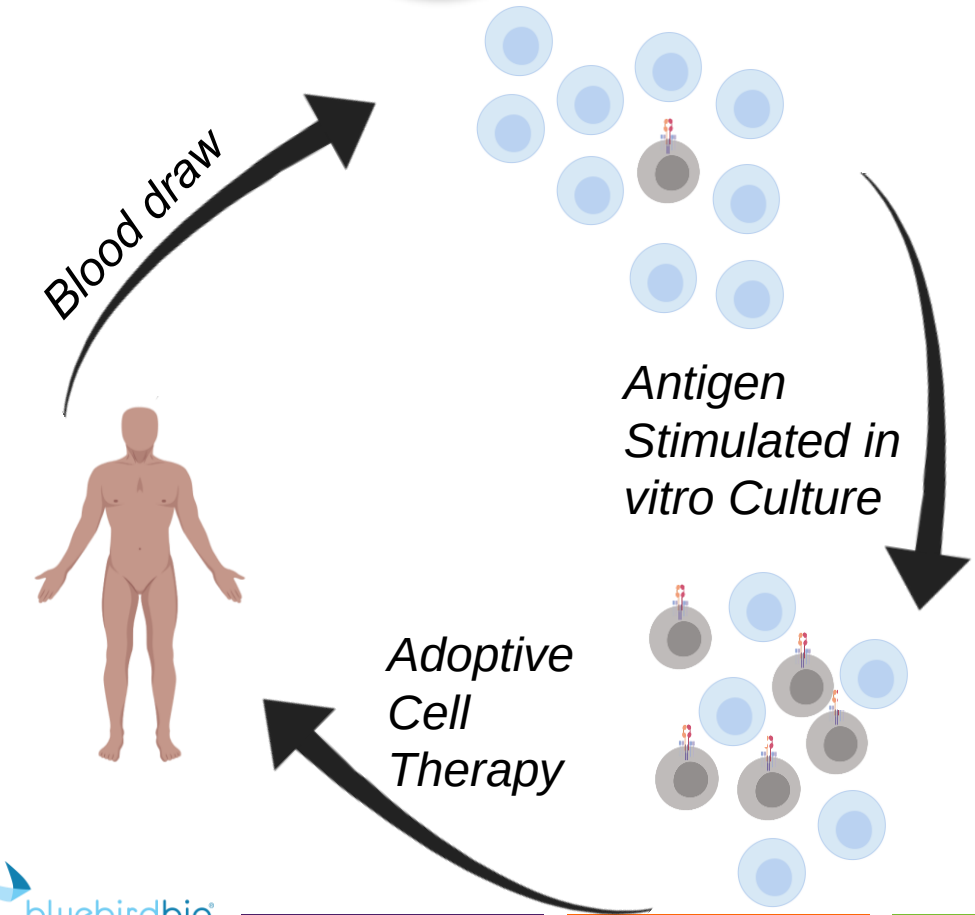
Key Observations from Prior POC Studies

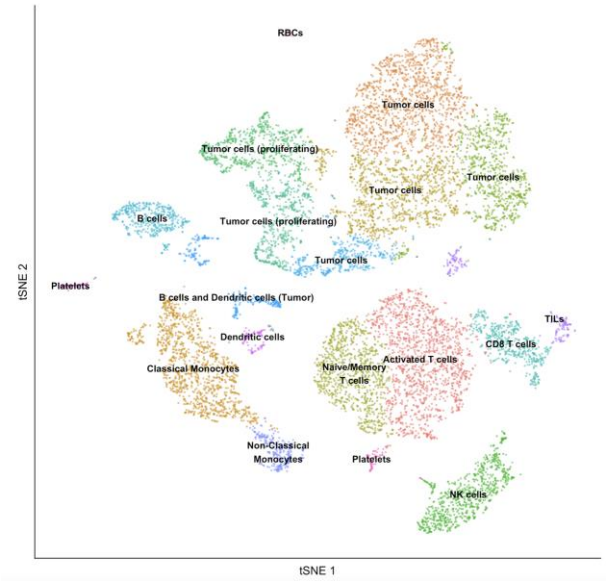
- Some (~14%) patients **naturally have MCPyV reactive cells** in their blood and thus **can be expanded in culture and reinfused**
- **~67 percent** overall response rate when **combined with PD-L1 inhibition**
- **~20 percent** response rate **without PD-L1 inhibition**

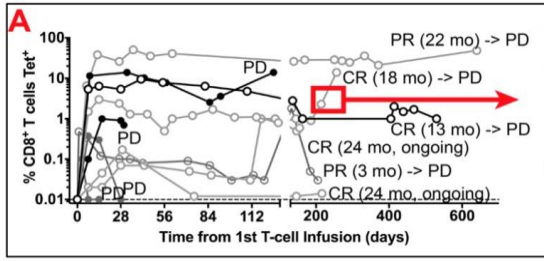
Lyngaa et al. Clin Cancer Res. 2014 Apr;20(7); Miller et al. Cancer Immunol Res. 2017 Feb;5(2): 137-147.; Chapius et al. Cancer Immunol Res. 2014 Jan;2(1):27-36; Chapuis and Paulson, Unpublished communication.

Initial Proof of Concept for MCPyV-specific T Cell Therapy Approach
Translational Data Supports Role of PD-1/L1 Axis in T Cell Therapies

Proof of Concept







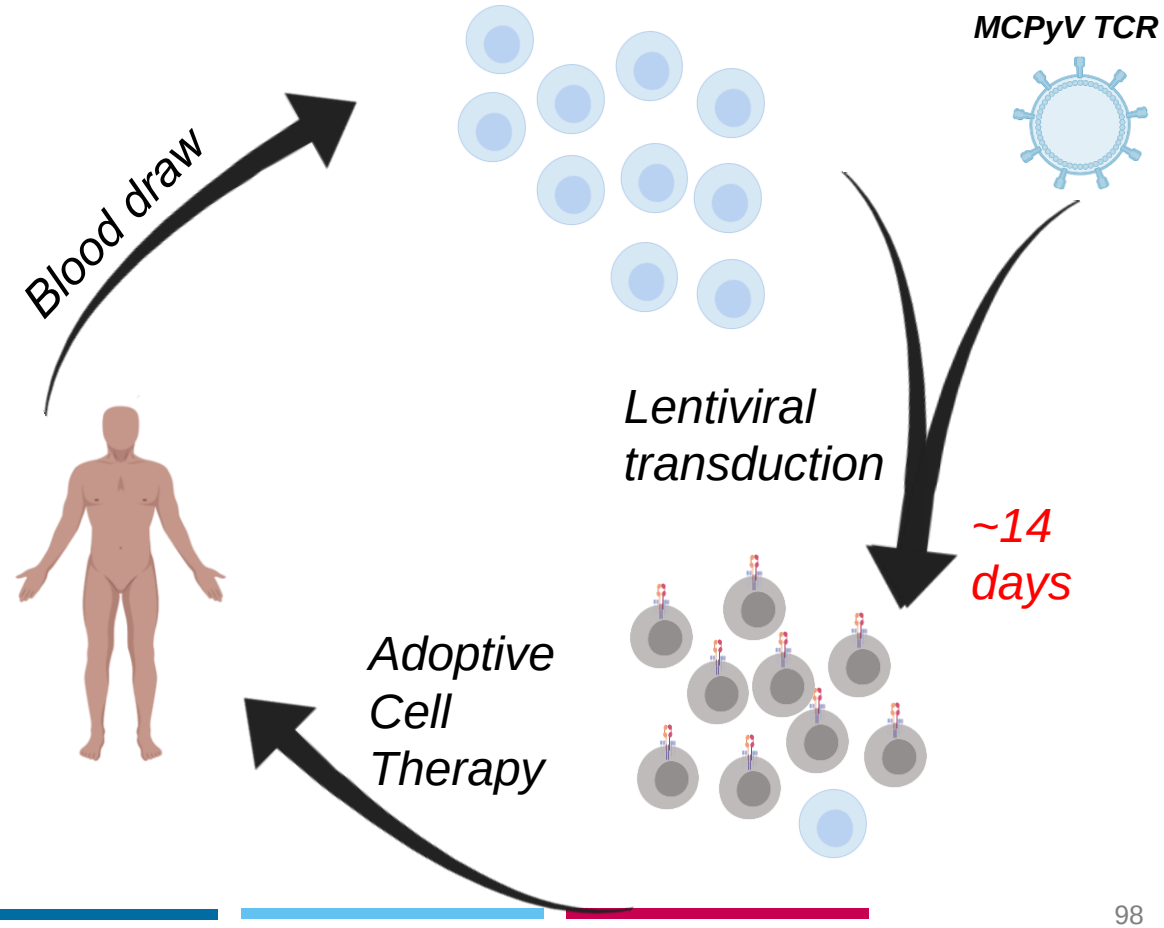
First Generation Engineered MCC1 TCR T Cell Product

Industrialize and Improve Efficacy of Merkel Cell Carcinoma T Cell Therapy

First Generation Product

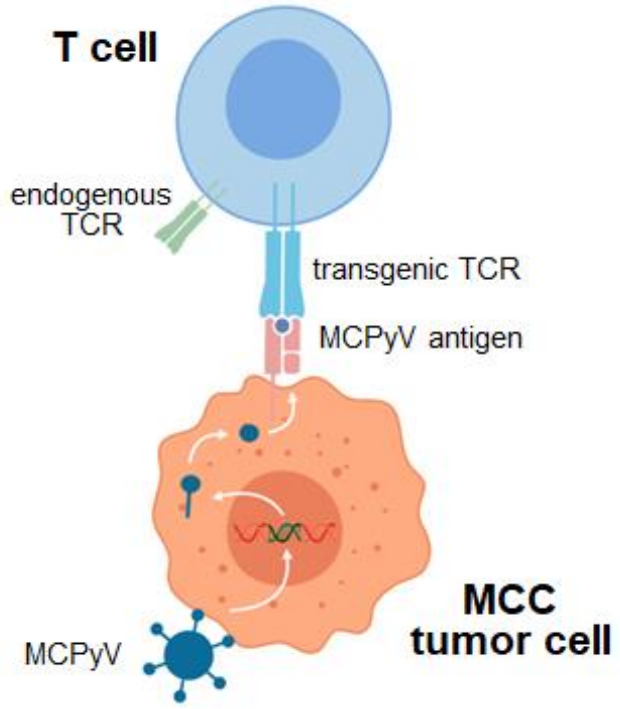
Advantages of a Transgenic TCR Approach

- **Reduced manufacturing complexity and time**
- **Potentially more potent T cell product**
- **Deliver larger number of MCC-specific T cells**
- **Ability to reach more patients**

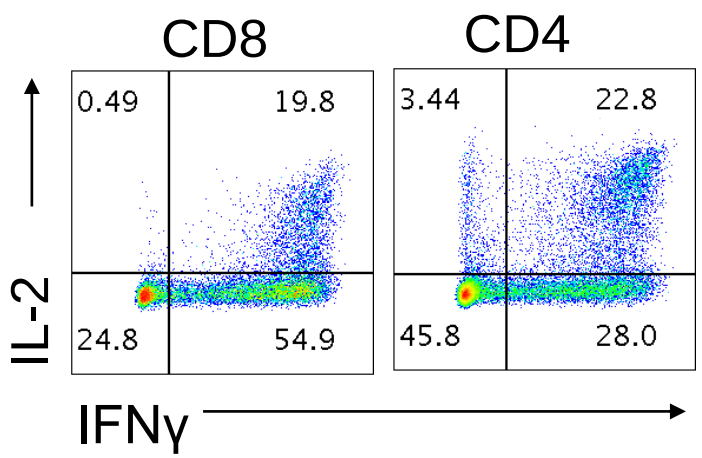


MCPyV TCR Identified from the Natural T Cell Repertoire
Highly Functional in Both CD4 and CD8 T Cells

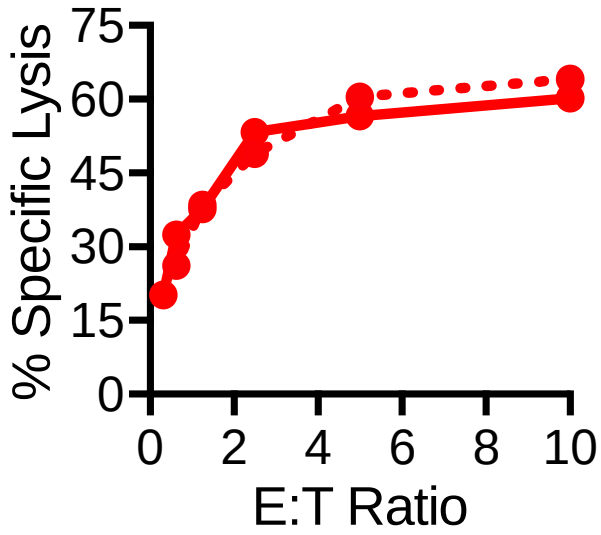
MCPyV TCR recognizes highly conserved viral antigen not present in healthy tissues



MCPyV TCR releases cytokine from both CD4 and CD8 T cells

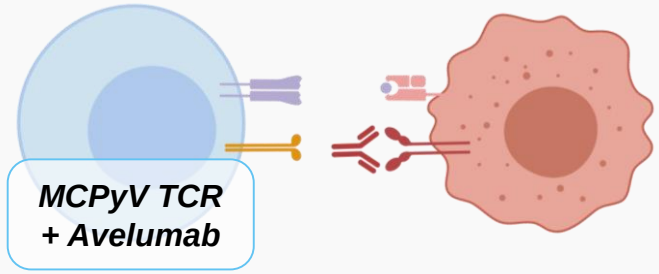


CD4 and CD8 MCC1 TCR T cells cause specific lysis of MCPyV-positive cells

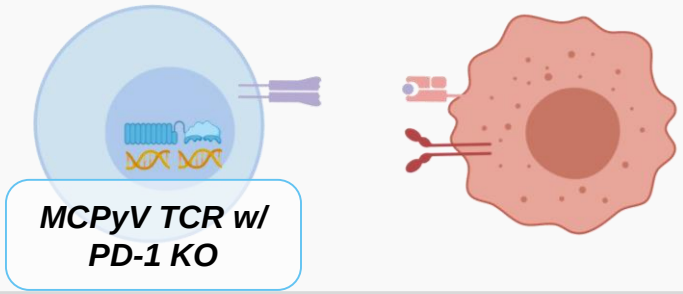


Potential Next Generation Approach
Replace I/O Combination with Gene Edited Checkpoint Evasion

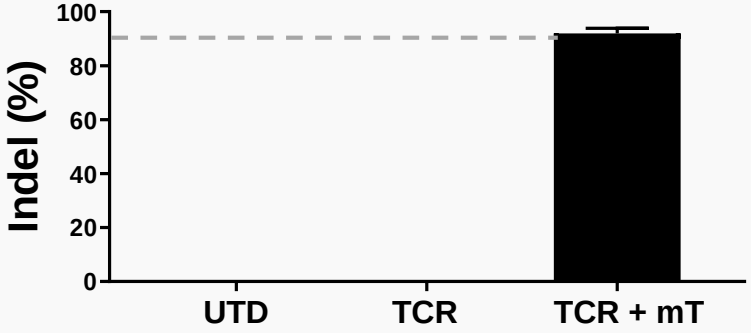
First Gen Approach



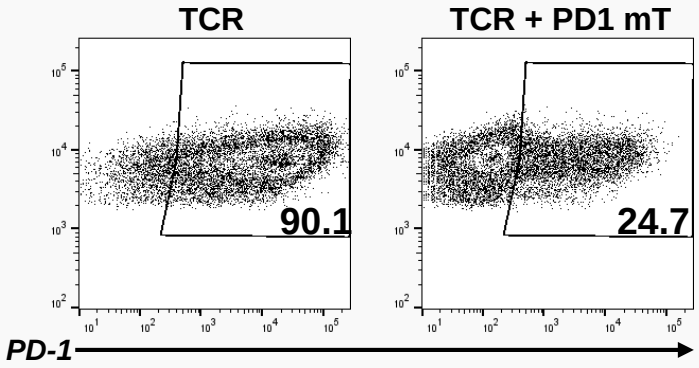
Potential NextGen Approach



PD-1 Gene Deletion Rates



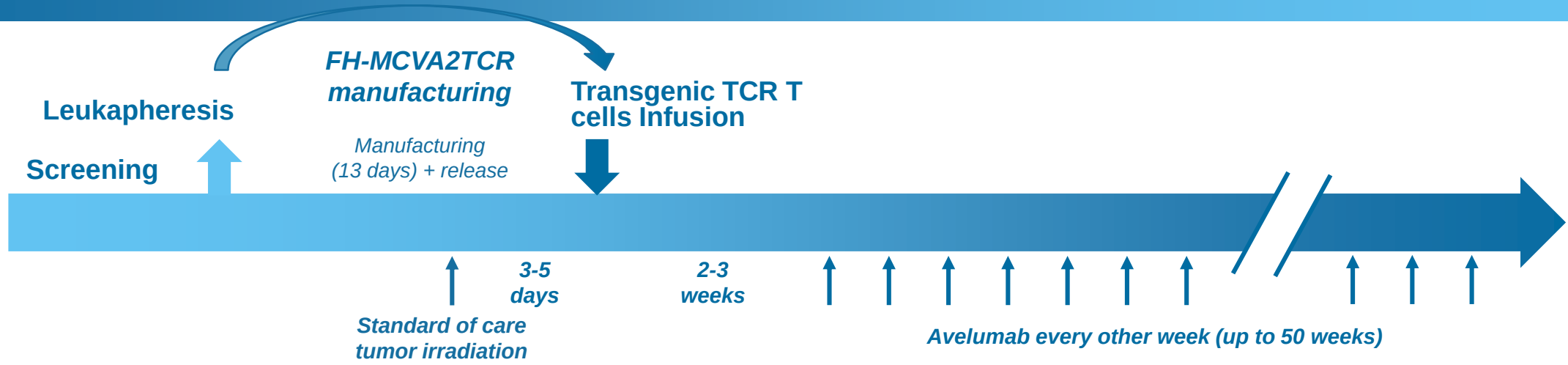
PD-1 Protein KO Rates



ATTAC-MCC Trial (NCT03747484)

Phase 1 Study in Metastatic or Unresectable Merkel Cell Carcinoma

IND Accepted



ATTAC-MCC Open-label Phase 1 Clinical Study of MCC1 TCR Targeted Autologous T-cells

Trial designed based on experience with MCPyV-specific peripheral blood cells

- Avelumab (anti-PD-L1) to enhance activity to tumor
- Tumor irradiation (SFRT) to increase tumor recognition by MCC1 TCR T cells

Objectives:

- **Primary:** Safety and Efficacy
- **Secondary:** T cell persistence, tumor migration, progression-free survival, immune RECIST
- **Exploratory:** T cell phenotype, T cell function, epitope spreading of T cell responses, tumor microenvironment

Study Population:

- **N =16 patients** with dose escalation
- **Eligibility:** HLA-A02 and Merkel cell polyomavirus -positive with metastatic Merkel cell carcinoma who have progressed after treatment with a PD-1 axis checkpoint inhibitor

Diffuse Large B Cell Lymphoma Program

bluebirdbio®

Our Research Strategy in Action:
Diffuse Large B Cell Lymphoma (DLBCL) Program

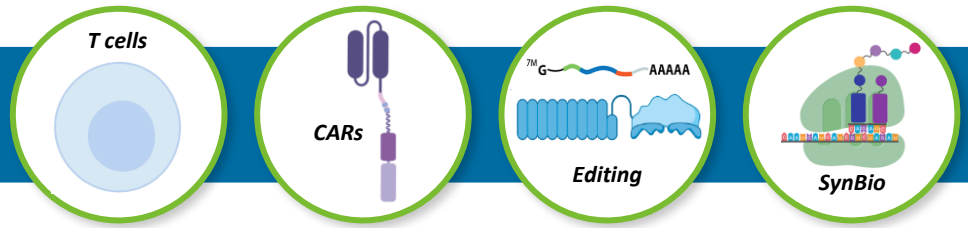
The Problem that Needs to be Solved

Achieving more durable complete responses in DLBCL likely requires more active CAR-T cells that target novel and additional antigens

Why it Matters

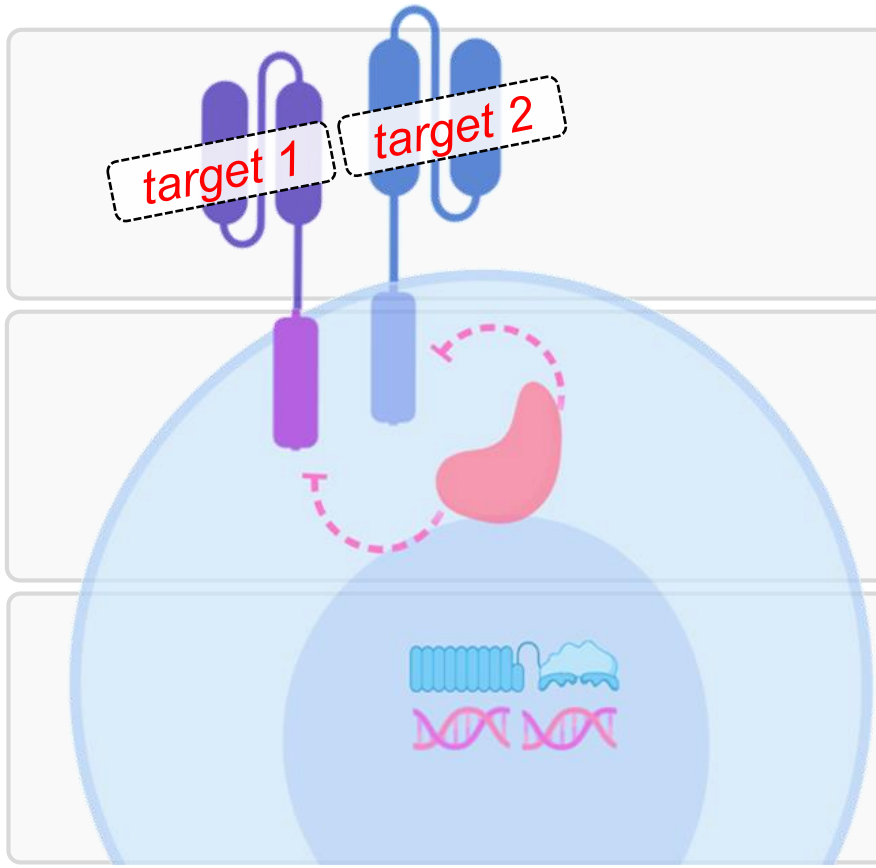
DLBCL is responsive to CAR T cell therapies but there is still need for improvement in the depth and durability of clinical responses

Our Un-Incremental Approach



Bring multi-layered enhancements including dual targeting, innovative CAR design, and potency enhancement with gene editing (i.e., T cell triple play)

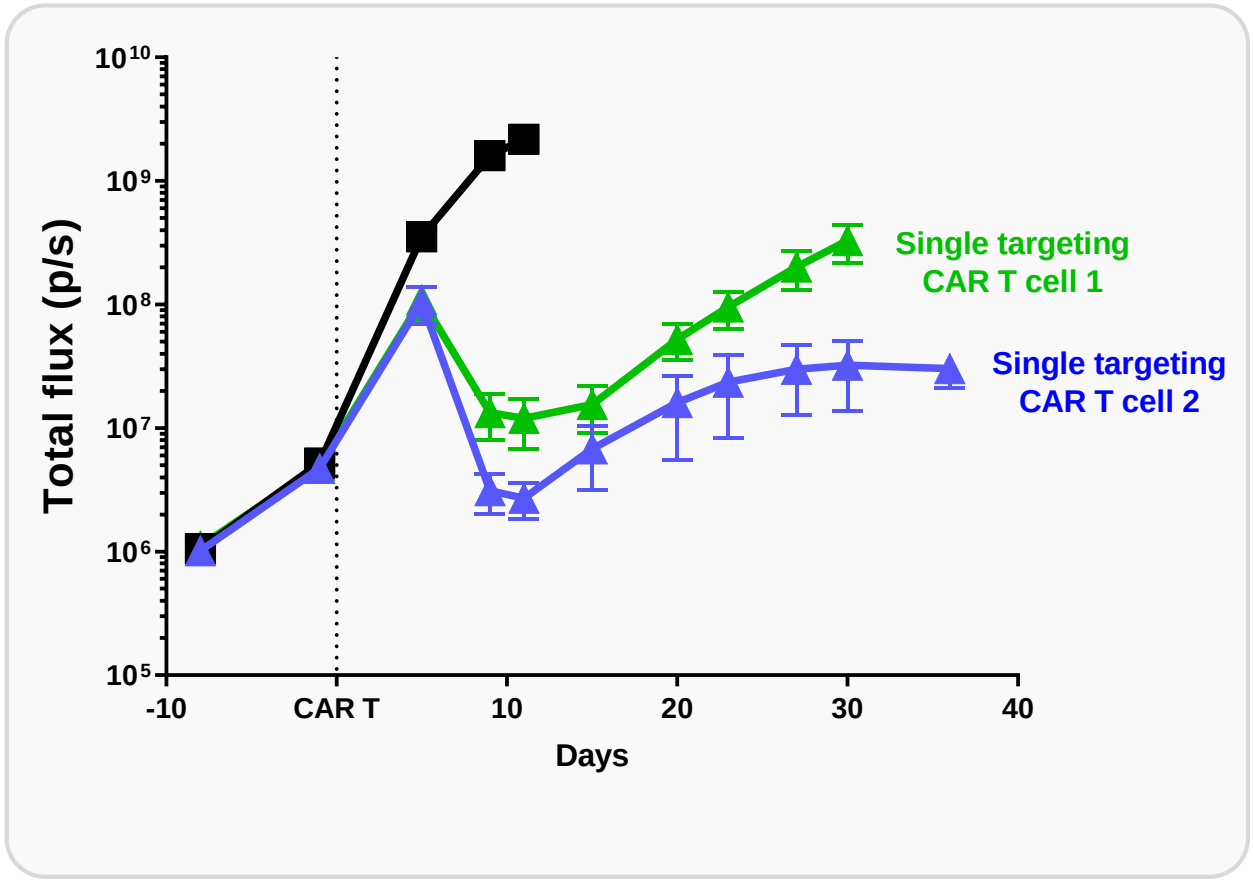
Our Approach for NextGen Cell Therapy in DLBCL
Layering Technologies to Optimize Anti-Tumor Response

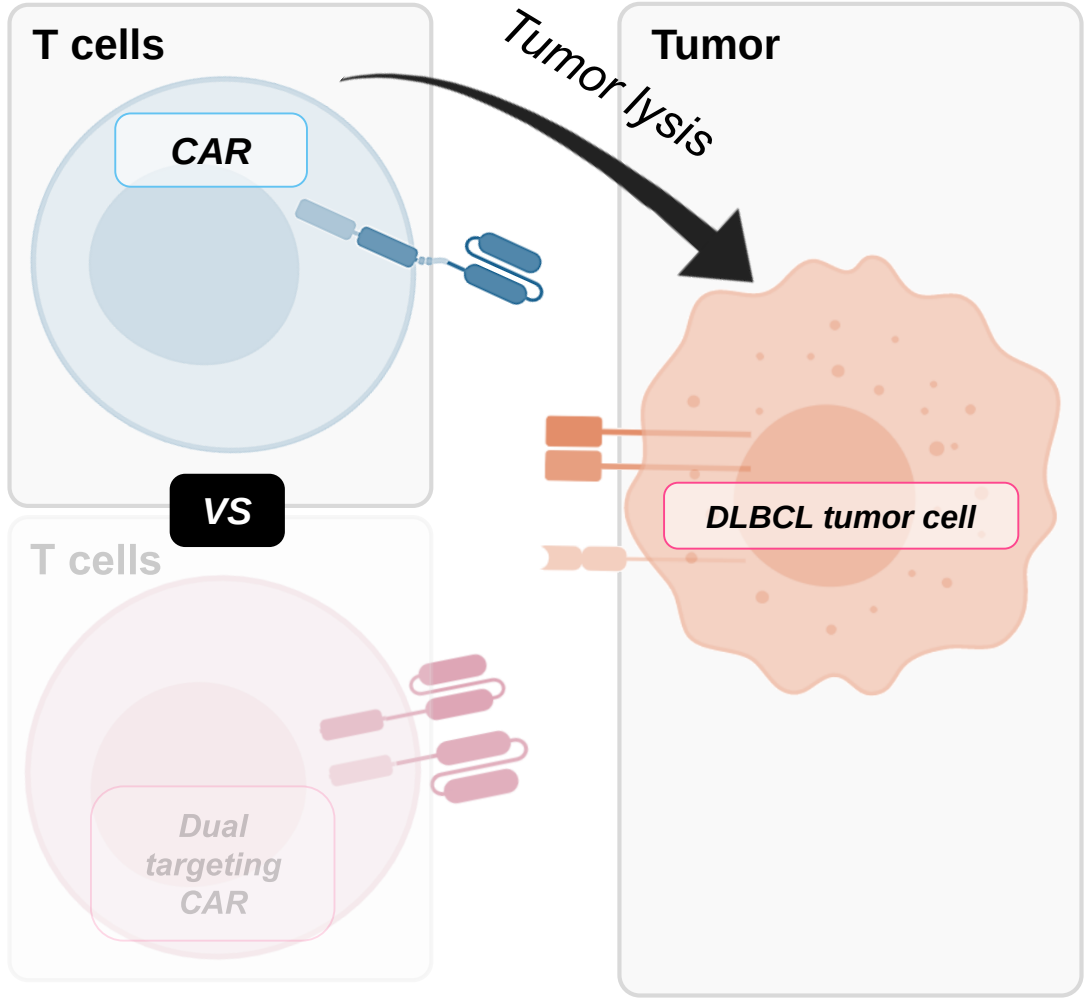


Layer		Purpose
1	dual-targeting	Target tumor driver and passenger proteins to limit DLBCL escape
2	signal extension	Unique CAR construction integrated with dual target technology to enhance T cell activation
3	signal amplification	T cell chassis intended to improve persistence of CAR T cell activity

Limited Anti-Tumor Activity of Single Target CARs in "Stress Test" Lymphoma Animal Model

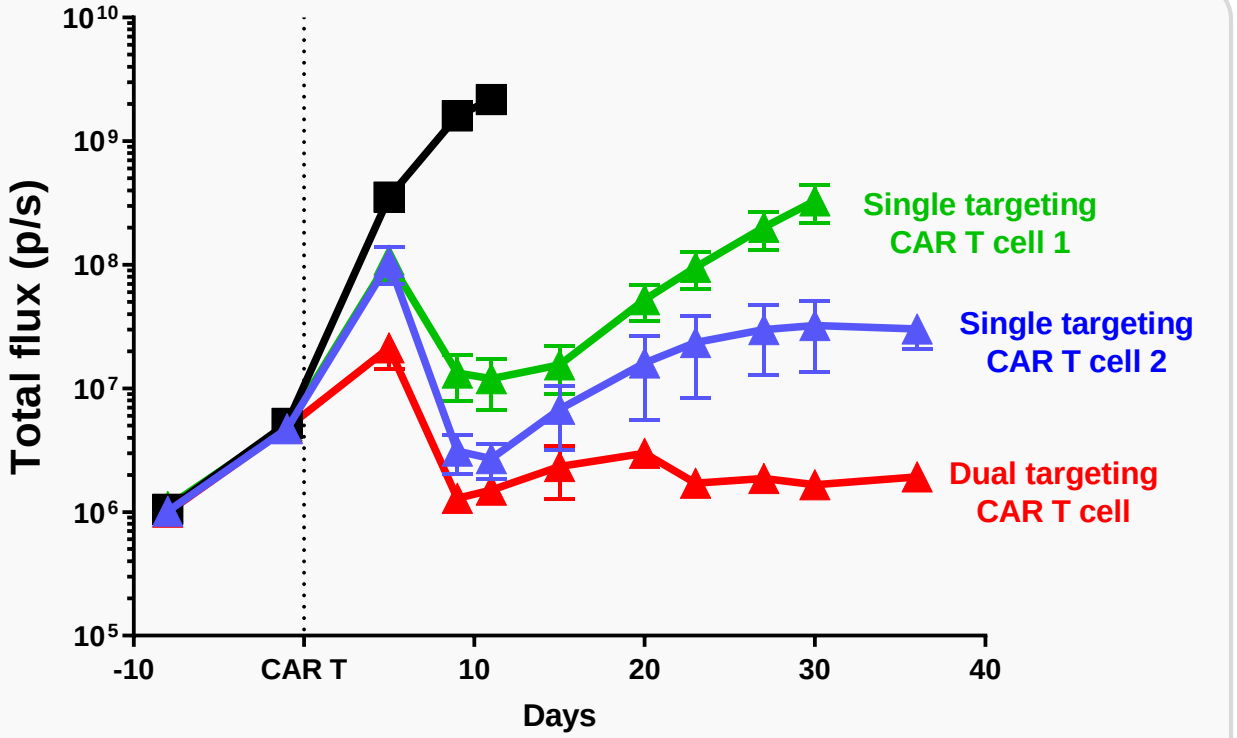
Individual CAR T cells exhibit anti-tumor function in a stringent lymphoma animal model

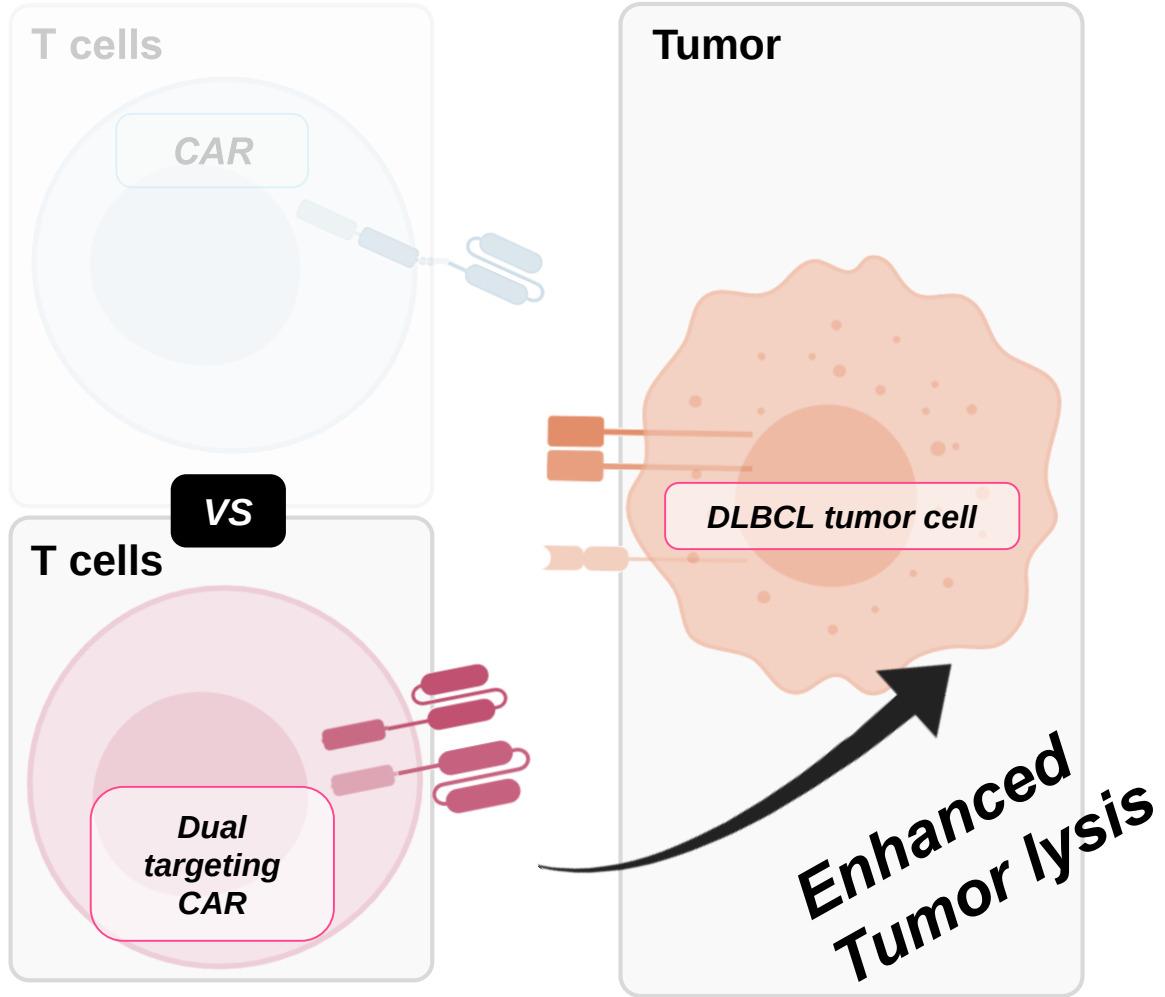




Potent Anti-Tumor Activity with Dual Targeted CARs in "Stress Test" Lymphoma Animal Model

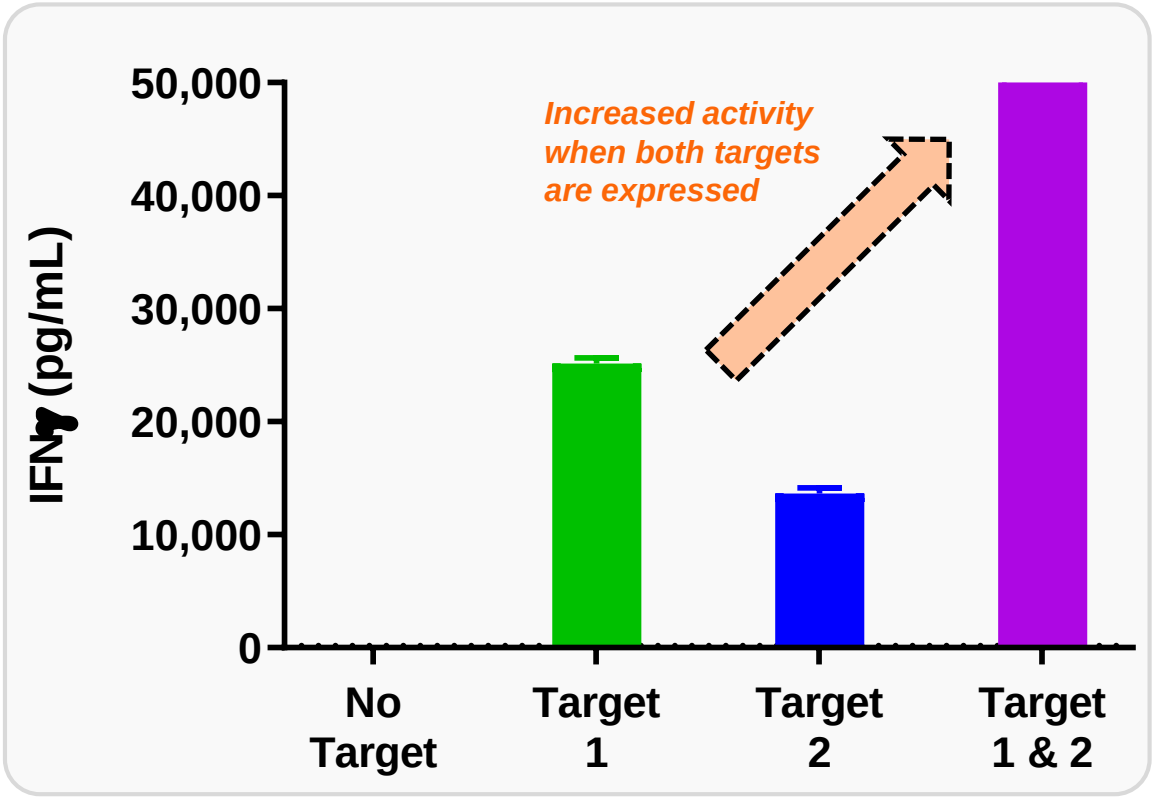
Dual targeting CAR T cell exhibit superior tumor control compared to individual CAR T cells

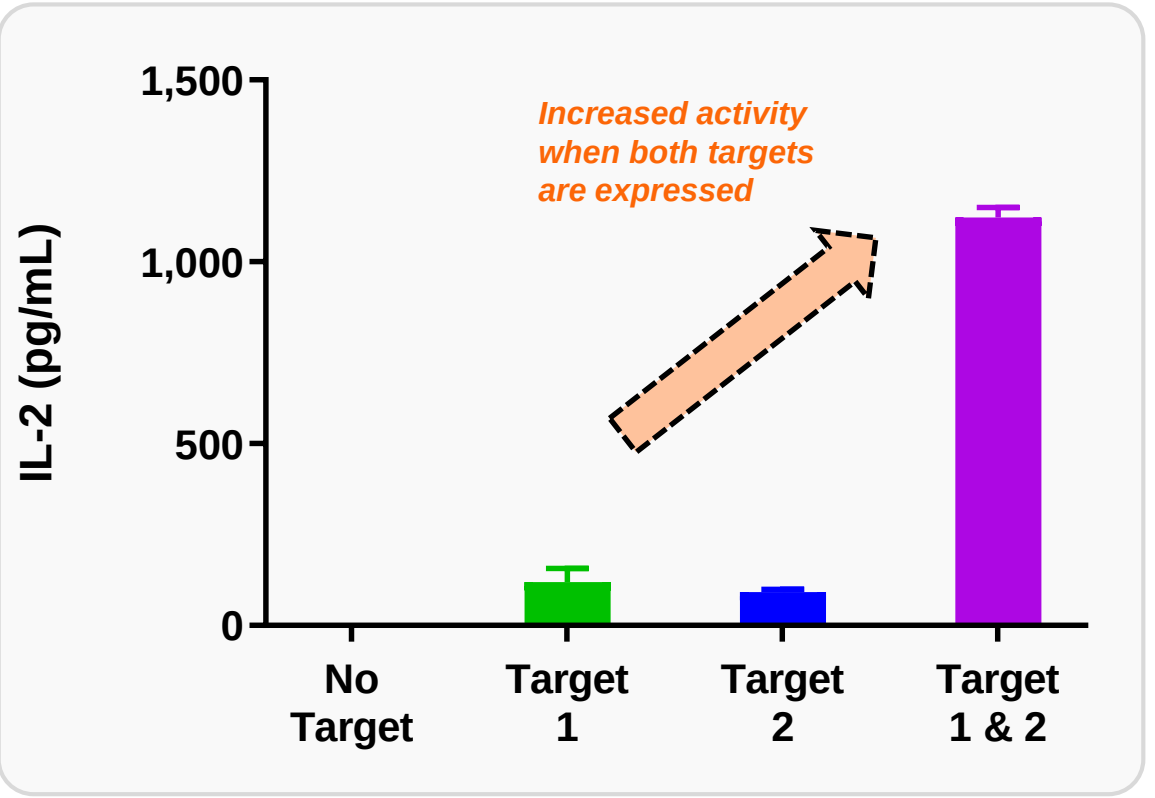




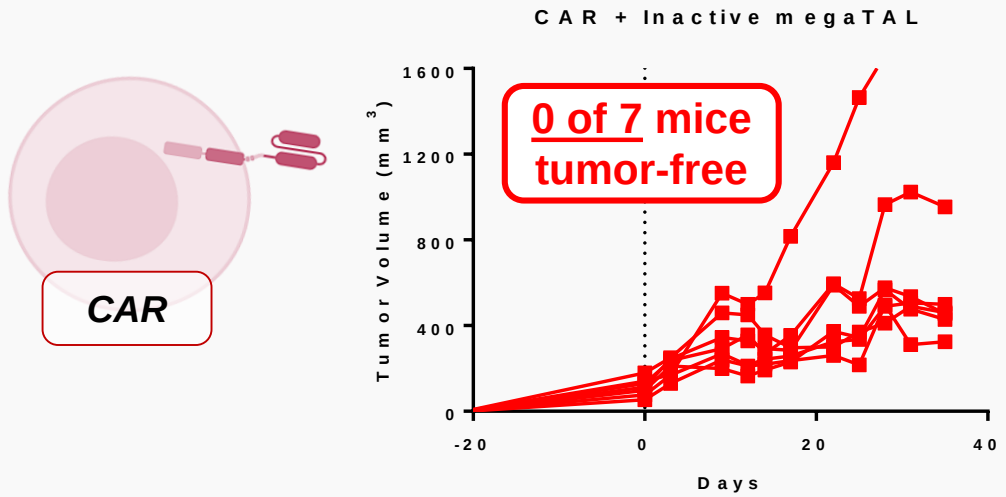
Signal Extension: Enhanced Activity When Both Targets are Expressed

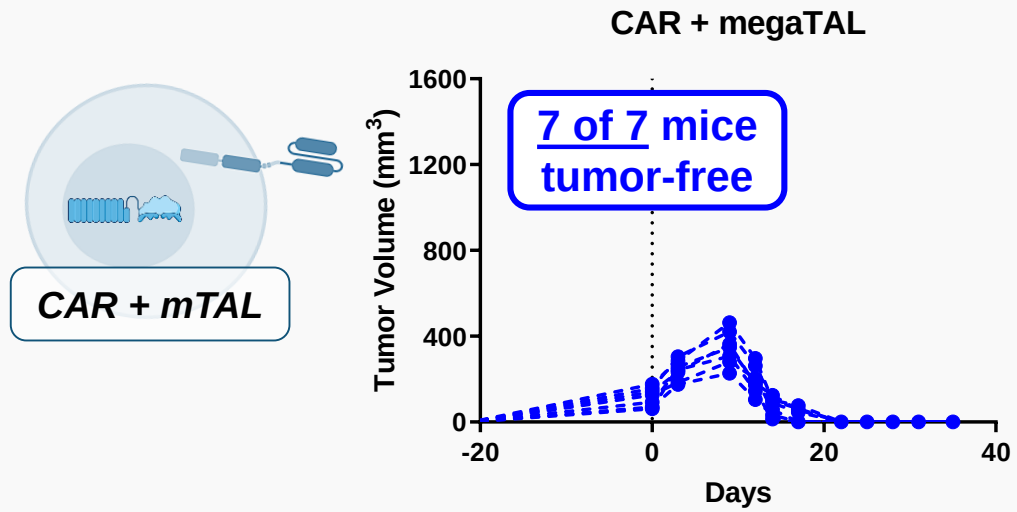
Enhanced inflammatory cytokine secretion to tumors expressing both target antigens





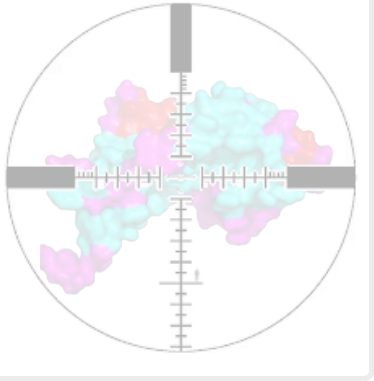
Signal Amplification: Taking the Brakes Off the CAR T Cells

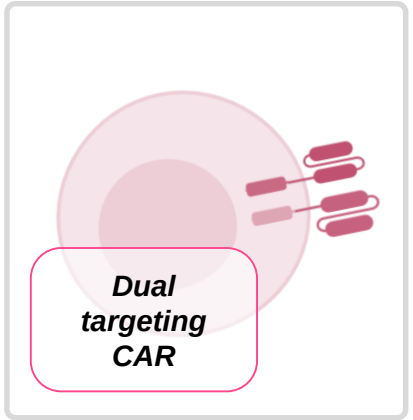


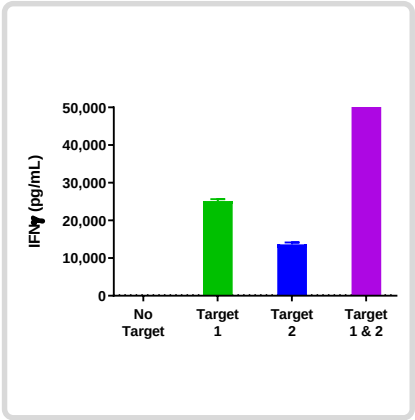


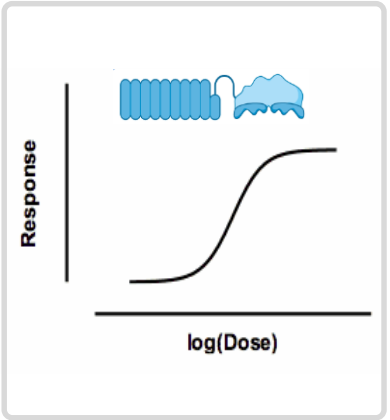
The DLBCL Program

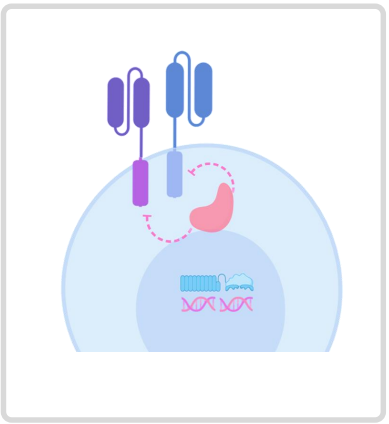
TARGET ID → Dual Targeting → Signal Extension → Signal Amplification → NEXT GEN 1:MANY











↑ Tumor
↓ Tissue

Prevent DLBCL Escape

Enhanced T cell Activation

Persistence of T cell Activity

Applications Across Platform

MAGE-A4 Solid Tumor TCR Program

bluebirdbio®

Our Research Strategy in Action:
MAGE-A4 Solid Tumor TCR Program

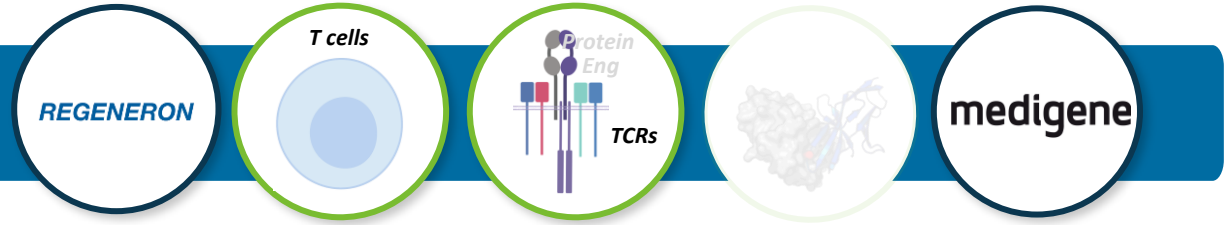
The Problem that Needs to be Solved

Achieving CD19/BCMA-like outcomes in solid tumors will require best-in-class targeting of intracellular antigens

Why it Matters

MAGE-A4 is one of most commonly expressed cancer-testis antigens found in a large array of solid tumors

Our Un-Incremental Approach



Develop a TCR targeting MAGE-A4 with exceptional anti-tumor activity

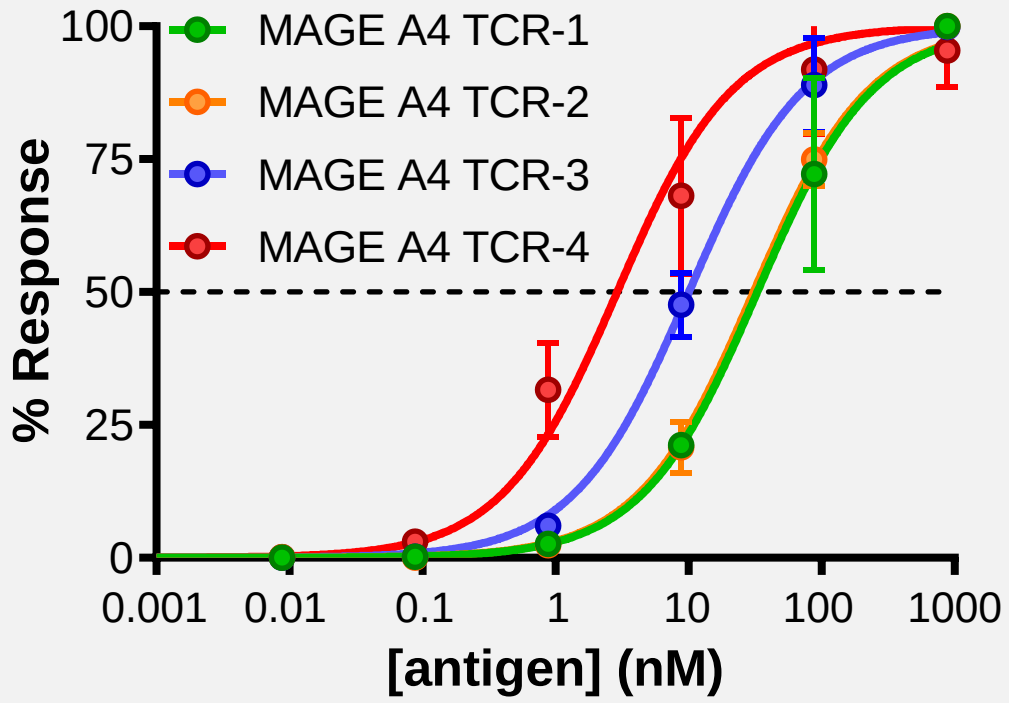
Integrate technologies that address multiple barriers including the tumor microenvironment

MAGE-A4, Our First Medigene Target

medigene TCRs

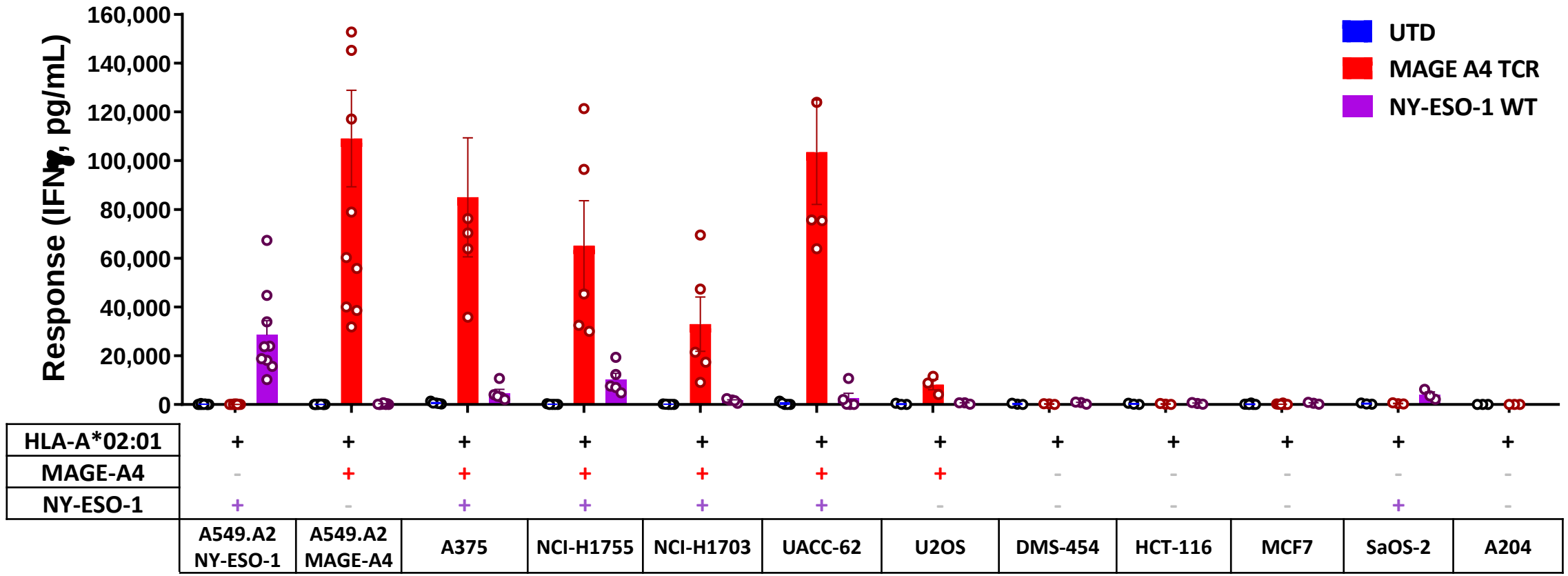
TCR Discovery

Functional Screen



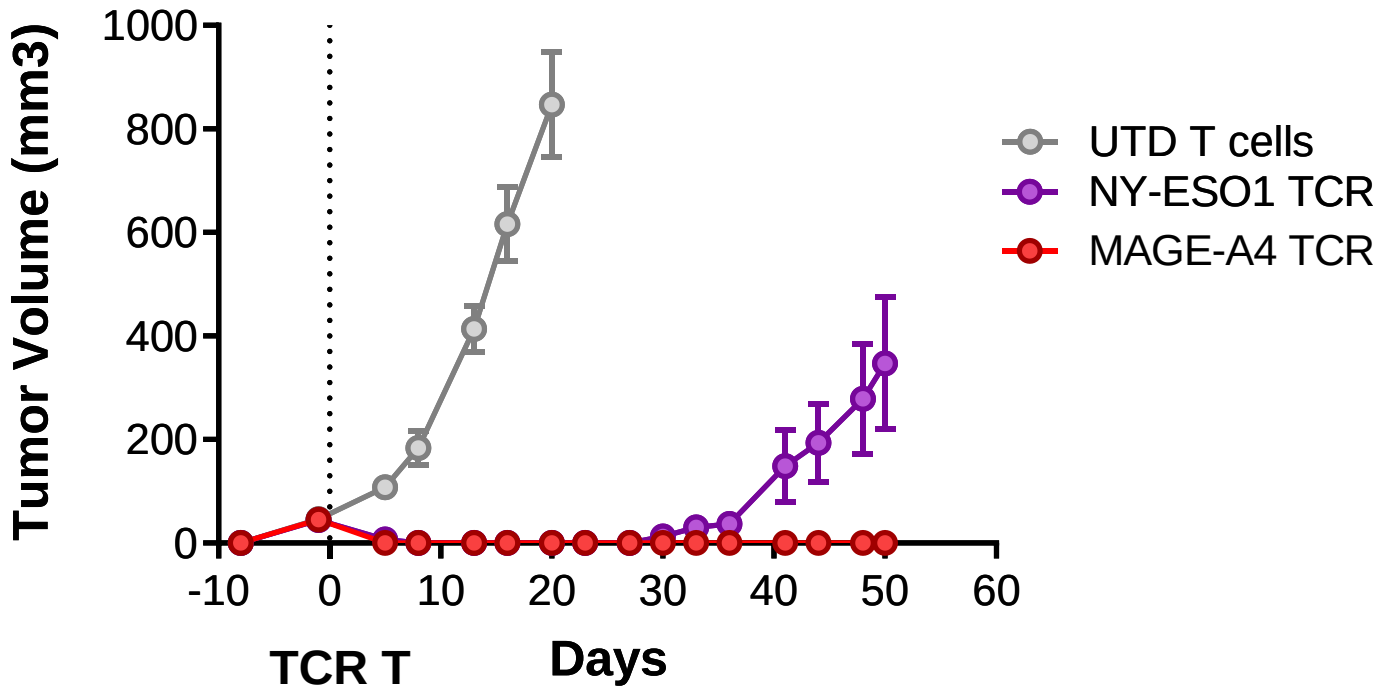
High-avidity TCR selected for further characterization

MAGE-A4 TCR T Cells Respond Vigorously to Tumor Cell Lines



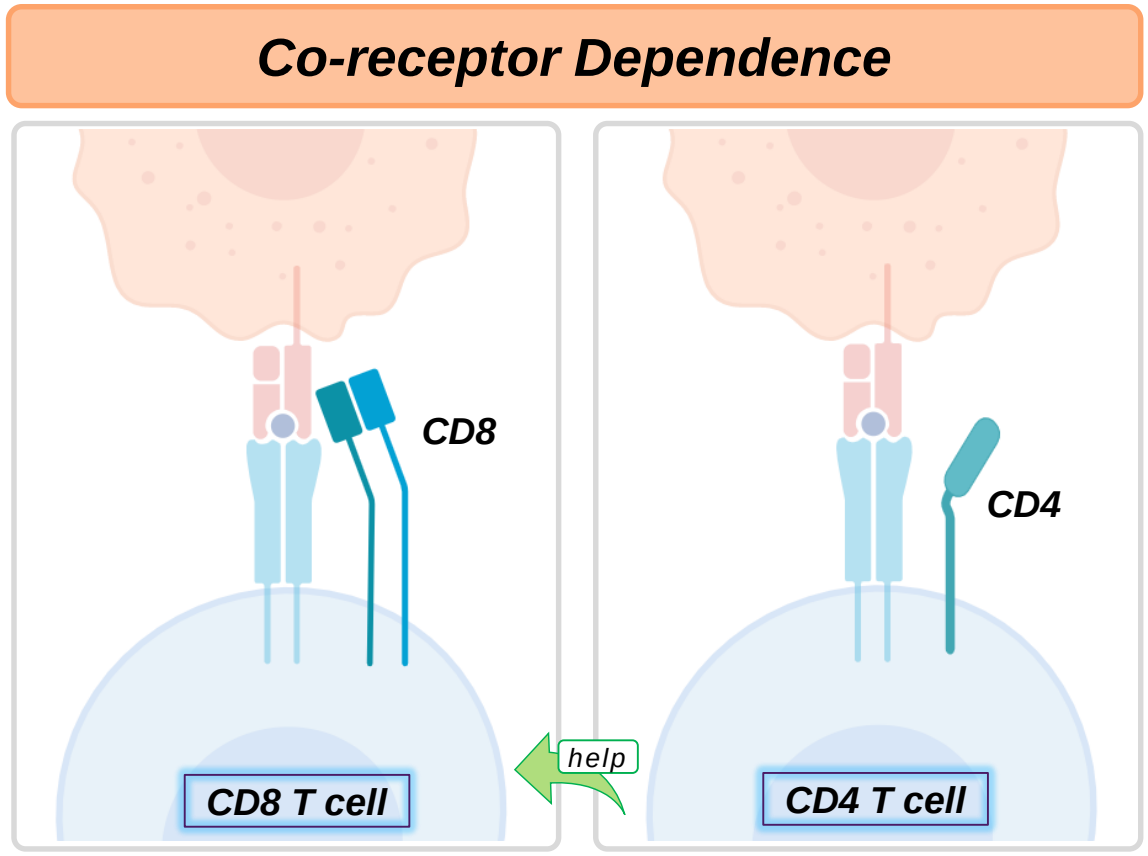
High-magnitude, specific responses to 6-of-6 MAGE-A4^{+} cell lines

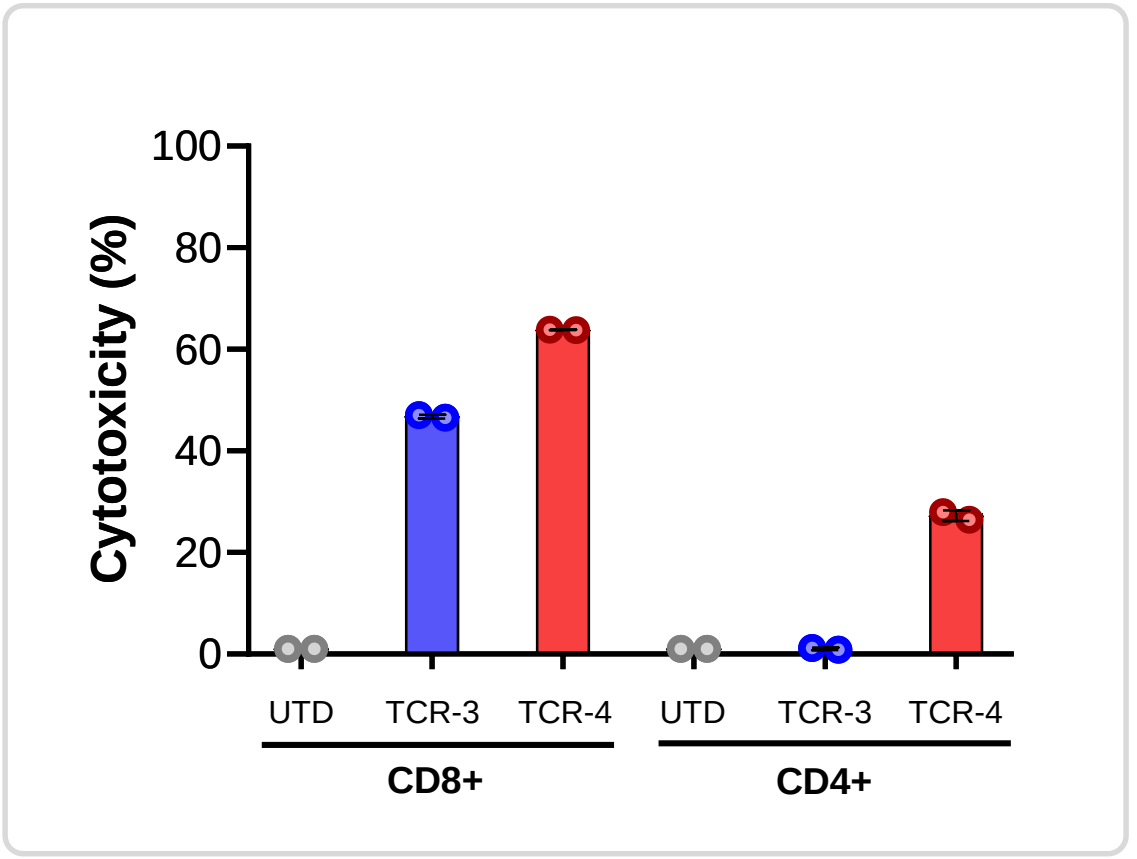
Potent MAGE-A4 TCR T Cell Activity *in vivo* Against Tumor Xenografts



Durable tumor elimination in a subcutaneous melanoma model

Our MAGE-A4 TCR is Co-receptor Independent





Functional responses (cytokine and cytotoxicity) in both CD8 and CD4 T cell populations

Our Research Strategy in Action: MAGE-A4

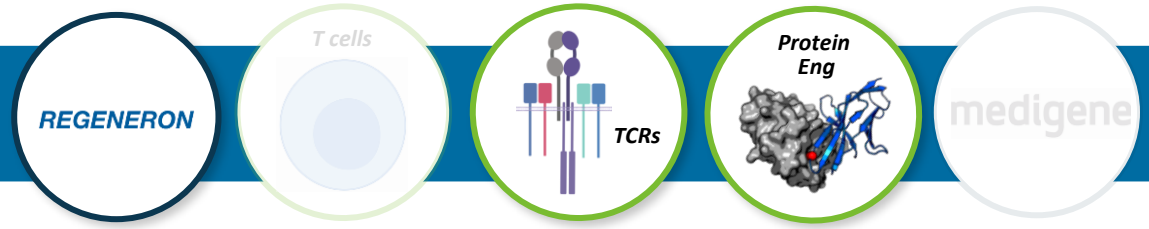
The Problem that Needs to be Solved

Achieving CD19/BCMA-like outcomes in solid tumors will require best-in-class targeting of intracellular antigens

Why it Matters

MAGE-A4 is one of most commonly expressed cancer-testis antigens found in a large array of solid tumors

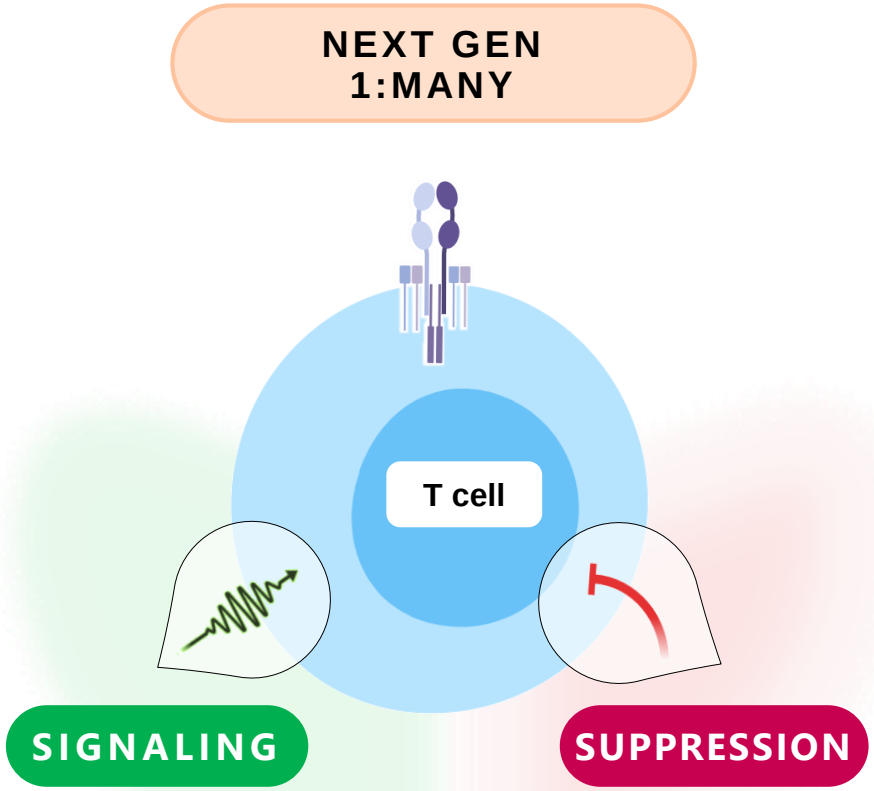
Our Un-Incremental Approach

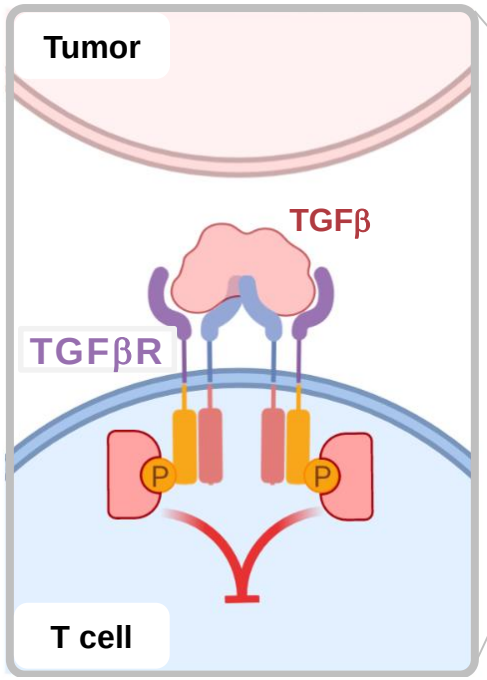


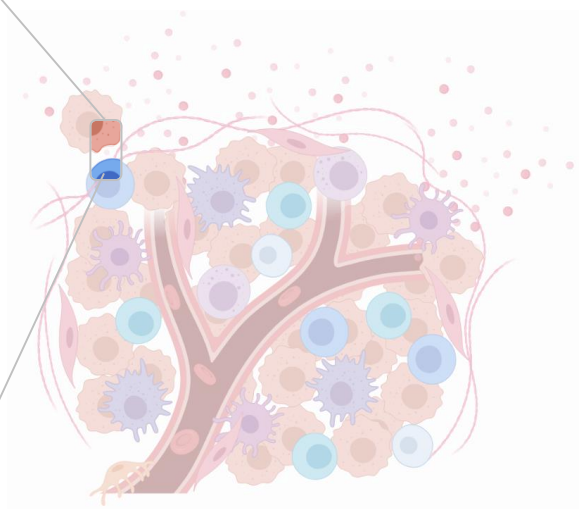
Develop a TCR targeting MAGE-A4 with exceptional anti-tumor activity

Integrate technologies that address multiple barriers including the tumor microenvironment

TCR T Cells Can Be Limited by Strength of Signal & Immunosuppression

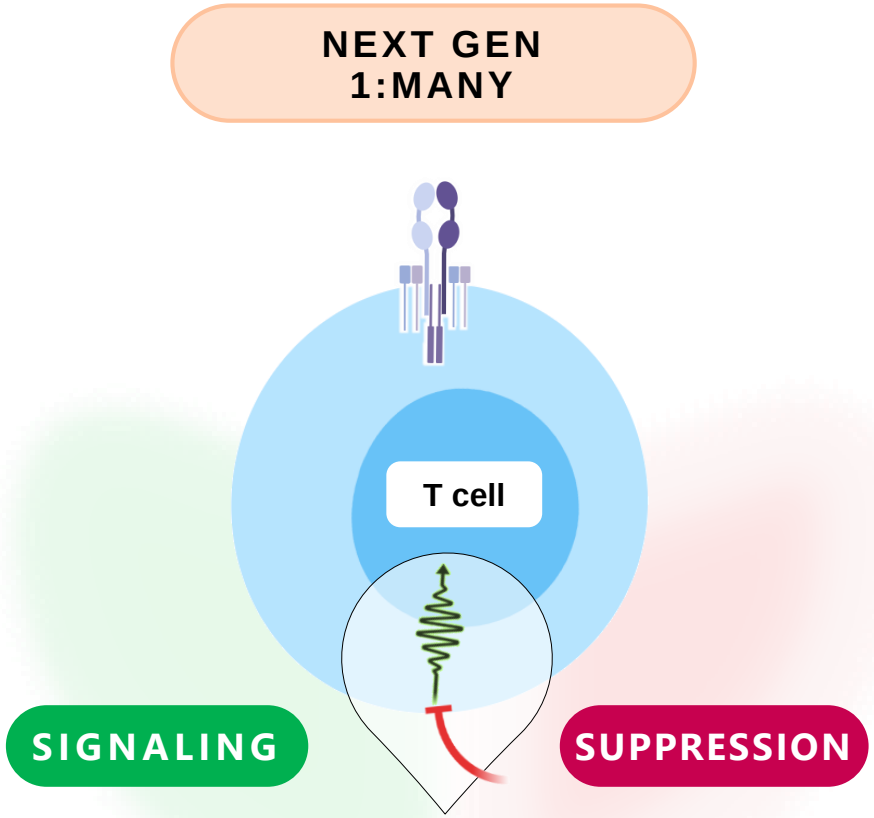


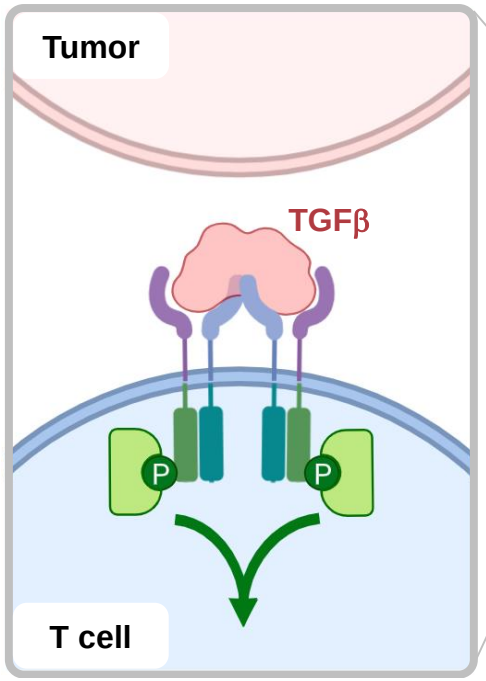


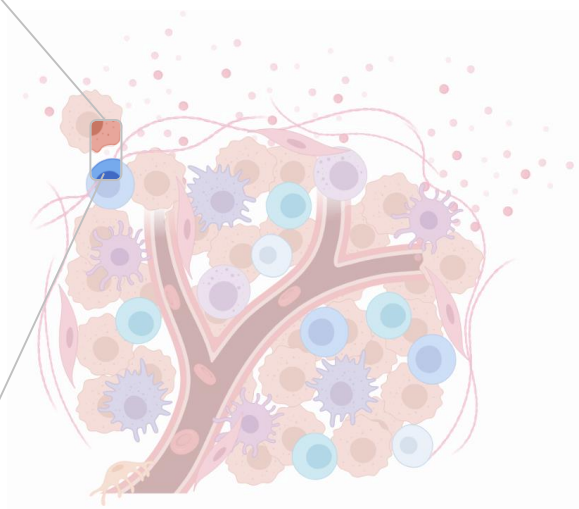


↓ cytokine production
↓ proliferation
↓ anti-tumor activity

Signal Converter Technology: A 2-for-1 Attack on the Tumor Microenvironment (TME)

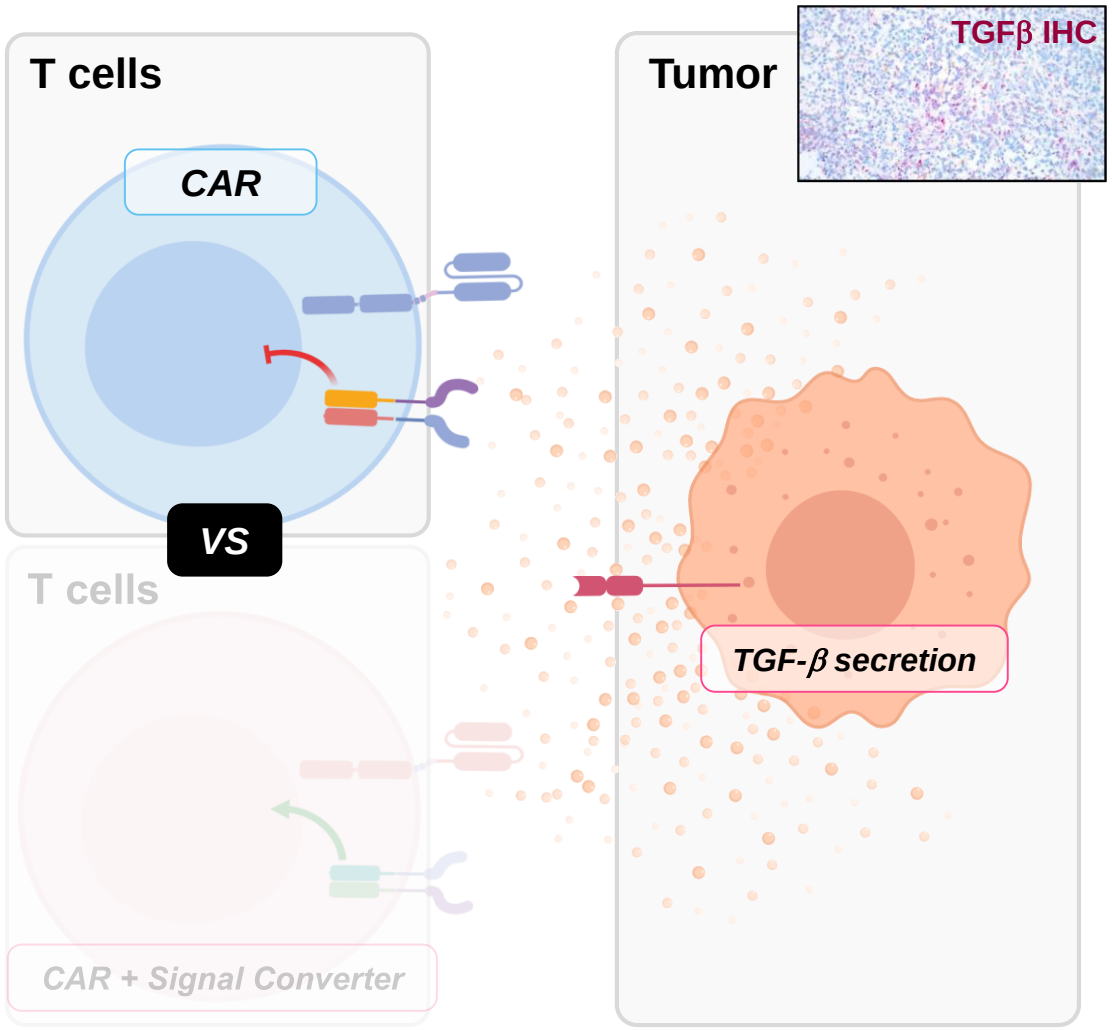


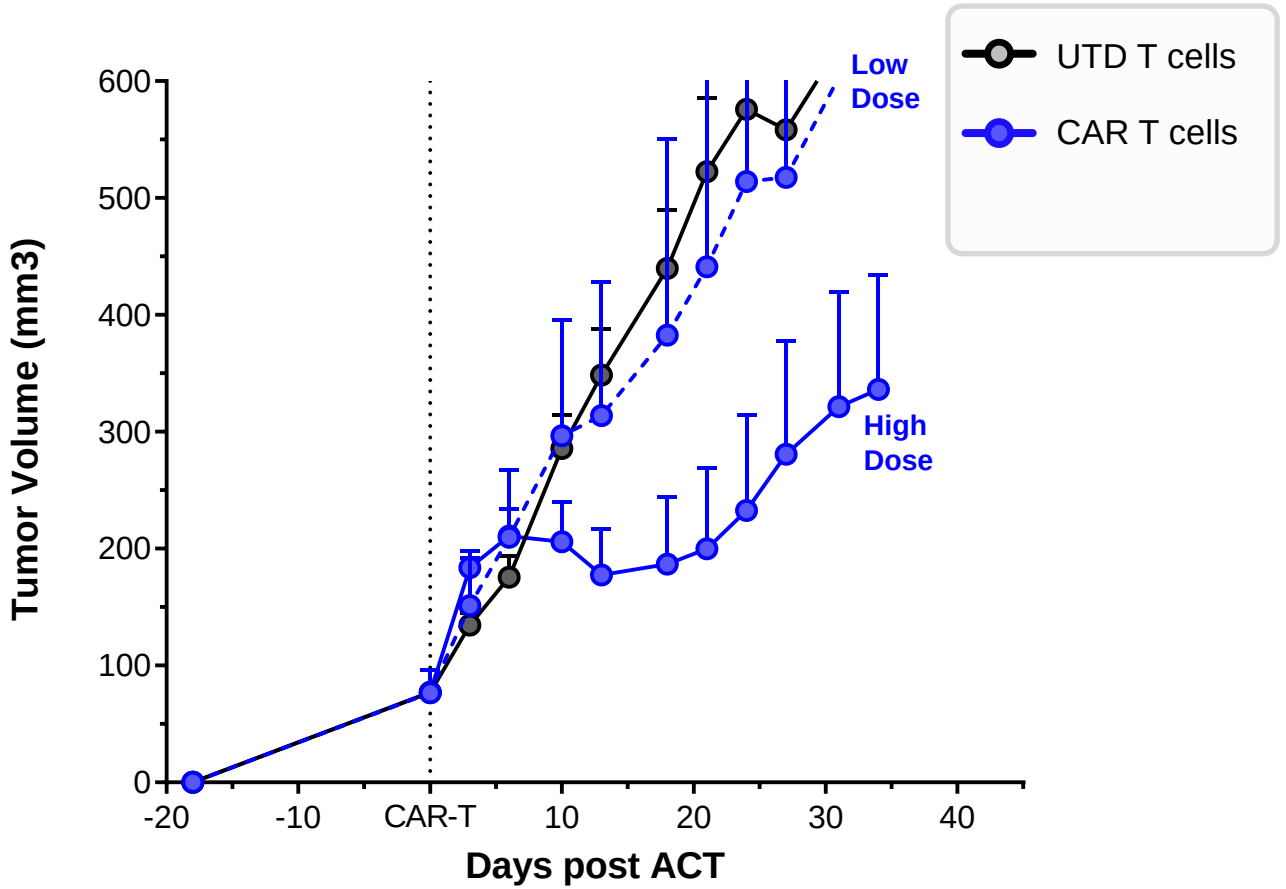




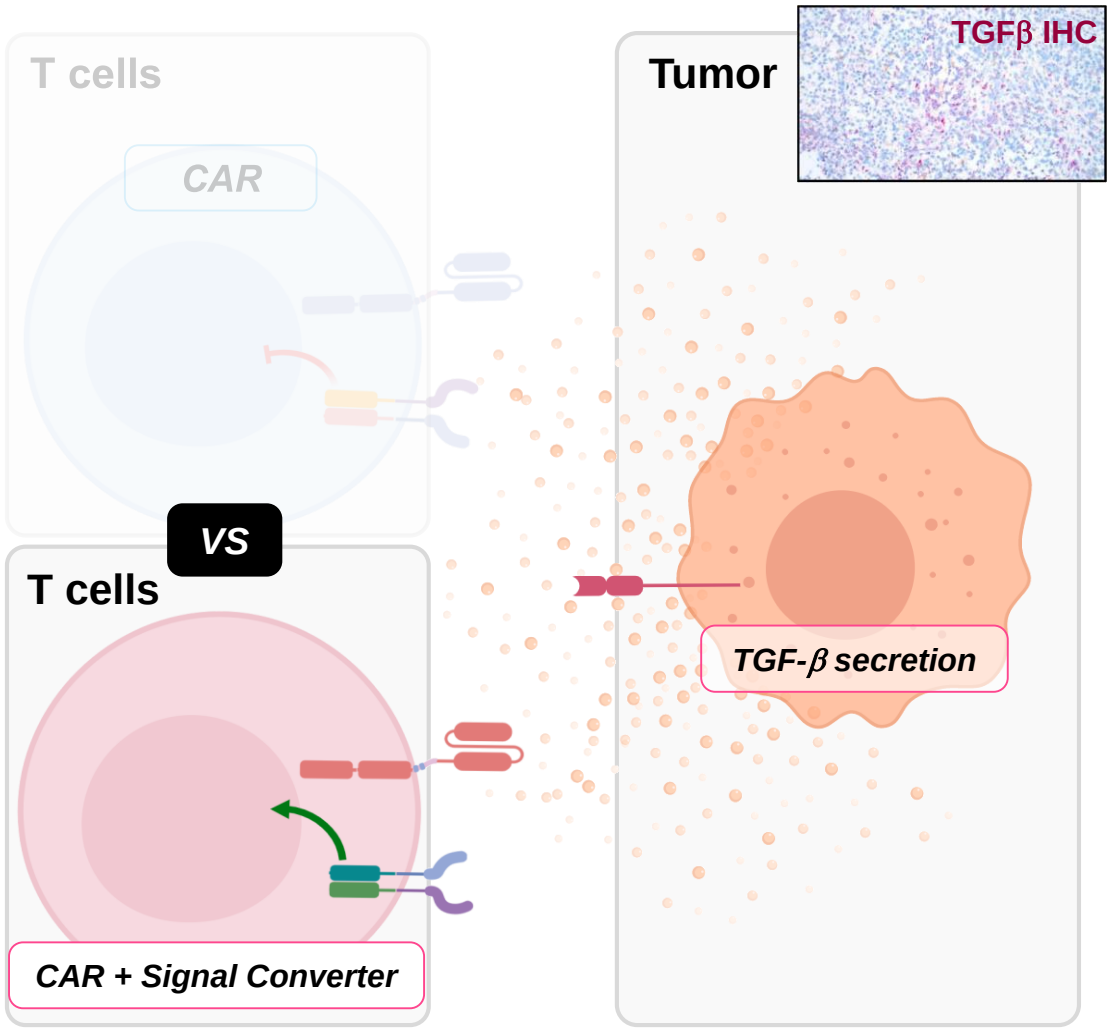
↑ cytokine production
↑ proliferation
↑ anti-tumor activity

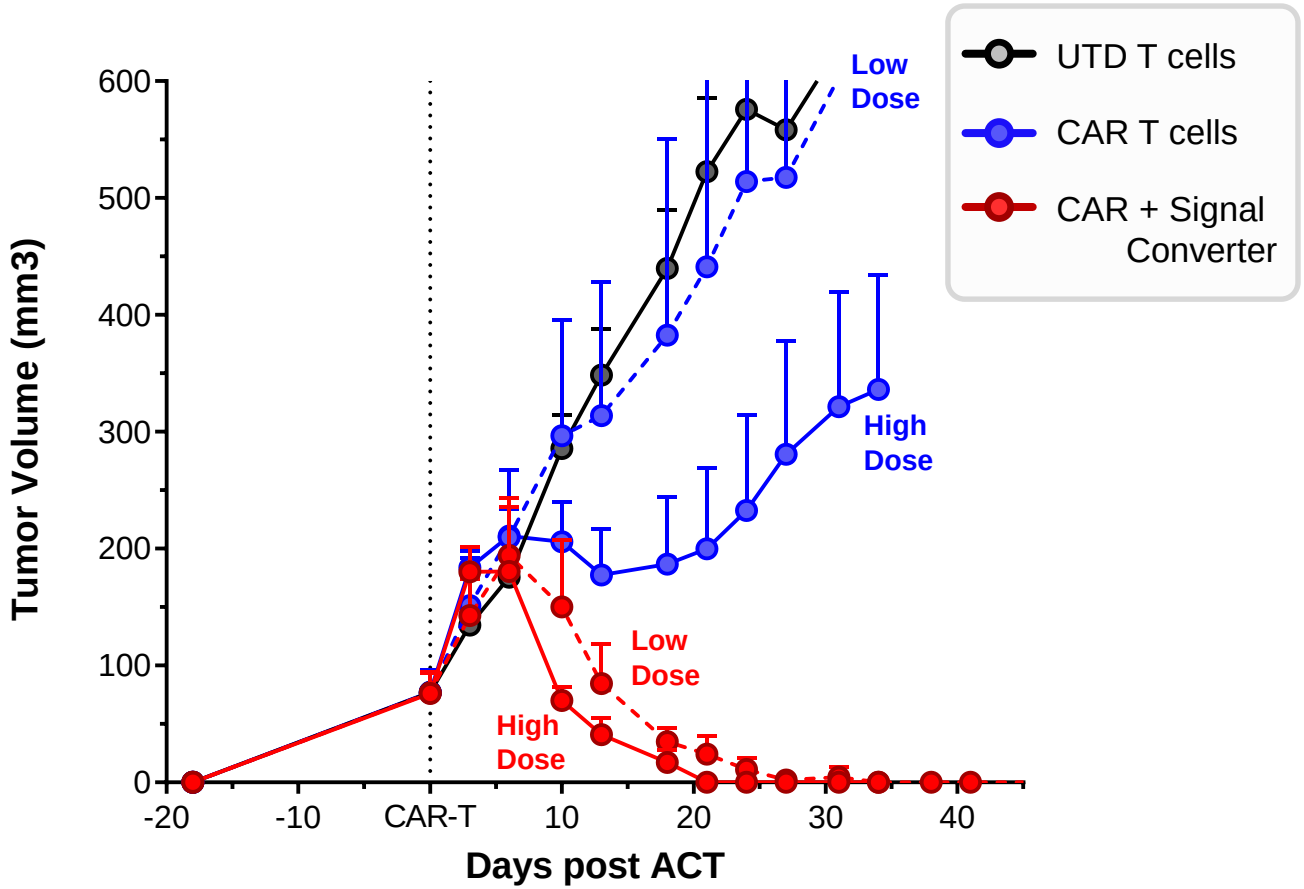
T Cells Struggle to Respond in an Immunosuppressive Microenvironment



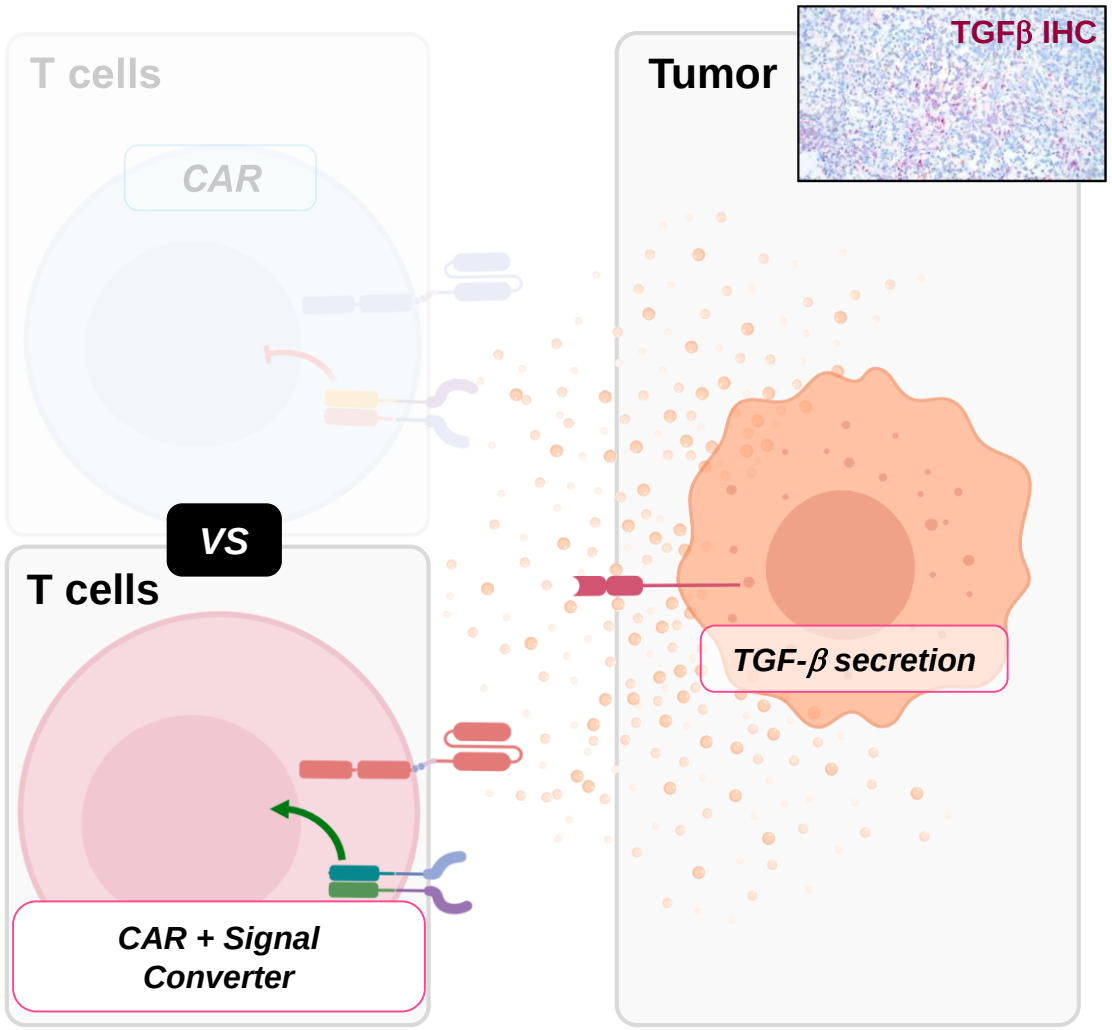


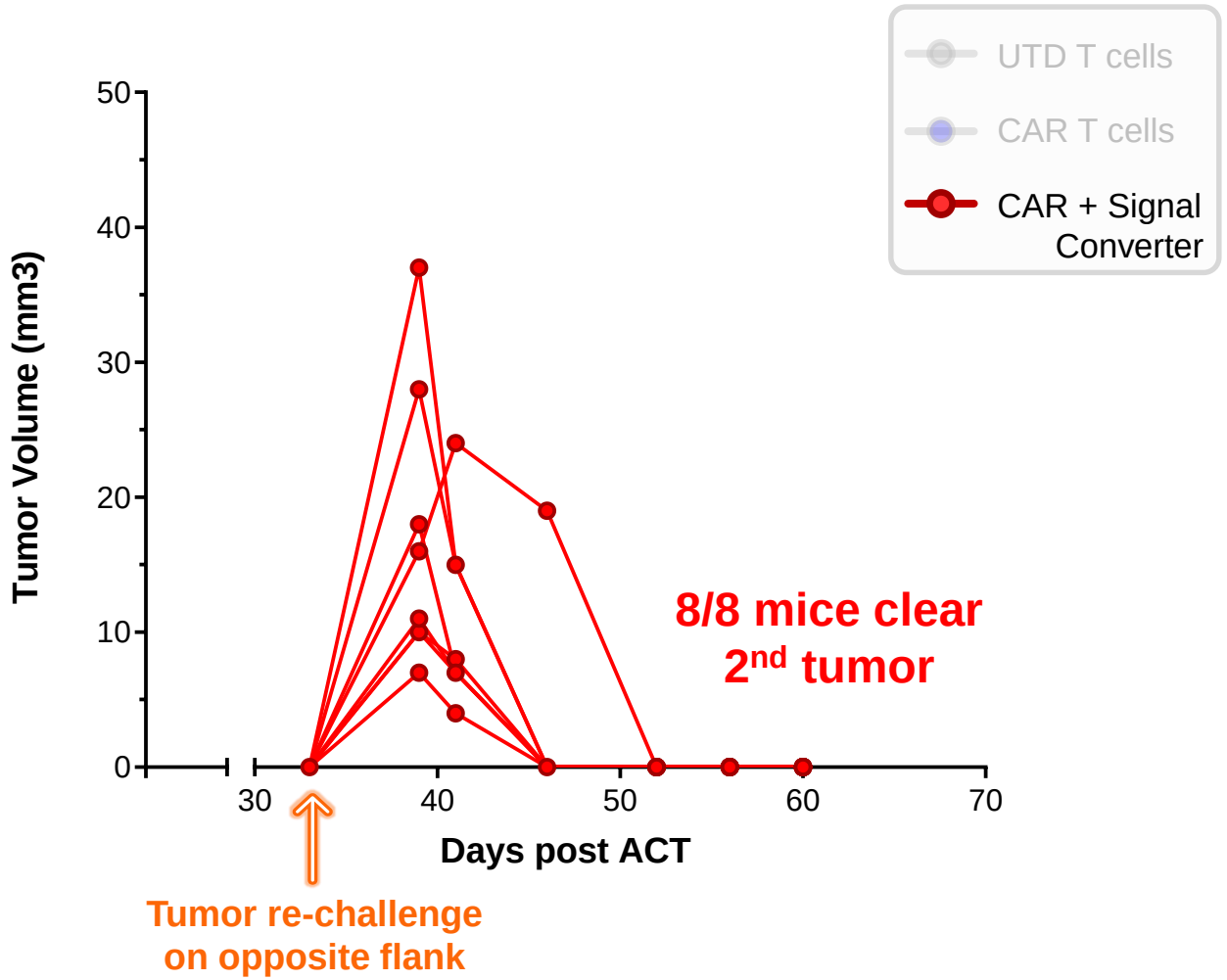
TME Signal Converter T Cells Regain Robust Anti-Tumor Activity





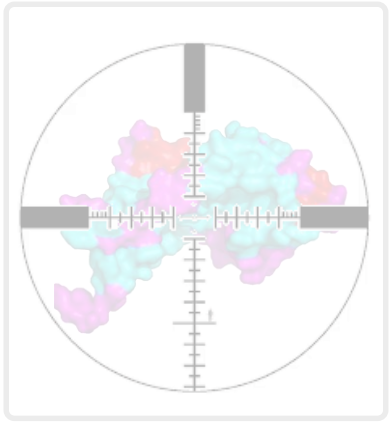
TME Signal Converter T Cells Regain Robust Anti-Tumor Activity



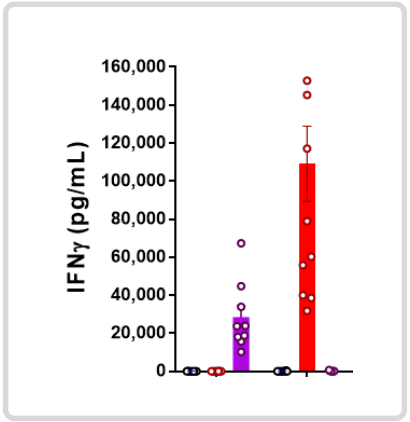


The MAGE-A4 Program

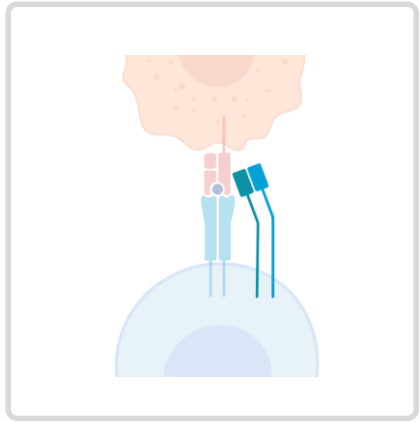
TARGET ID → TCR ID & FUNCTION → CO-RECEPTOR INDEPENEDENCE → TCR SPECIFICITY → *IN VIVO* FUNCTION → NEXT GEN 1:MANY



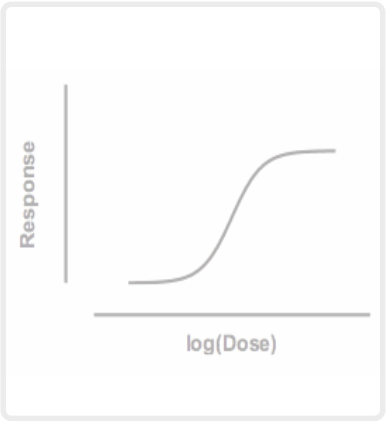
↑ Tumor
↓ Tissue



High-avidity TCR

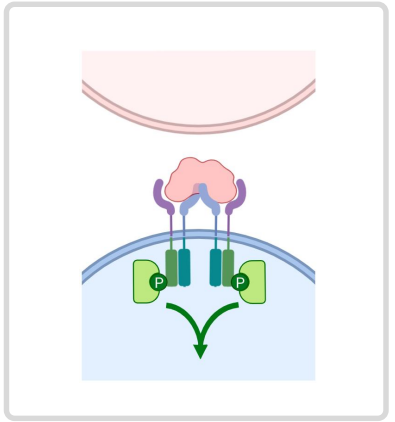


CD4 & CD8 T cell activity



De-risked cross-reactivity

Preclinical efficacy



Fast-to-clinic, impact to patients

AML Research Collaboration

bluebirdbio®

Our Research Strategy in Action:
AML Program

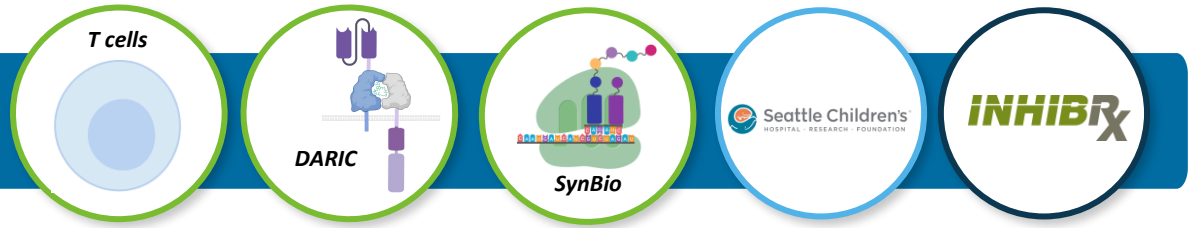
The Problem that Needs to be Solved

Targets are well documented in AML, but disease has unique characteristics where success must balance efficacy vs on-target / off-tumor toxicity

Why it Matters

AML is one of the most devastating cancers and conventional therapies have shown modest progress

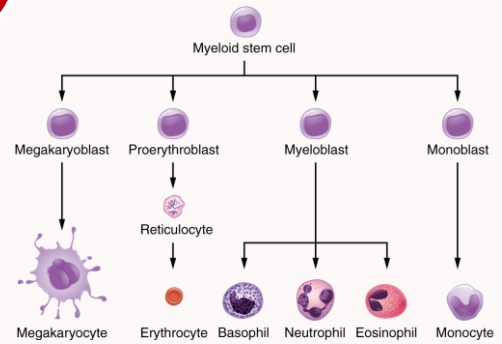
Our Un-Incremental Approach



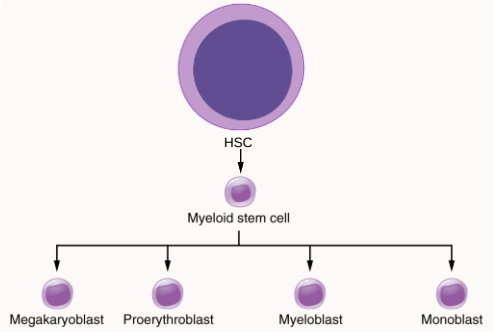
Integrate regulatable CAR architectures, multiplexed single-domain binders to tackle escape, and world-class academic partners to enable rapid clinical translation

Targeting AML is Challenging…

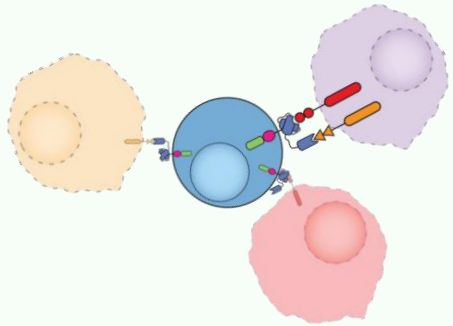
1 disease heterogeneity



2 hematopoietic risk



1 multiplex targeting

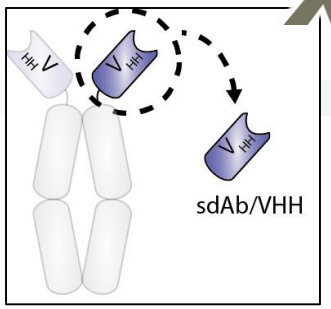


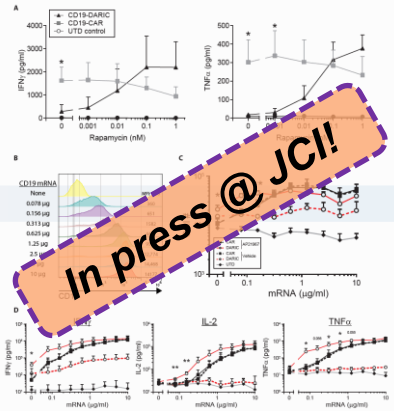
2 regulated targeting

Targeting AML is Challenging… Develop the Tech… Build a Path

Fast-to-clinic

INHIBRx



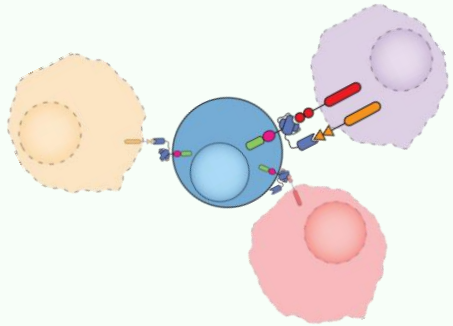


Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

CureWorks
A NEW WAY TO BETTER CURES

Solutions

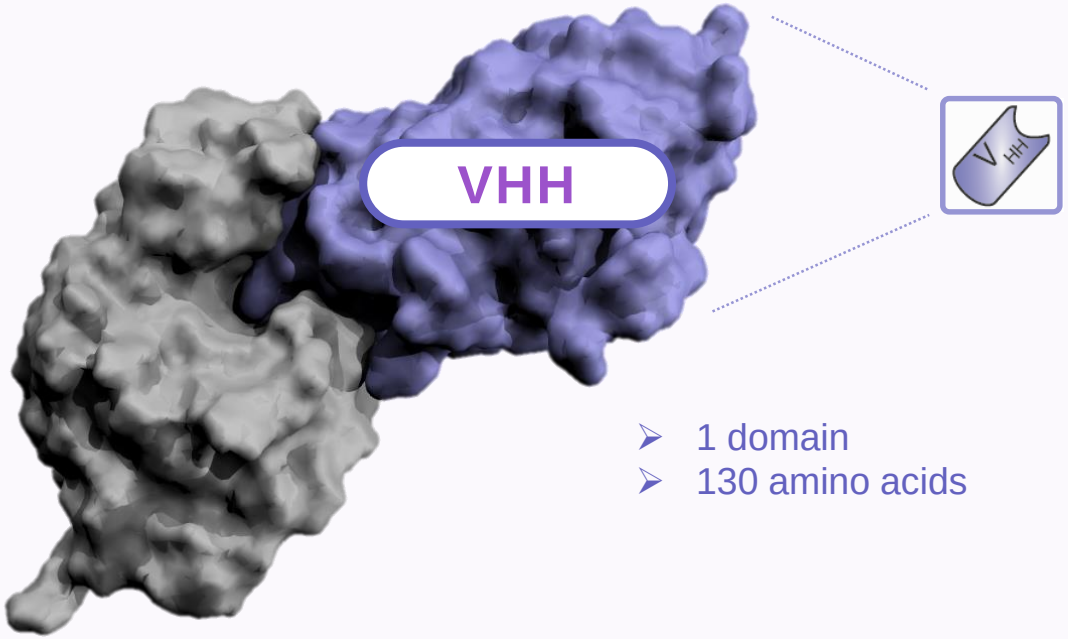
1 multiplex targeting



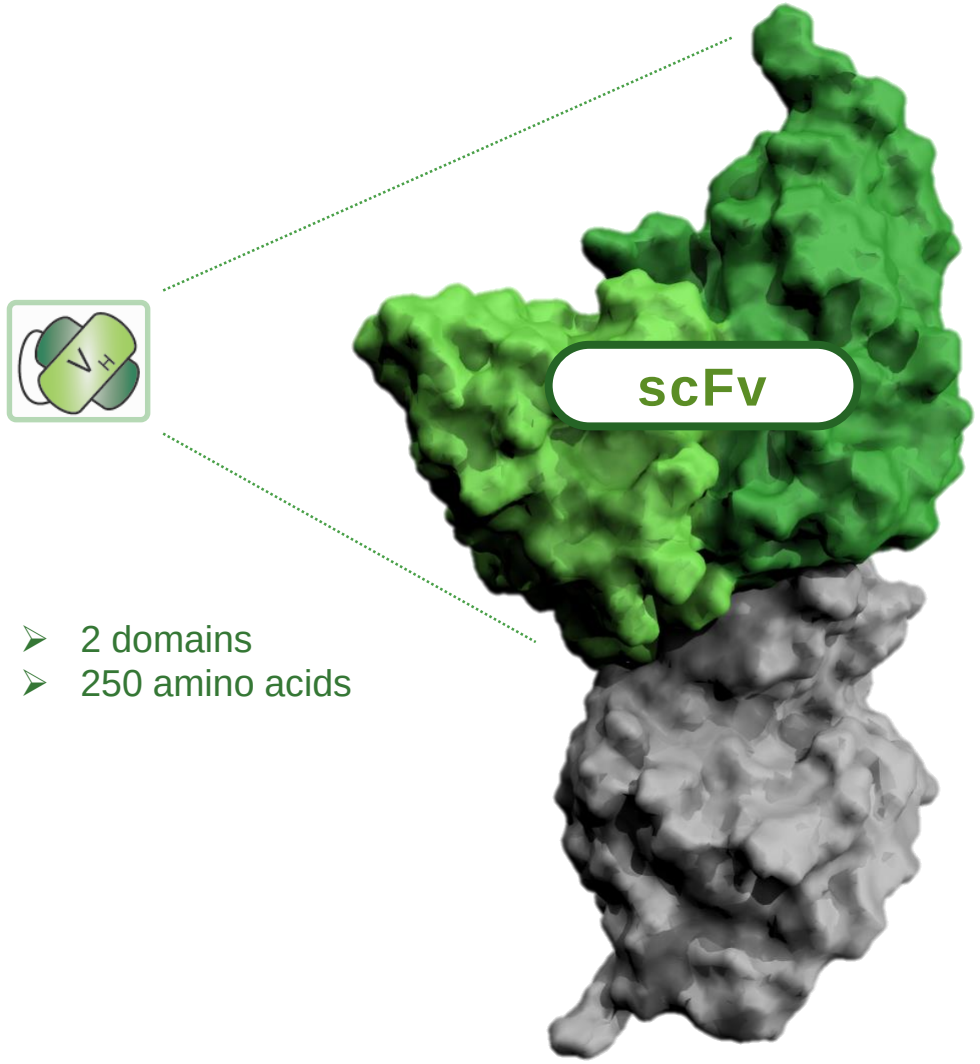
2 regulated targeting

VHH Raise the CAR Formatting Ceiling

1 multiplex targeting



- 1 domain
- 130 amino acids

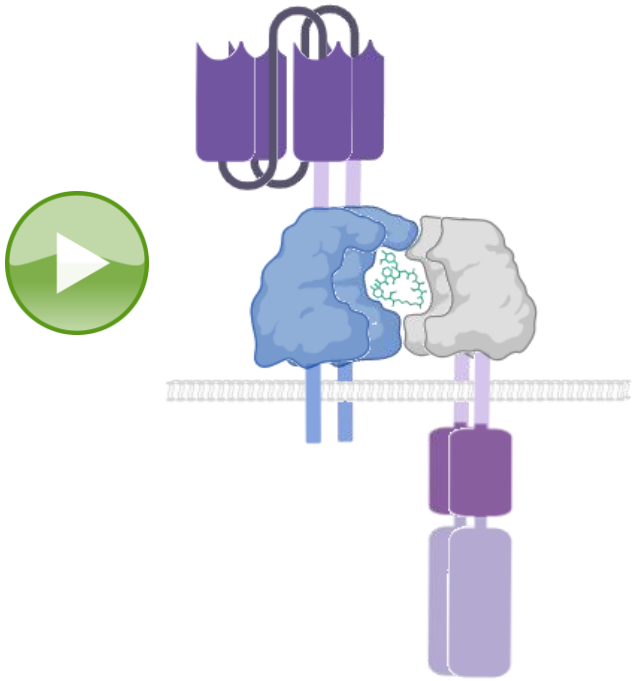


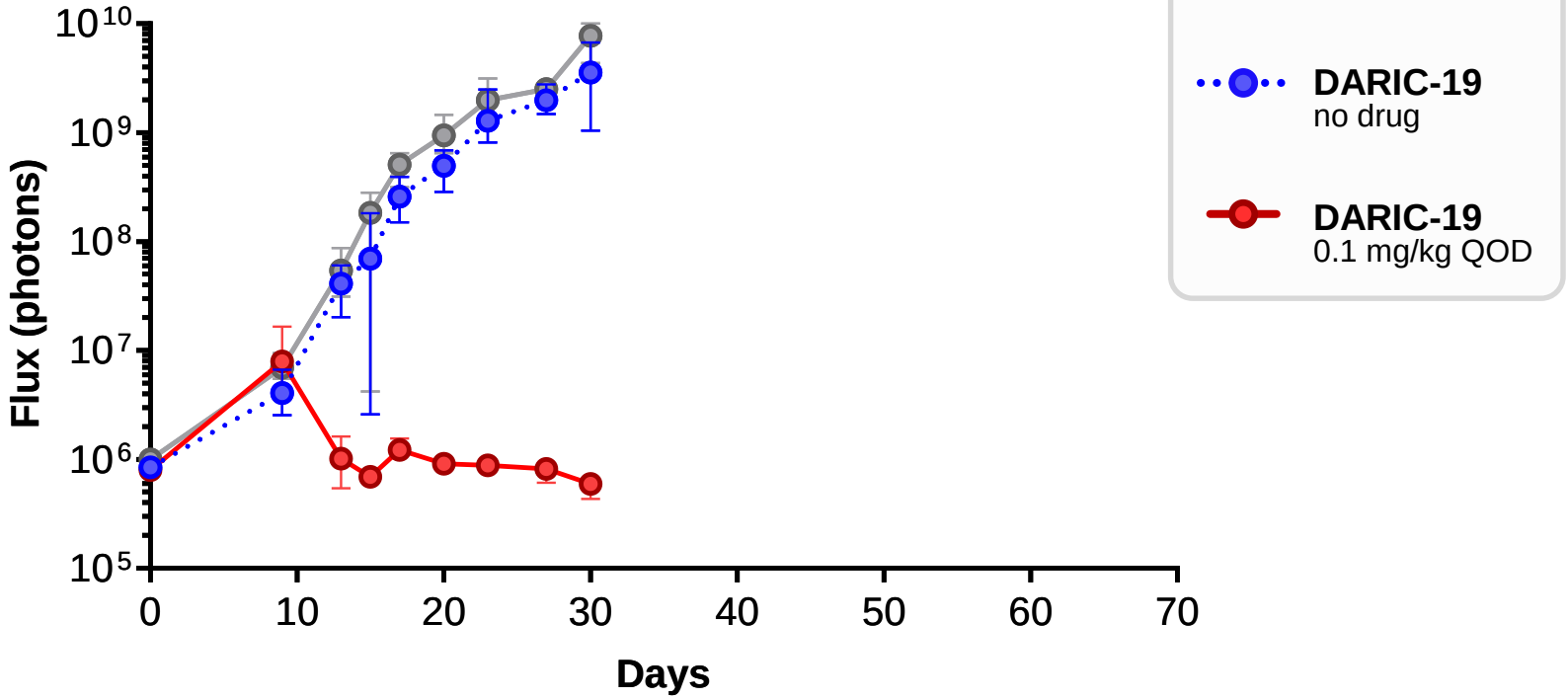
- 2 domains
- 250 amino acids

Streamlined, versatile binders that enable advanced receptor formats

DARIC T Cells Can Be Sequentially Activated and Deactivated *in vivo*

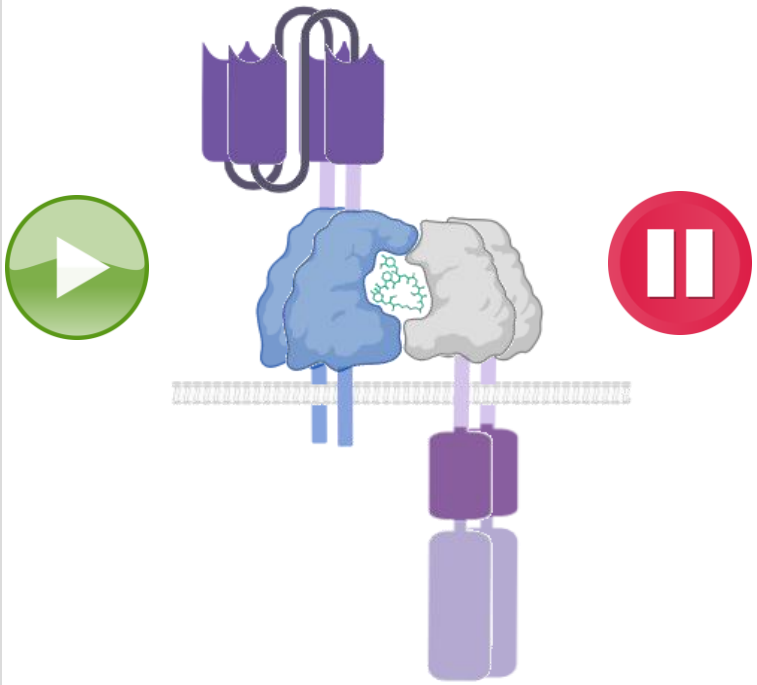
2 regulated targeting

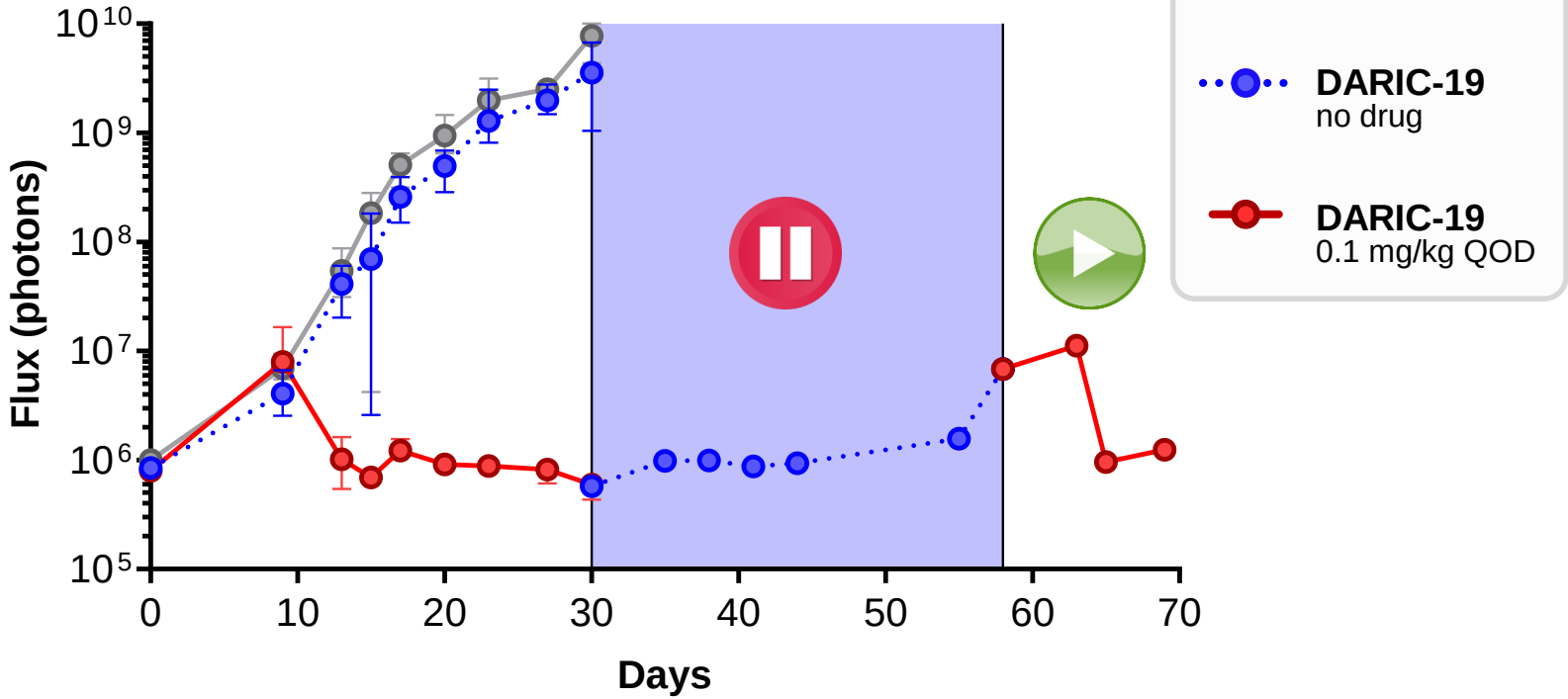




DARIC T Cells Can Be Sequentially Activated and Deactivated *in vivo*

2 regulated targeting





Highly potent, FDA-approved drug responsive, multiplex compatible

Fast-to-Clinic Strategy to Inform Product Design & Development Strategy

First-in-human exploratory clinical studies
Academic translational collaboration

- Staged multiplex candidate progression
- Regulatable CAR & 'antigen-rest' hypothesis testing

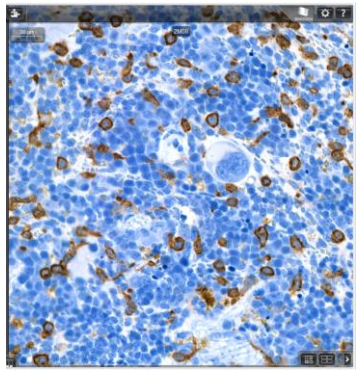
Ph1/2 Development
bbb-sponsored

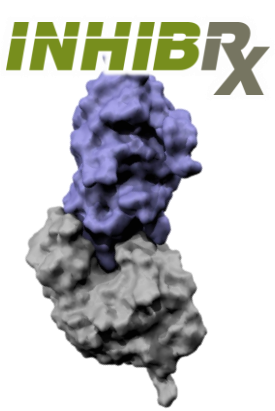
- Data-driven lead candidate expansion to suitable patients

Rapid clinical safety, efficacy, and mechanistic insight to inform best product design & development strategy

An Integrated Plan to Unlock AML

TRACTABLE SETTING → VHH BINDERS → DRUG REGULATED → FAST-TO-CLINIC





Lead targets defined	Multiplex targeting	On / off cycling	Inside-out collaboration
☑	☑	☑	☑

Hurler Syndrome (MPSI) Program

bluebirdbio®

Our Research Strategy in Action:
Hurler Syndrome (Mucopolysaccharidosis Type I)

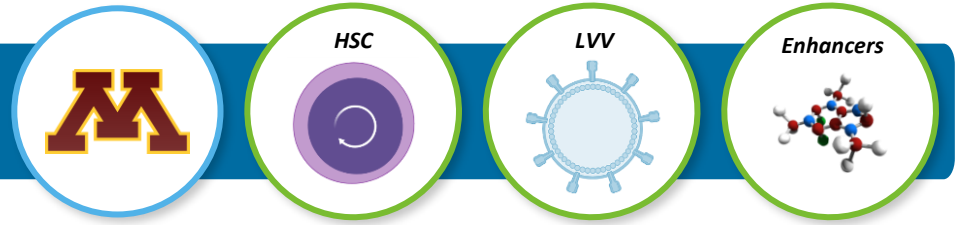
The Problem that Needs to be Solved

Ultra-rare lysosomal storage disease with neurologic impairment and likely need for over-expression of protein in the brain and periphery for full therapeutic impact

Why it Matters

The most severe MPSI patients (Hurler) are poorly served by conventional therapies (allo transplant and ERT)

Our Un-Incremental Approach



Deliver gene modified cells to the brain with high levels of gene correction leveraging the lessons learned from our HSC LVV platform

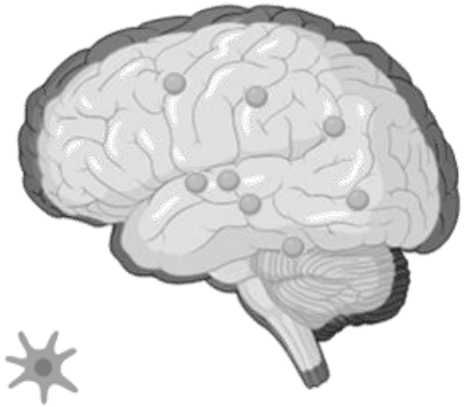
Leveraging Lessons Learned:
Lenti-D and LentiGlobin

Lenti-D:
Correction of CNS Disease

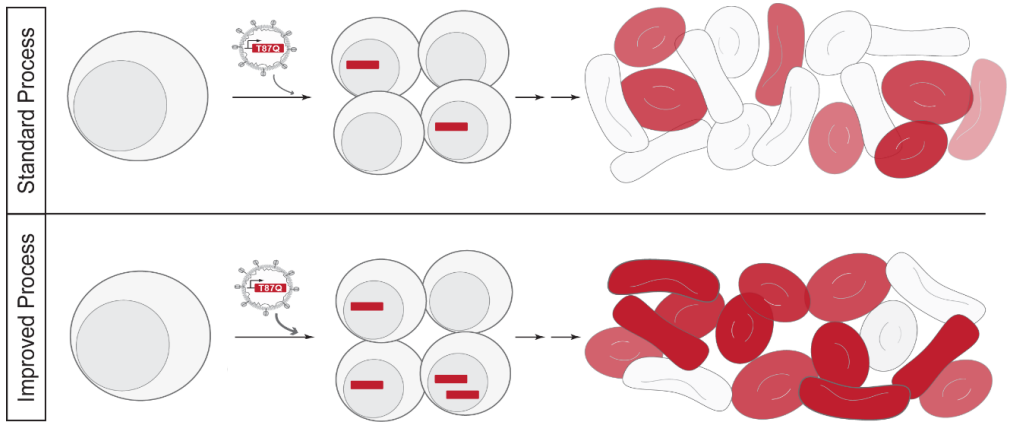
The NEW ENGLAND JOURNAL of MEDICINE

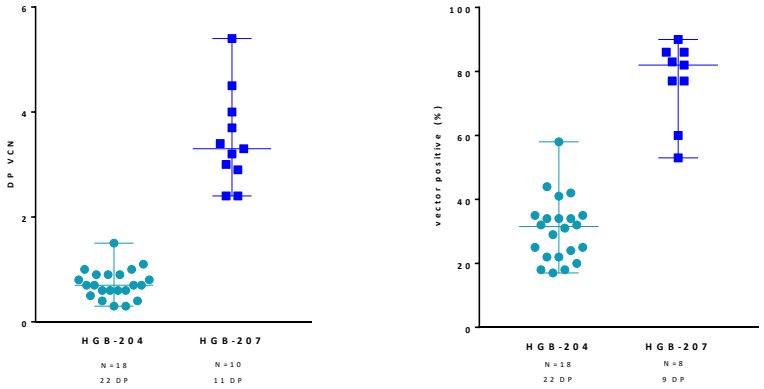
Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.



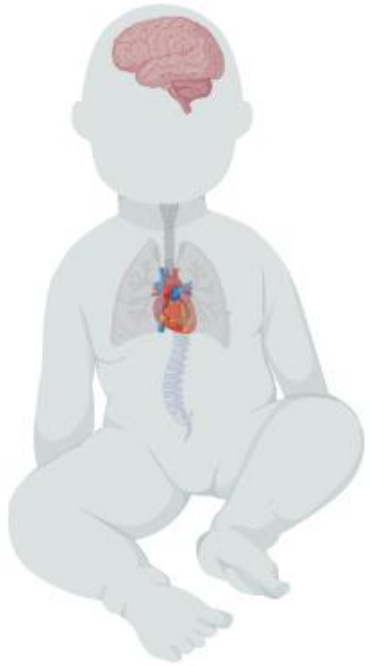
LentiGlobin:
Efficient Transduction of HSCs





Our Un-Incremental Approach to Hurler Syndrome (MPSI)

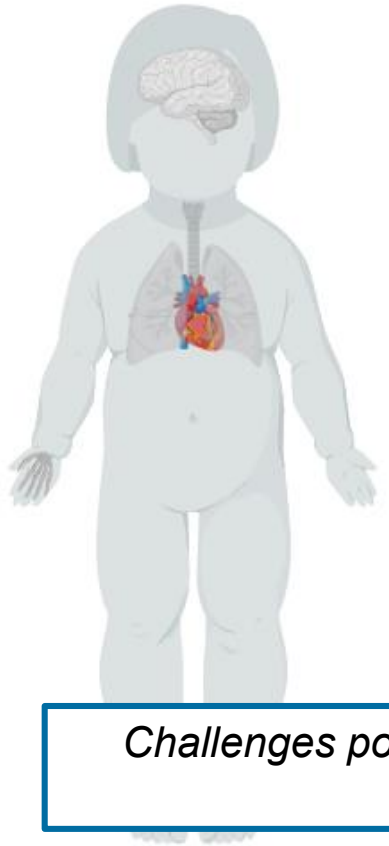
Hurler



Standard of Care:
Allogeneic HSC Transplant

Key Challenges:
- Finding a match
- Mortality risk (GVHD)
- *Need for speed* – rapid progression of disease
- May not be sufficiently ameliorative
- ERT insufficient to address neurological symptoms

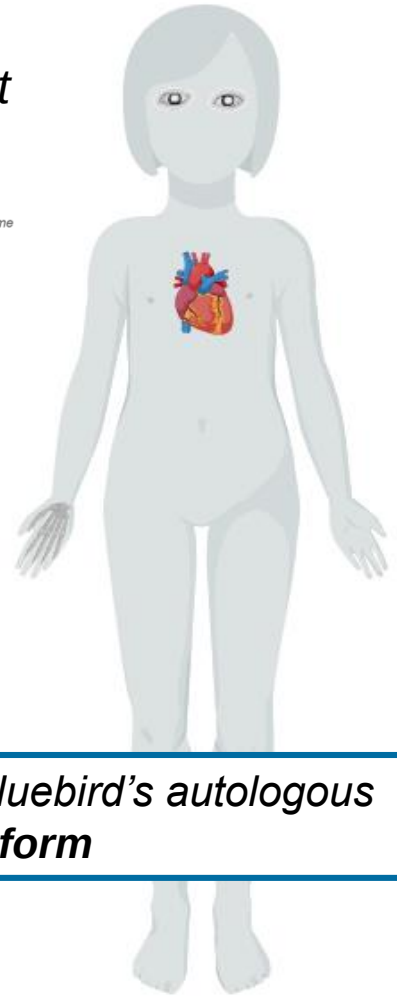
Hurler-Scheie



Standard of Care:
Enzyme Replacement Therapy

Key Challenges:
- Does not cross blood-brain barrier
- Potential for neutralizing antibodies
- Enzyme levels not sustained
- Burden of administration

Scheie

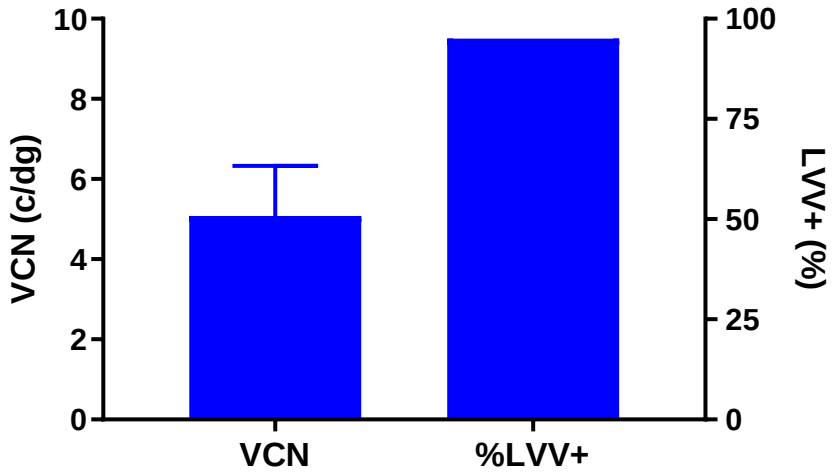


*Challenges potentially overcome with bluebird's autologous gene-modified **HSC platform***

Severity

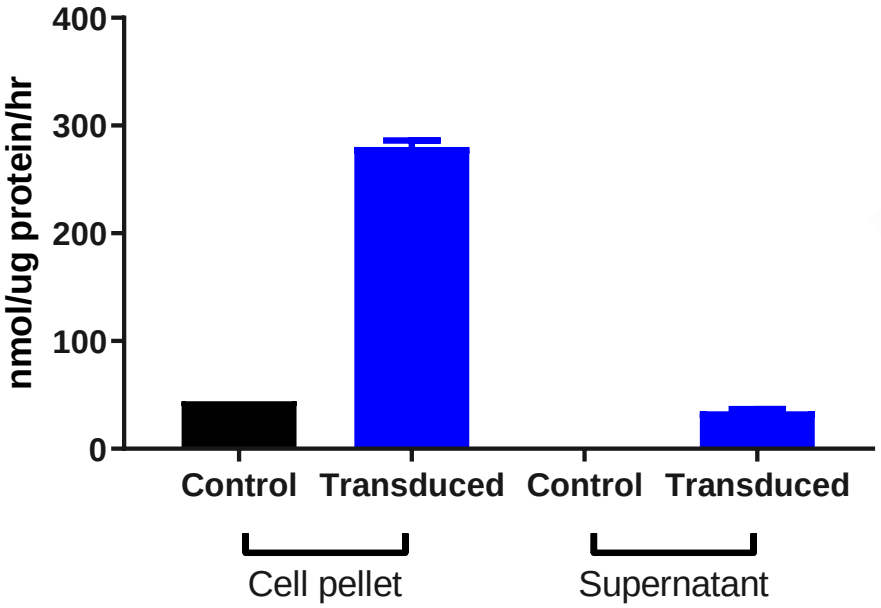
Leveraging Our HSC LVV Platform Technology:
Development of Efficient Lentiviral Vector to Overexpress IDUA

Efficiently transduce HSCs

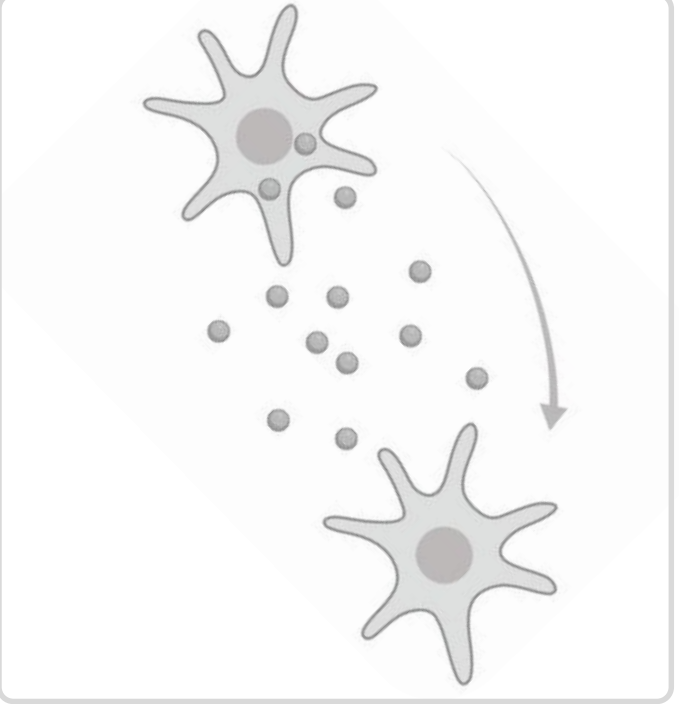


Codon optimized human IDUA
Reproducible high titers (>1e9 tu/mL)

Supraphysiological levels of IDUA

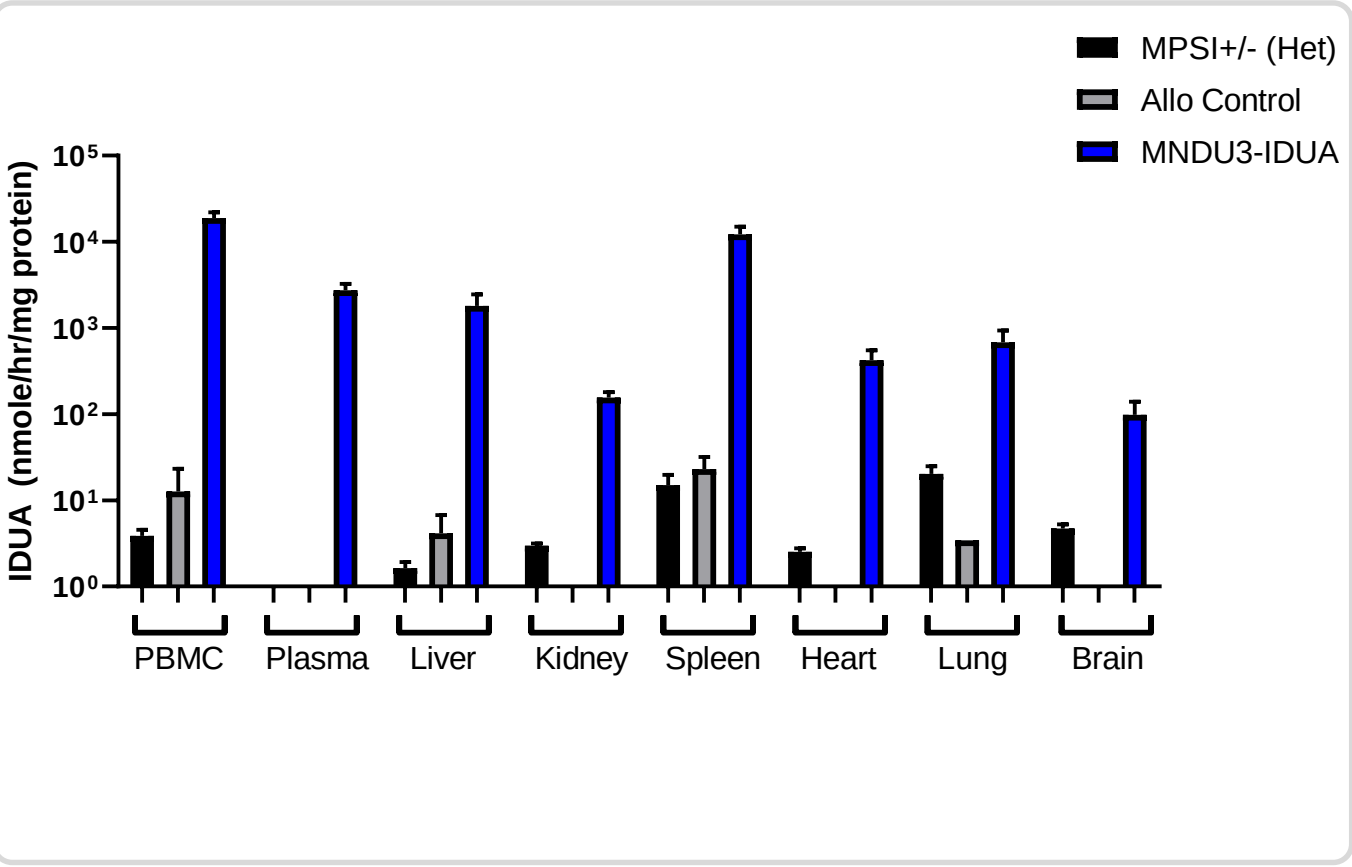


Cross-correction

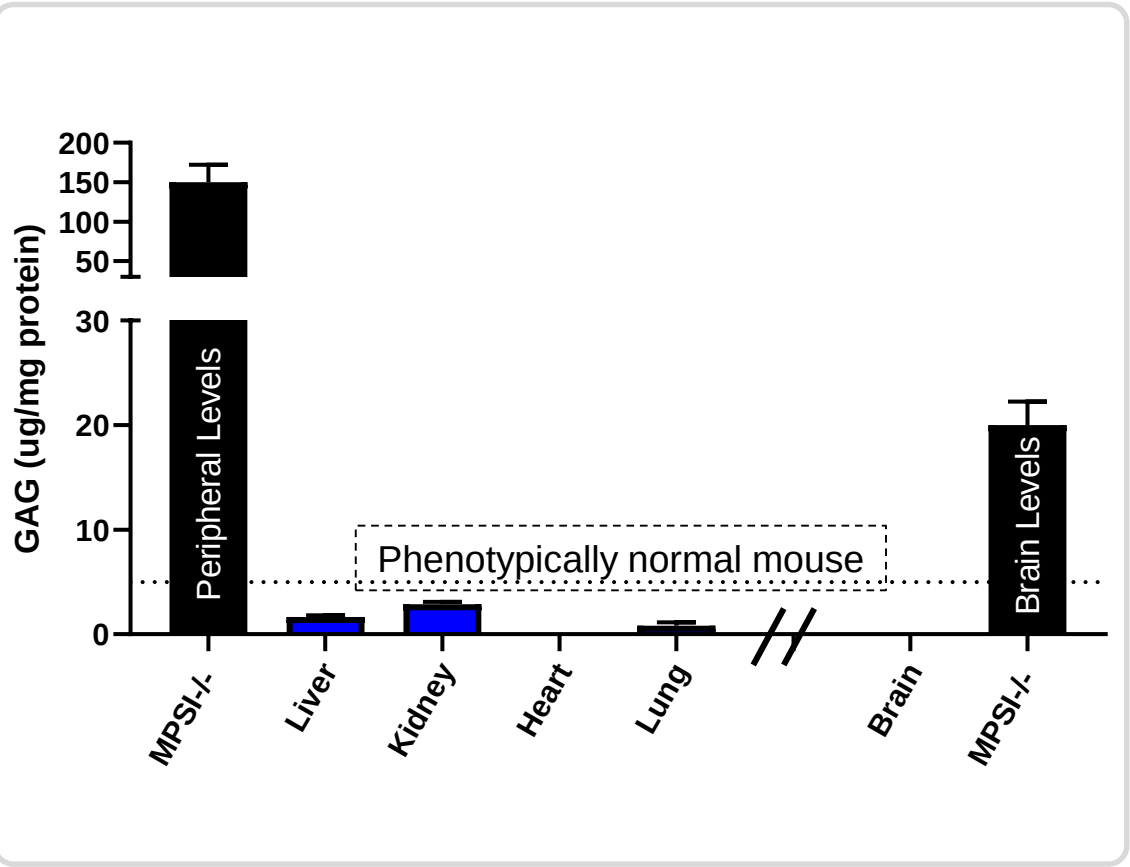


Gene-Modified HSCs Transplanted into MPSI$^{-/-}$ Mice Lead to Supraphysiological Levels of Circulating IDUA Resulting in Reduction of Glycosaminoglycans

Accumulation of IDUA in non-hematopoietic tissues

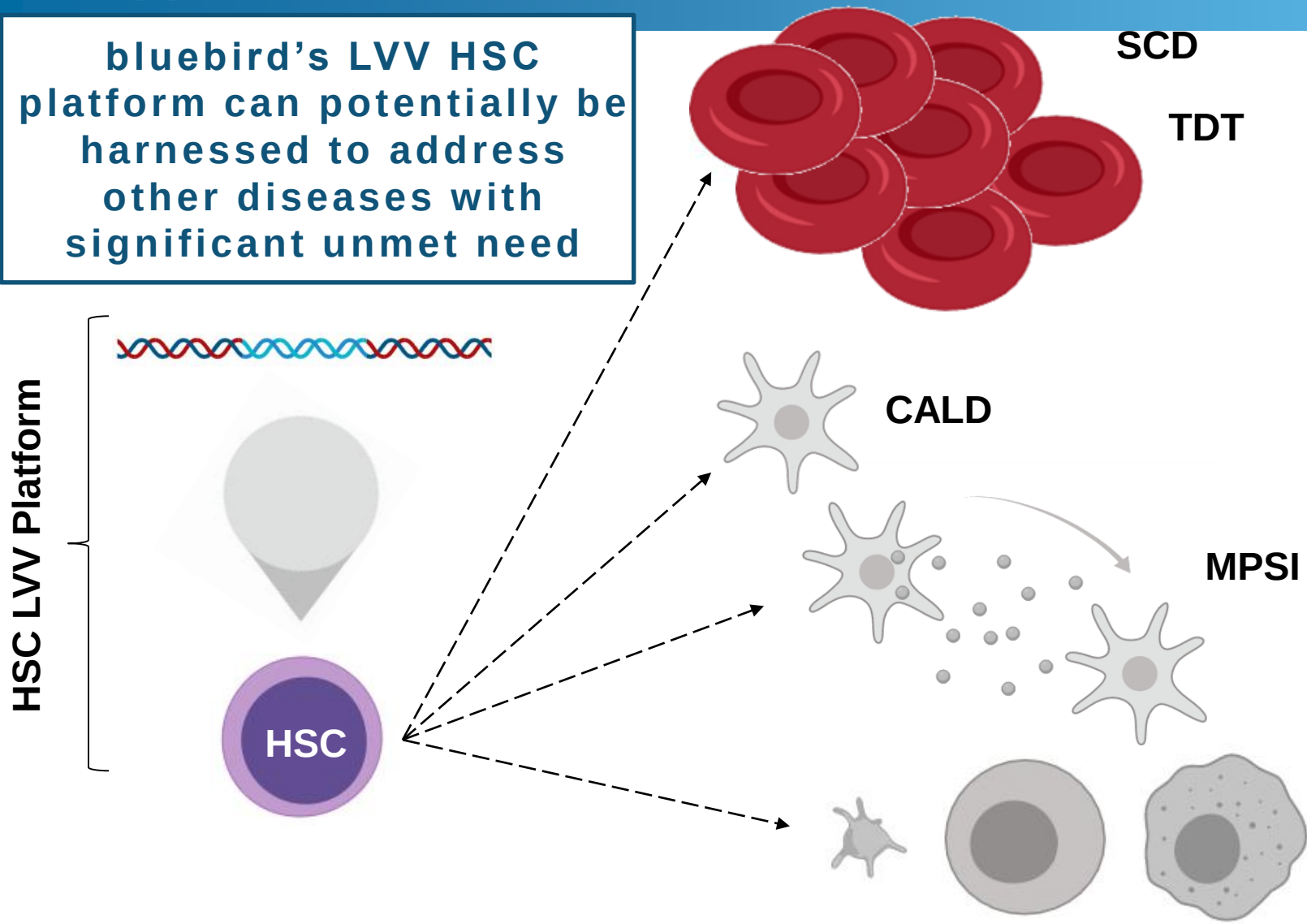


Reduction of pathological storage material in tissues to normal levels



Iterating from the Clinic:
Applications to Severe Genetic Disease Platform

bluebird's LVV HSC platform can potentially be harnessed to address other diseases with significant unmet need



Lessons from LentiGlobin:
Enhanced transduction protocol enables supraphysiological expression of secreted enzyme

Lessons from Lenti-D:
HSC LVV platform has potential in non-hematopoietic diseases where sustained CNS protein overexpression is desired