2seventy R&D Deep Dive: ASGCT and Beyond

May 19, 2023

2seventybio

Cautionary note regarding forward-looking statements

These slides and the accompanying oral presentation may contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to: statements about our plans, strategies, timelines and expectations with respect to the research, development, manufacture or sale of our product candidates, including the design, initiation, enrollment, completion and results of pre-clinical and clinical studies; timelines for the results of ongoing and planned clinical trials for our product candidates and for ABECMA (ide-cel) in additional indications; the timing or likelihood of regulatory filings and acceptances and approvals thereof; expectations as to the market size for ABECMA and any other approved product we may successfully develop; the progress and results of our commercialization of ABECMA, including our goal of increasing manufacturing capacity and improving the manufacturing process and the number of patients that are expected to be treated with ABECMA in the commercial setting and potential late line global revenue for ABECMA; anticipated revenues resulting from sales of ABECMA; statements about the efficacy and perceived therapeutic benefits of our product candidates and the potential indications and market opportunities therefor; statements about the strategic plans for 2seventy bio and potential corporate development opportunities, including manufacturing expectations and benefits received from collaborations; statements about our ability execute our strategic priorities; and expectations regarding our use of capital, expenses and other future financial results, including our net cash spend, cash runway and U.S. net revenue for ABECMA in 2023 and beyond. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, the risk that the market opportunities for our approved product or any future approved product are smaller than we believe they are; the risk that BMS, upon whom we rely for the successful development and commercialization of ABECMA does not devote sufficient resources thereto, is unsuccessful in its efforts, or chooses to terminate its agreements with us; the risk that we and/or BMS or our third party vendors will be unable to increase manufacturing and supply capacity for ABECMA; the risk that our BLAs, sBLAs and INDs will not be accepted for filing by the FDA on the timeline that we expect, or at all; the risk that our plans with respect to the preclinical and clinical development and regulatory approval of our product candidates may not be successfully achieved on the planned timeline, or at all; the risk that ABECMA will not be as commercially successful as we may anticipate; and the risk that we are unable to manage our operating expenses or cash use for operations. No forward-looking statement can be guaranteed. Forward-looking statements in these slides and the accompanying oral presentation should be evaluated together with the many risks and uncertainties that affect 2seventy bio’s business, particularly those identified in the risk factors discussion in 2seventy bio’s Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and 2seventy bio undertakes no duty to update this information unless required by law. This presentation has been prepared by 2seventy bio for the exclusive use of the party to whom the Company delivers this presentation. This presentation does not constitute an offer to sell or the solicitation of an offer to buy any securities of the Company. The information contained herein is for informational purpose and may not be relied upon in connection with the purchase or sale of any security. Neither the Company nor any of its affiliates or representatives makes any representation or warranty, expressed or implied, as to the accuracy or completeness of this presentation or any of the information contained herein, or any other written or oral communication transmitted or made available to the you or your affiliates or representatives. The Company and its affiliates and representatives expressly disclaim to the fullest extent permitted by law any and all liability based, in whole or in part, on the presentation or any information contained herein or any other written or oral communication transmitted or made available to you or your affiliates or representatives, including, without limitation, with respect to errors therein or omissions therefrom. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Agenda and Vision

Nick Leschly, chief kairos officer

The sole mission of 2seventy is to “unleash the curative potential of the T cell”

Our experience in drug development and deep execution capabilities in cell therapy allow us to design & deliver multi-layered, multi-modality T cell-based solutions that have the potential to address and overcome the immunologically evasive and suppressive properties of tumors.

2seventy – At a Glance

BMS 50/50 US
$297M 2022 / $470-570M 2023*
Potential $2-3B US Peak

ABECMA®
Capacity Expansion
Predictable Delivery

3rd Line K3 & FDA Submission
Initiation of Front Line K9

ABECMA
Commercial

ABECMA
Development

Unleash Curative Potential of T cells

People & Culture & Experience

Next Gen T cell Engineering Toolkit &
Clinical POC Insight Engine

Clinical Heme
B-NHL & AML

Clinical Solid
MUC & More (REGN)

Horizon Dev
In-Vivo Editing (Novo)
In-Vivo CARs

Suspension LVV Mftg
In-House Clinical DP Mftg (270-MPH)
Next Gen Mftg Improvements

ABECMA profitable in 2023**

Cash runway into 2026**

425 employees

*Anticipated revenue, US topline revenue, profit and loss shared 50/50 with BMS
**Projected, based on current operating plan and anticipated revenue

B-NHL: B-cell non-Hodgkin lymphoma
AML: acute myeloid leukemia

2seventybio

Agenda

TOPIC	SPEAKER
Corporate Strategy and Vision	Nick Leschly, chief kairos officer
ABECMA Clinical, Operational and Financial Progress	Chip Baird, chief financial officer
Advances Across Pipeline and Internal DP Manufacturing	Philip Gregory, D.Phil., chief scientific officer
AML Clinical and Preclinical Developments	Steve Bernstein, M.D., chief medical officer Steve Shamah, Ph.D., SVP, oncology research
Ex Vivo and In Vivo Gene Editing Applications	Mike Certo, Ph.D., VP, head of genome editing
Wrap-Up and Questions	All

ABECMA and R&D Financial Overview

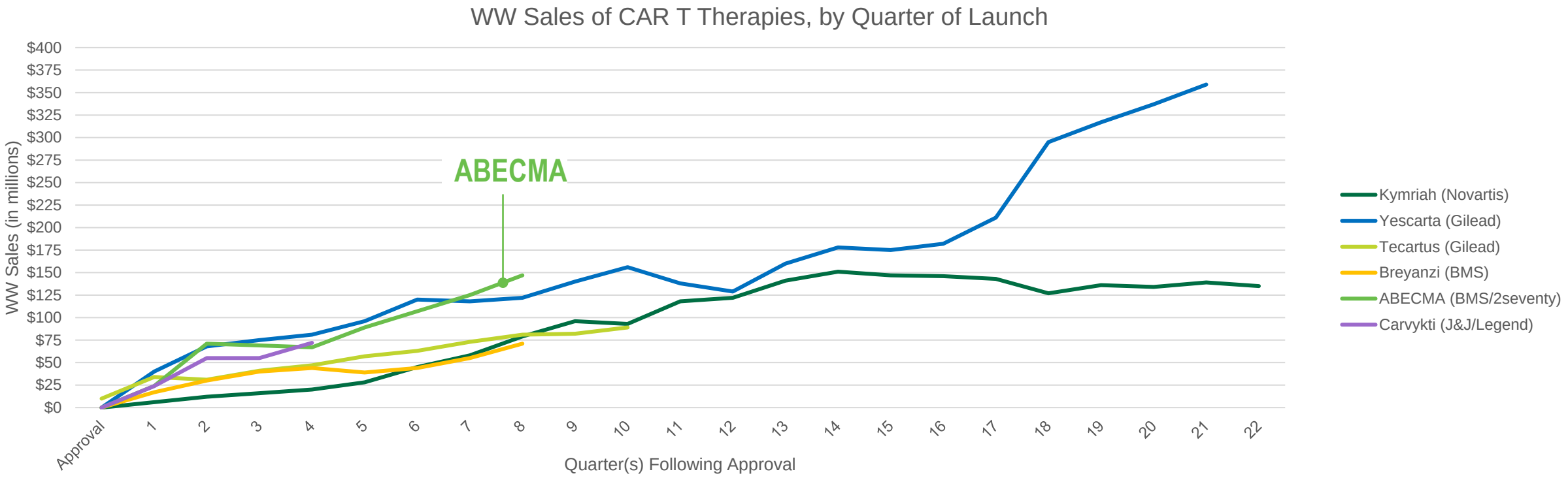
Chip Baird, chief financial officer

ABECMA and Financial Overview

Four key takeaways…

1. ABECMA continues to achieve strong revenue growth
2. ABECMA is cash flow positive with improving margins
3. ABECMA has an attractive and long-term commercial trajectory
4. 2seventy is efficient with its R&D investment

ABECMA launch growth trajectory driven by efficacy profile, strong patient demand, and manufacturing step-ups



Average Annual Growth Rate	Year 2	Year 3	Year 4	Year 5
	94%	49%	29%	33%

Class CAGR for years 3-5: 37%

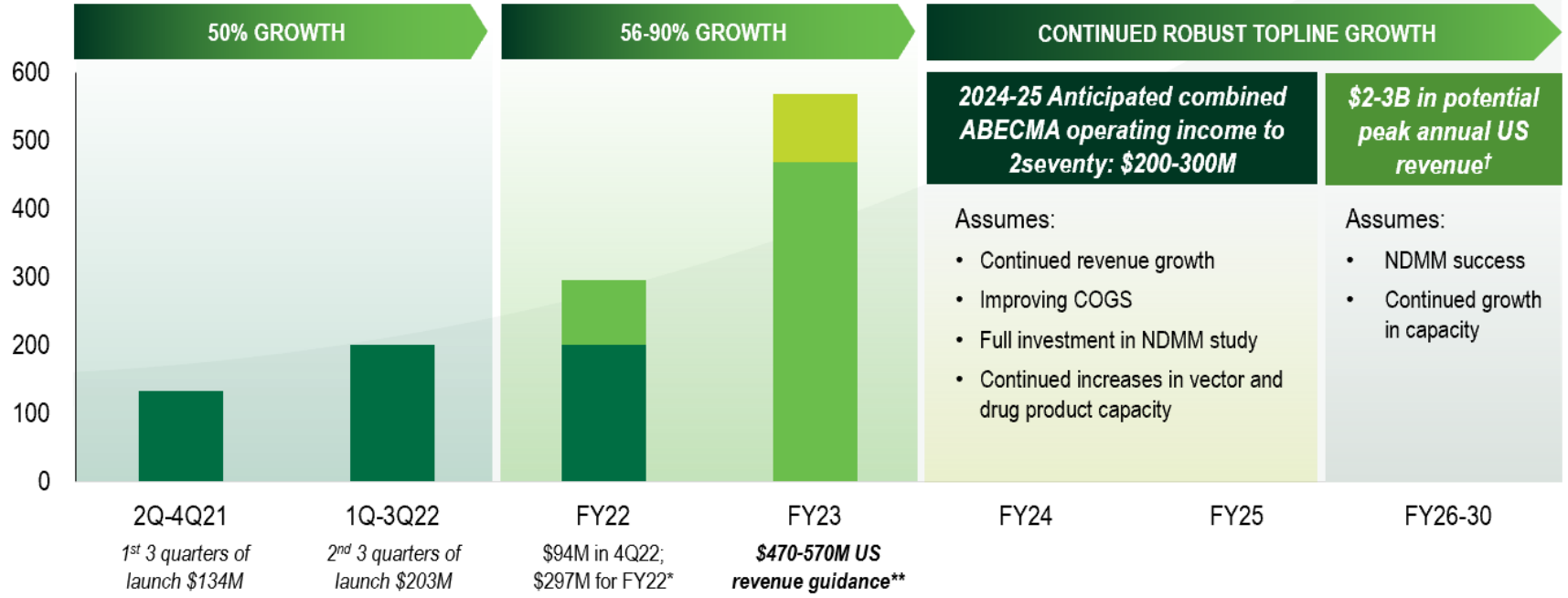
Source: Company filings

2seventybio

Strong start to 2023 for ABECMA

ABECMA Financial Outlook

Strong US revenue growth. Blockbuster potential.
2024-25 cashflow significantly reduces future capital needs.



*US ABECMA profit and loss shared 50/50 between 2seventy and BMS as part of the collaboration agreement
**Anticipated revenue based on current operating plan
†based on continued label expansion into earlier lines of therapy and growth in manufacturing capacity

3

2seventybio

May 2023 update

- **Cash flow positive in 1Q23**
- On track to achieve upper end of $470-570M* revenue guidance
- Second aLVV suite approved; on track for sLVV approval in 1H24
- Successful DP step-up complete; additional step-ups on track for 2023
- **$200-300M of operating income expected for the 2024-25 timeframe****

2seventybio

Real-world MM treatment decisions are practical and patient-driven

Efficacy
Potential for deep and durable response

Availability
Slot availability in the relevant time frame

Safety
Predictable and manageable side-effect profile

Turn-around time
Speed to manufacturing and deliver patient cells

Real World Experience
Physician real-world experience with the product

Out of Spec Risk
Percentage of time cells are out of spec

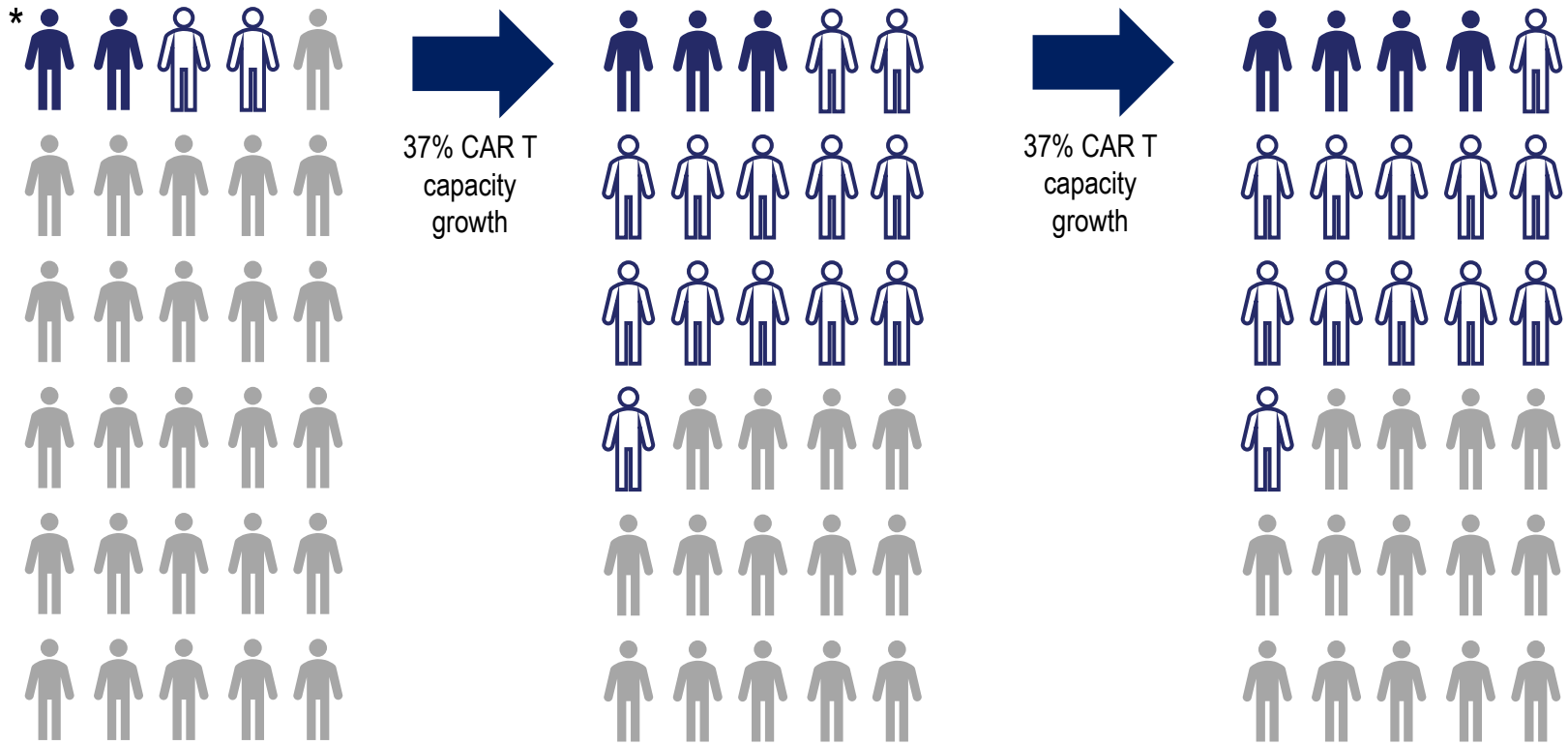
End-to-End Patient and Provider Experience

Select ABECMA Launch Metrics
Through Dec 2022

- Over 1,100 US commercial patients treated since launch
- ~70 treatment centers online in the U.S.; additional centers planned in 2023
- 85-90% average in-spec manufacturing success since launch
- ~30-day average turn-around-time

Assuming capacity growth in-line with CD-19 experience, more than half of eligible patients will not have access to a CAR T in 2025

Illustrative US Multiple Myeloma CAR T Capacity Growth Scenario



Assumptions and Methodology

- 30,000 US MM patients
- 2023 patients treated based on analyst estimates for commercially approved BCMA CAR Ts
- 2024 & 2025 patients treated based on 37% annual growth from 2023 levels
- Assumes commercially approved BCMA CAR Ts achieve 3L+ label by end of 2023

2023 (5L+) | **2024 (3L+)** | **2025 (3L+)** | **2026-30 (label expansion)**

*Each figure = ~1,000 patients

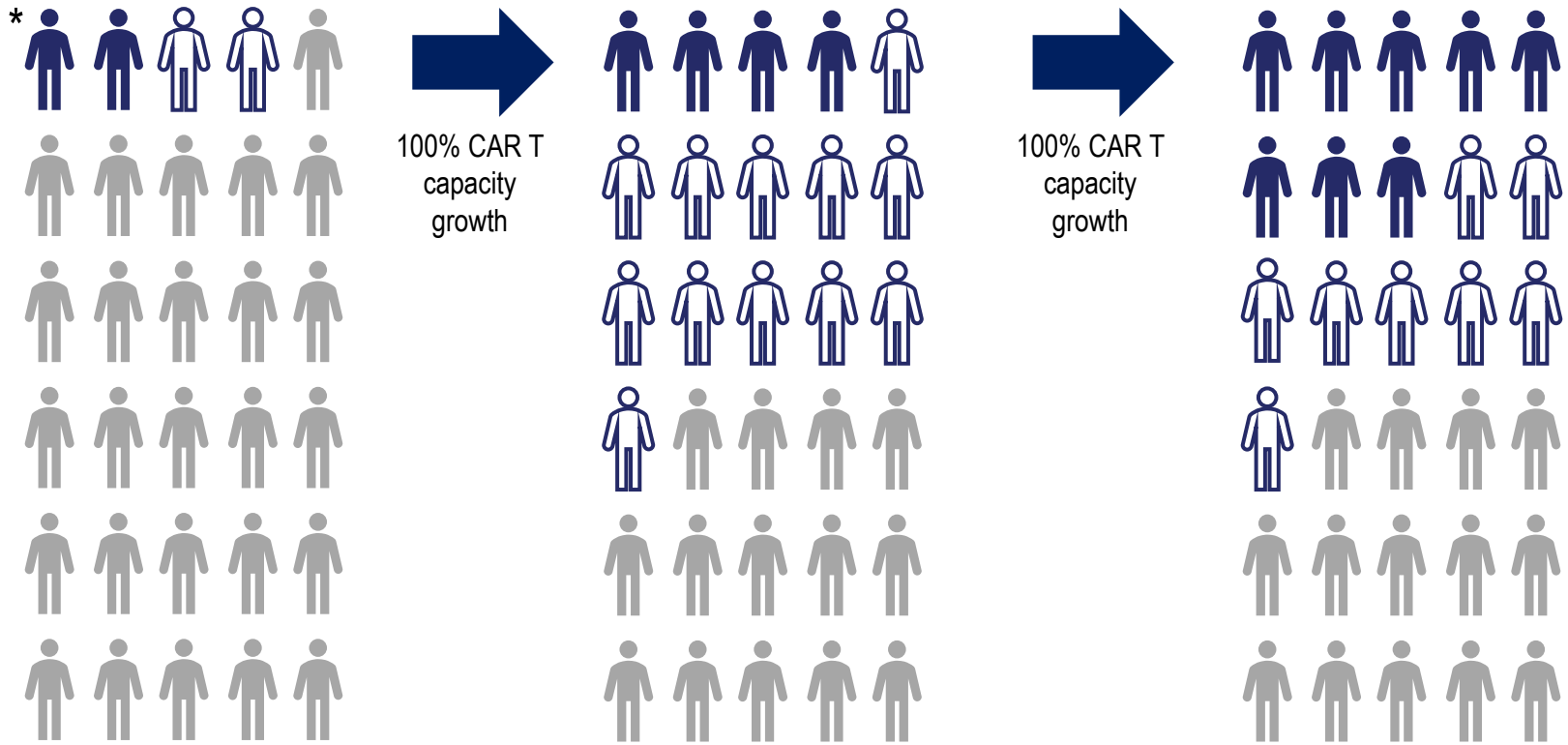
= RRMM patients treated with CAR T

= RRMM patients eligible for CAR T but cannot be served due to capacity constraint

= not eligible for CAR T

Even with 100% annual growth in commercial capacity, 50% of eligible patients will not be able to receive a CAR T in 2025

Illustrative US Multiple Myeloma CAR T Capacity Growth Scenario



Assumptions and Methodology

- 30,000 US MM patients
- 2023 patients treated based on analyst estimates for commercially approved BCMA CAR Ts
- 2024 & 2025 patients treated based on 100% annual growth from 2023 levels
- Assumes commercially approved BCMA CAR Ts achieve 3L+ label by end of 2023

2023 (5L+) | **2024 (3L+)** | **2025 (3L+)** | **2026-30 (label expansion)**

*Each figure = ~1,000 patients

= RRMM patients treated with CAR T

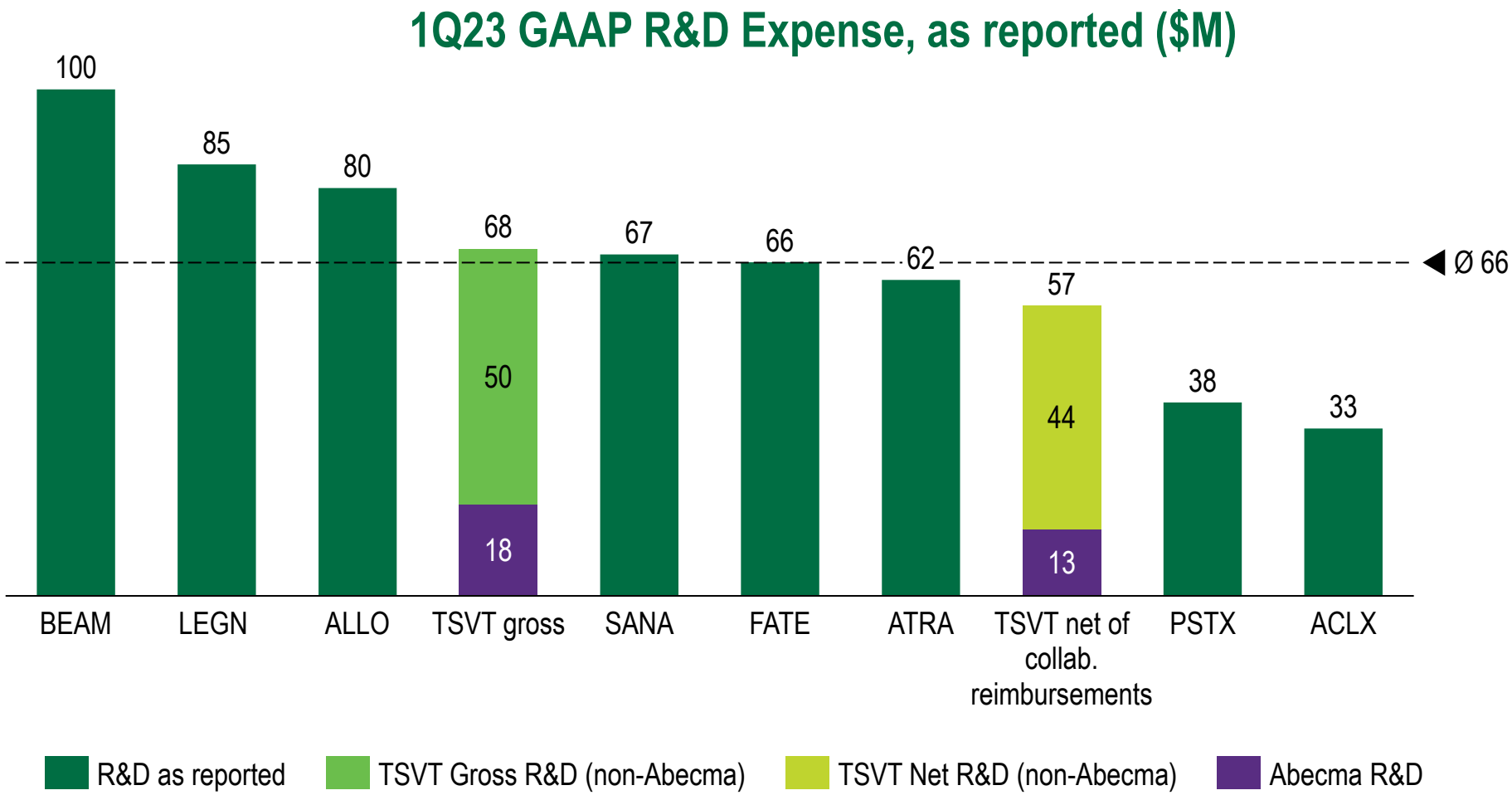
= RRMM patients eligible for CAR T but cannot be served due to capacity constraint

= not eligible for CAR T

2seventybio

R&D Spend in Context

Disciplined investment across the portfolio to drive innovation



- R&D supported by $11M of funding support from BMS, REGN, and Novo
- Gated approach to capital allocation
- Win-or-go-home study design
- ABECMA commercial cash flows fund increasing share of R&D over time

Advances Across Pipeline and Internal DP Manufacturing

Philip Gregory, D.Phil., chief scientific officer

2seventy bio's R&D philosophy

Identify the Key Problem

Understand **tumor** resistance
Explore new biology
Focus on the **hard problem**

Layer Innovations

Define clear hypotheses
Deploy our **unique** toolbox
Deliver **multi-nodal** solutions

Learn Fast in the Clinic

270-MPH (Internal DP Mfg)
Turbo-charge Clin. Translation
Operational **flex & efficiency**

Accelerate with Industry Leading Partnerships

Bristol Myers Squibb · gritstone ONCOLOGY · INHIBRX · 药明巨诺 JW Therapeutics · medigene · novo nordisk® · REGENERON

Our Innovation Ecosystem

~10 years in the making

Layer Innovations

Define clear hypotheses
Deploy our unique toolbox
Deliver multi-nodal solutions

DIMENSION	CAPABILITIES	TECHNOLOGY
TARGETING ARCHITECTURE	BINDER TECHNOLOGIES ADVANCED SCREENING PROTEIN ENGINEERING TUMOR IMMUNOLOGY	CAR, TCR, CCR, DARIC
RECEPTOR SIGNALING	megaTAL PLATFORM PROTEIN ENGINEERING CELL/DRUG PHARMACOLOGY MOLECULAR IMMUNOLOGY	ENHANCED, COSTIM, REGULATED
POTENCY ENHANCEMENT	megaTAL PLATFORM PROTEIN ENGINEERING IN VIVO MODELING MOLECULAR IMMUNOLOGY	TME, BIOLOGICS, EXHAUSTION (IL15*)
CELL CHASSIS	IN VIVO PHARMACOLOGY PROCESS INNOVATION CELLULAR IMMUNOLOGY APPLIED IMMUNOLOGY	ab T CELLS, gd T CELLS, NK CELLS, METABOLISM, PROCESS

WORLD CLASS mRNA & LVV VECTOROLOGY / MANUFACTURING

2seventybio

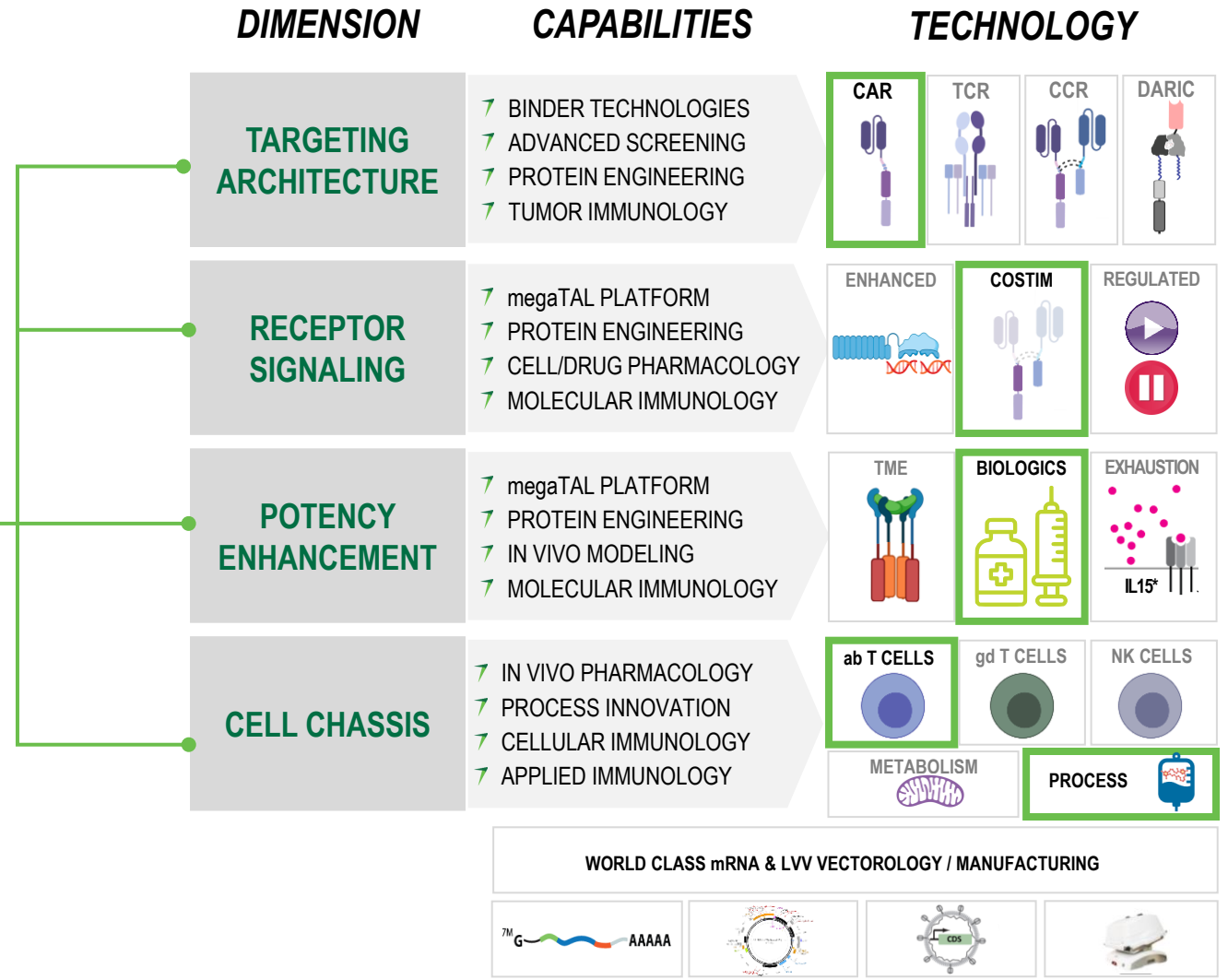
Our Innovation Ecosystem

~10 years in the making

Solid Tumor Example: MUC16

Layer Innovations

Define clear hypotheses
Deploy our unique toolbox
Deliver multi-nodal solutions



2seventybio

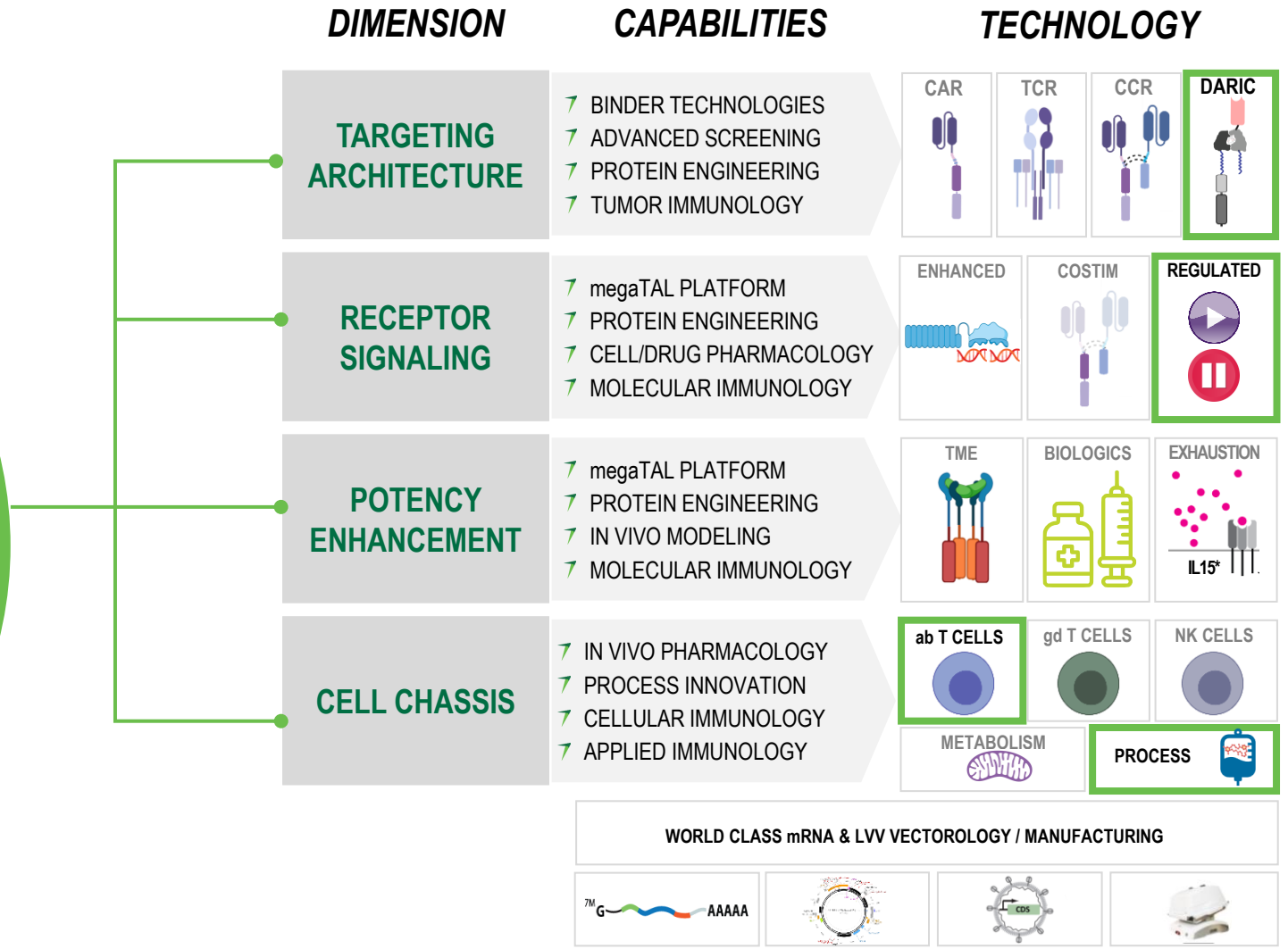
Our Innovation Ecosystem

~10 years in the making

Example: SC-DARIC33

Layer Innovations

Define clear hypotheses
Deploy our unique toolbox
Deliver multi-nodal solutions



2seventybio

Our Innovation Ecosystem

~10 years in the making

Example: NG-AML – 27T32

Layer Innovations

Define clear hypotheses
Deploy our unique toolbox
Deliver multi-nodal solutions

DIMENSION	CAPABILITIES	TECHNOLOGY
TARGETING ARCHITECTURE	BINDER TECHNOLOGIES ADVANCED SCREENING PROTEIN ENGINEERING TUMOR IMMUNOLOGY	CAR, TCR, CCR, DARIC, DUAL
RECEPTOR SIGNALING	megaTAL PLATFORM PROTEIN ENGINEERING CELL/DRUG PHARMACOLOGY MOLECULAR IMMUNOLOGY	ENHANCED, COSTIM, REGULATED, RESET
POTENCY ENHANCEMENT	megaTAL PLATFORM PROTEIN ENGINEERING IN VIVO MODELING MOLECULAR IMMUNOLOGY	TME, BIOLOGICS, EXHAUSTION (IL15*)
CELL CHASSIS	IN VIVO PHARMACOLOGY PROCESS INNOVATION CELLULAR IMMUNOLOGY APPLIED IMMUNOLOGY	ab T CELLS, gd T CELLS, NK CELLS, METABOLISM, PROCESS

WORLD CLASS mRNA & LVV VECTOROLOGY / MANUFACTURING

2seventybio

2seventy bio's NEW in-house manufacturing facility (270-MPH)
The heart of our translational cell therapy engine

Enable Fully Integrated Translational Cell Therapy Platform

- Enables manufacture and release of drug product for multiple Phase I clinical trials
- Co-located @ 60 Binney with research, PD and analytics
- Anticipated ~300 patients/year capacity
- Accelerates product development learnings and iteration

Enhance Clinical Study Flexibility, Speed and Efficiency

- Provides clinical slot flexibility and faster patient data turnaround/analysis
- Shortens DP turnaround time and enables efficient monitoring/trouble shooting
- Significant costs savings through Phase 1 compared to CDMO costs

Facility qualification nearing completion and we expect to be fully GMP operational by summer 2023

Innovative cell therapy candidates targeting broad potential indications

INDICATION [DRUG]	TARGET	TECHNOLOGY	DISCOVERY STAGE R&D	IND-ENABLING PRECLINICAL STUDIES	CLINICAL STUDIES	APPROVED PRODUCTS
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Approved in 5L+			Abecma
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Earlier Line Studies			3L+ potential approval 2023 NDMM study initiation 2023
AML-Pediatric [SC-DARIC33]	CD33	Drug-Regulated; CAR T cell (DARIC)	TSVT Owned; SCRI Collaboration			Patients Enrolling; Update mid 2023
B-NHL [bbT369]	CD79a CD20 CBLB Edit	Dual-Targeted CAR T cell Signal Enhanced Gene Edited	TSVT Owned			Patients Enrolling; Update in 2023
Ovarian Cancer	MUC16	CAR T cell Pharmacologic Enhancements	REGN Collaboration		IND potential EOY 2023	
Solid Tumors	MAGE-A4	TCR T cell Potency Enhanced	REGN/JW Collaboration		IIT potential EOY 2023 (JW / China)	
AML-Adult [SC-DARIC33 Next-Gen]	CD33 CLL-1	Drug-Regulated RESET T cell Dual-Targeted Potency Enhanced	TSVT Owned			
Solid Tumors	Multiple	CAR / TCR T cell Potency Enhanced	Multiple TSVT Owned; Plus Regeneron Collab.			
Multiple Myeloma	Multiple	Multi-Targeted CAR T cell Potency Enhanced	TSVT Owned			
Additional Indications	Undisclosed	Multiple	Multiple TSVT Owned; Plus Novo Nordisk Collab.			

Product engine generating ~1+ INDs per year

*Investigational New Drug application – IND;
Investigator Initiated Trial – IIT; Newly Diagnosed Multiple Myeloma – NDMM

Collaboration program
TSVT-owned program

MUC16 and MAGE-A4 solid tumor programs are on track for 2023 milestones

INDICATION [DRUG]	TARGET	TECHNOLOGY	DISCOVERY STAGE R&D	IND-ENABLING PRECLINICAL STUDIES	CLINICAL STUDIES	APPROVED PRODUCTS
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Approved in 5L+			Abecma
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Earlier Line Studies			3L+ potential approval 2023 NDMM study initiation 2023
AML-Pediatric [SC-DARIC33]	CD33	Drug-Regulated; CAR T cell (DARIC)	TSVT Owned; SCRI Collaboration			Patients Enrolling; Update mid 2023
B-NHL [bbT369]	CD79a CD20 CBLB Edit	Dual-Targeted CAR T cell Signal Enhanced Gene Edited	TSVT Owned			Patients Enrolling; Update in 2023
Ovarian Cancer	MUC16	CAR T cell Pharmacologic Enhancements	REGN Collaboration		IND potential EOY 2023	
Solid Tumors	MAGE-A4	TCR T cell Potency Enhanced	REGN/JW Collaboration		IIT potential EOY 2023 (JW / China)	
AML-Adult [SC-DARIC33 Next-Gen]	CD33 CLL-1	Drug-Regulated RESET T cell Dual-Targeted Potency Enhanced	TSVT Owned			
Solid Tumors	Multiple	CAR / TCR T cell Potency Enhanced	Multiple TSVT Owned; Plus Regeneron Collab.			
Multiple Myeloma	Multiple	Multi-Targeted CAR T cell Potency Enhanced	TSVT Owned			
Additional Indications	Undisclosed	Multiple	Multiple TSVT Owned; Plus Novo Nordisk Collab.			

Product engine generating ~1+ INDs per year

*Investigational New Drug application – IND;
Investigator Initiated Trial – IIT; Newly Diagnosed Multiple Myeloma – NDMM

Collaboration program
TSVT-owned program

Programs featured today

INDICATION [DRUG]	TARGET	TECHNOLOGY	DISCOVERY STAGE R&D	IND-ENABLING PRECLINICAL STUDIES	CLINICAL STUDIES	APPROVED PRODUCTS
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Approved in 5L+			Abecma
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Earlier Line Studies			3L+ potential approval 2023 NDMM study initiation 2023
AML-Pediatric [SC-DARIC33]	CD33	Drug-Regulated; CAR T cell (DARIC)	TSVT Owned; SCRI Collaboration			Patients Enrolling; Update mid 2023
B-NHL [bbT369]	CD79a CD20 CBLB Edit	Dual-Targeted CAR T cell Signal Enhanced Gene Edited	TSVT Owned			Patients Enrolling; Update in 2023
Ovarian Cancer	MUC16	CAR T cell Pharmacologic Enhancements	REGN Collaboration		IND potential EOY 2023	
Solid Tumors	MAGE-A4	TCR T cell Potency Enhanced	REGN/JW Collaboration		IIT potential EOY 2023 (JW / China)	
AML-Adult [SC-DARIC33 Next-Gen]	CD33 CLL-1	Drug-Regulated RESET T cell Dual-Targeted Potency Enhanced	TSVT Owned			
Solid Tumors	Multiple	CAR / TCR T cell Potency Enhanced	Multiple TSVT Owned; Plus Regeneron Collab.		Product engine generating ~1+ INDs per year	
Multiple Myeloma	Multiple	Multi-Targeted CAR T cell Potency Enhanced	TSVT Owned			
Additional Indications	Undisclosed	Multiple	Multiple TSVT Owned; Plus Novo Nordisk Collab.			

*Investigational New Drug application – IND;
Investigator Initiated Trial – IIT; Newly Diagnosed Multiple Myeloma – NDMM

Collaboration program
TSVT-owned program

What you will hear today

Clinical progress with SC-DARIC33 in patients with AML

- First regulatable CAR T cell data from the clinical trial*
- Key questions we will address:
  - *Initial safety and tolerability?*
  - *Can we dose RAPA to target levels and turn the system on?*
  - *Do the SC-DARIC33 T cells activate and expand?*
  - *Do they engage and kill target cells?*

Potency of *ex vivo* CBL-B gene editing in CAR T cells

- Preclinical impact of CBL-B edits in CAR T cells*
- Supports enthusiasm for CBL-B gene editing in bbT369 (B-NHL program)
- First **clinical** application of our megaTAL technology

2seventy bio's NextGen AML approach…. *packed with innovation*

- Signal 1: Dual targeted
- Signal 2: Novel high antigen sensitivity regulatable CAR architecture (RESET)*
- Signal 3: Inducible IL-15 cytokine support*

Progress on our Hemophilia A Collaboration with Novo Nordisk

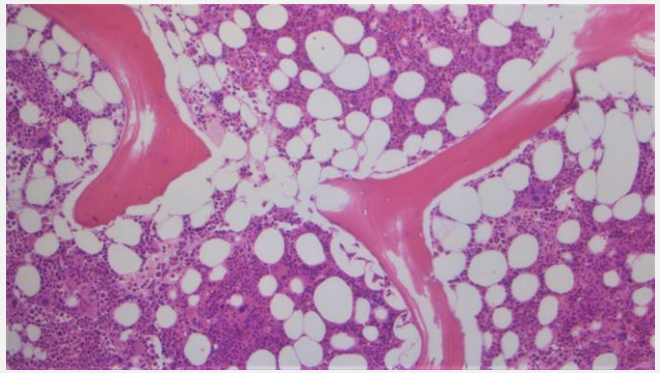
- First direct *in vivo* application of the megaTAL technology
- Key proof of concept data and pre-clinical milestones achieved
- Supports additional applications of our mRNA and megaTAL technology

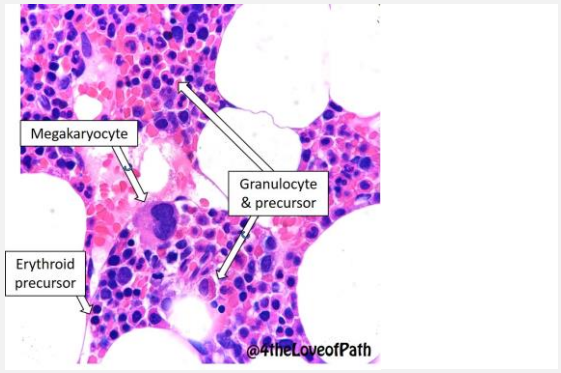
* *Presentations given at* ASGCT 26TH ANNUAL MEETING Los Angeles

AML Clinical and Preclinical Developments

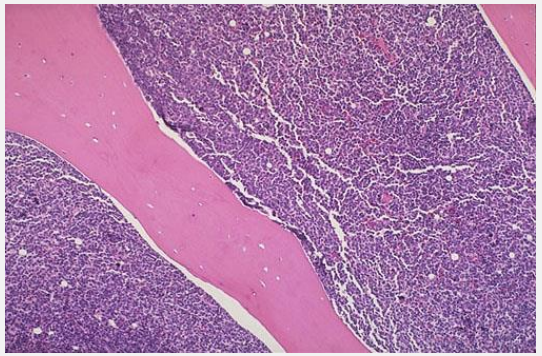
Steve Bernstein, M.D., chief medical officer
Steve Shamah, Ph.D., SVP, oncology research

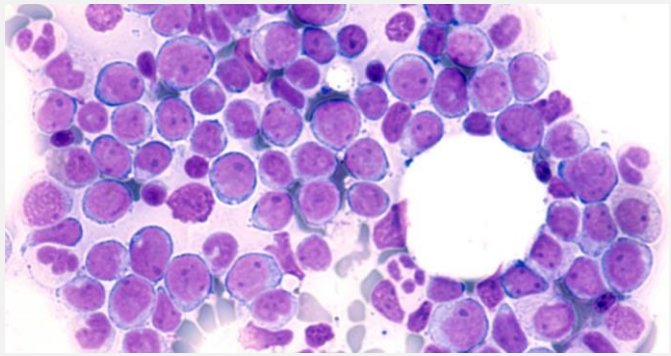
Acute Myeloid Leukemia is a devastating disease in desperate need of new therapeutic approaches



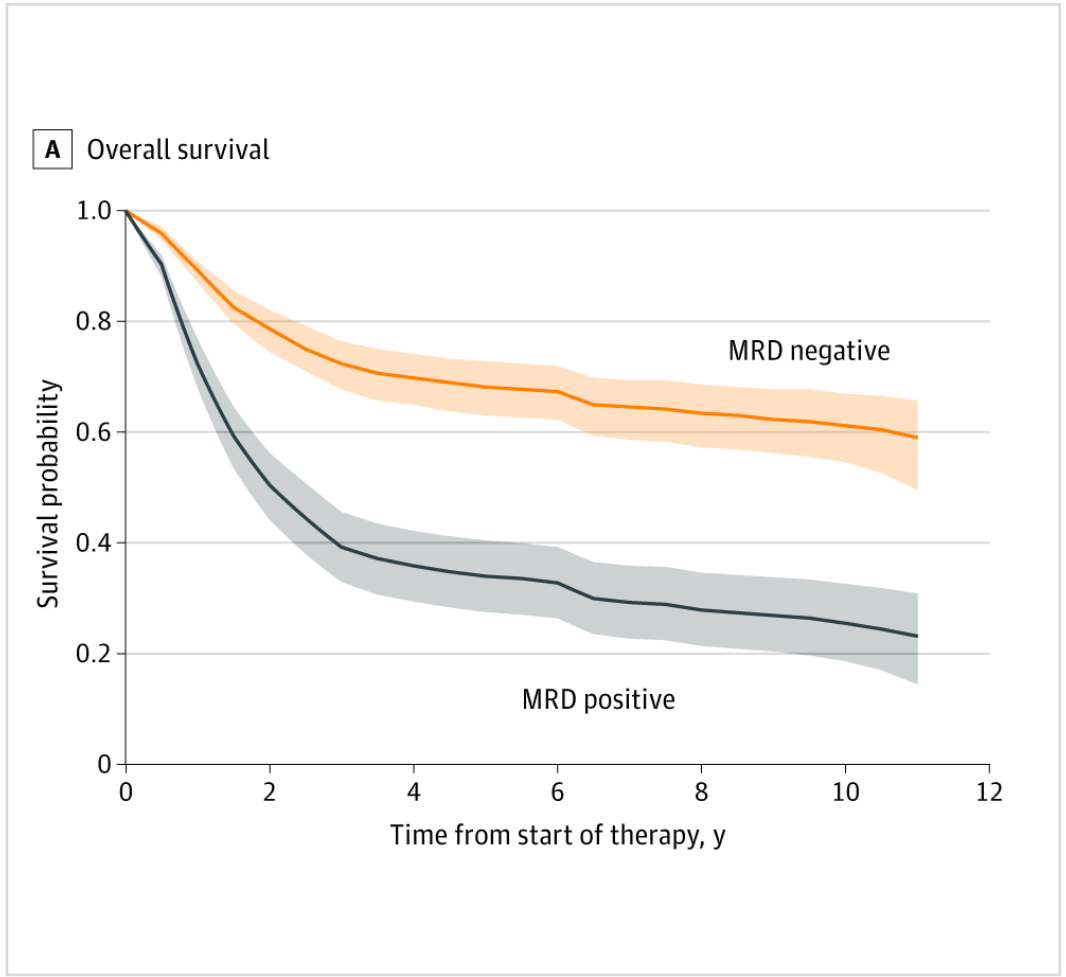


A normal bone marrow making WBC, RBC and platelets





A leukemic bone marrow packed with blasts preventing normal blood cell formation



2seventybio

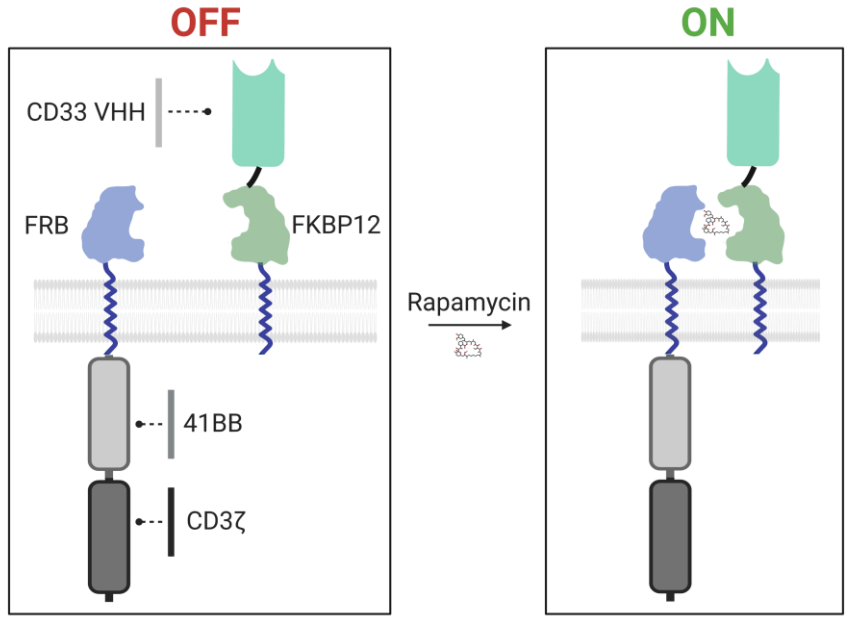
Challenges in developing T-cell therapies for AML and 2seventy's solutions

Challenges in AML	Description of issue	2seventy cell therapy solutions
1 Aplasia Risk	AML targets are expressed on healthy myeloid lineage & progenitor cells; aplasia related toxicities are likely to emerge if targeted robustly & constitutively	**Regulatable system** that can be turned ON & OFF designed to reduce risks associated with long term myeloaplasia
2 T cell Persistence	AML cell therapies have shown low response durability without consolidation with SCT	**Regulatable CAR reduces T cell exhaustion** and designed to promote memory during OFF cycle

DARIC Platform

Dimerizing Agent Regulated Immunoreceptor Complexes

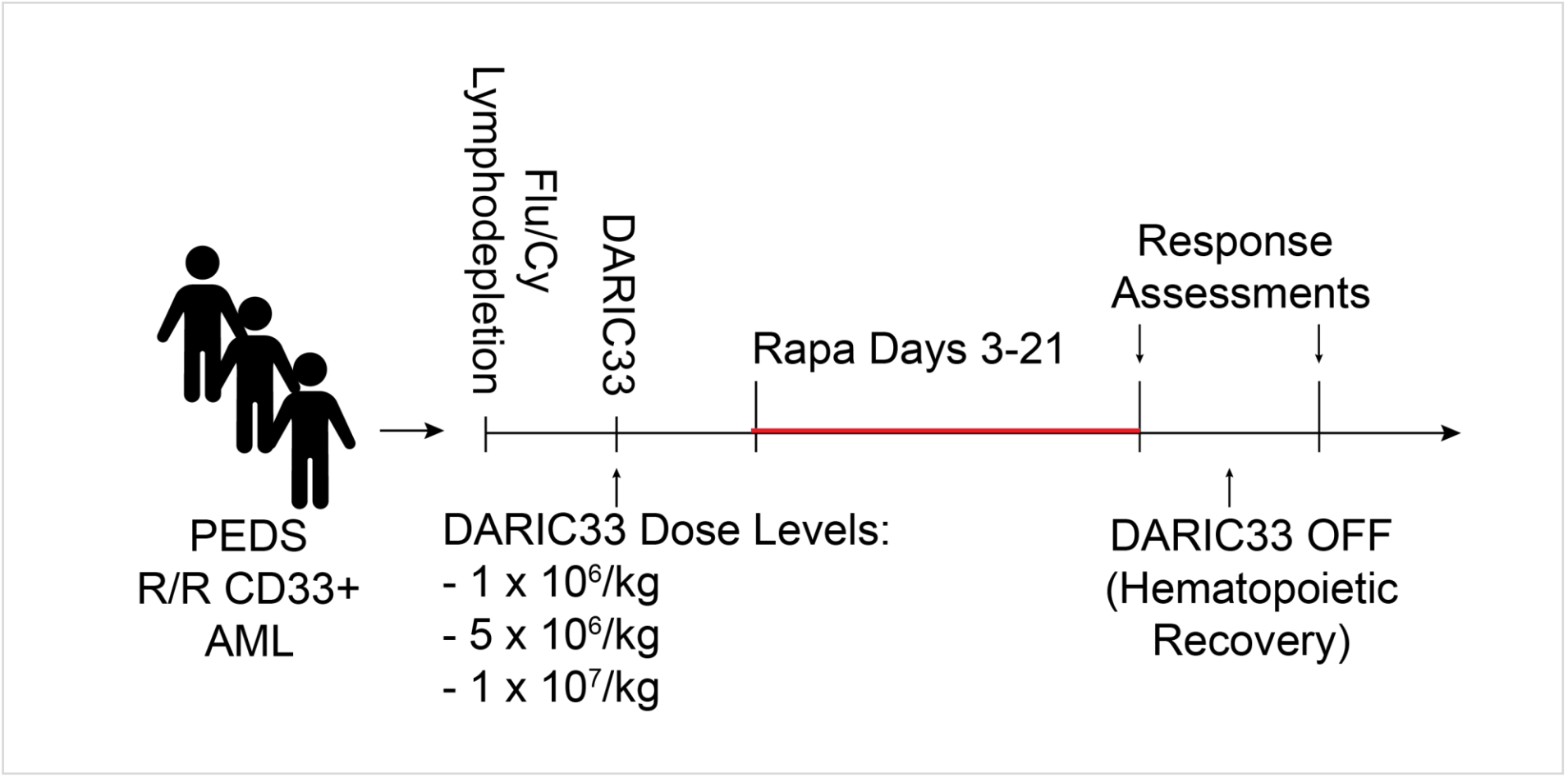
- Next-generation **Regulatable** CAR
- Separate antigen binding and signaling subunits contain drug-dependent dimerization domains
- Dimerizing drug (Rapamycin) required for antigen responses



PLAT-08: A first-in-human Phase 1 trial of SC-DARIC33

Primary Aim:
Determine the maximum tolerated and biologically effective dose

Eligibility:
Children and young adults with relapsed/refractory CD33+ AML



Link to ClinicalTrials.gov for full study information, including primary and secondary outcome measures:
PLAT-08: A Study Of SC-DARIC33 CAR T Cells In Pediatric And Young Adults With Relapsed Or Refractory CD33+ AML - Full Text View - ClinicalTrials.gov

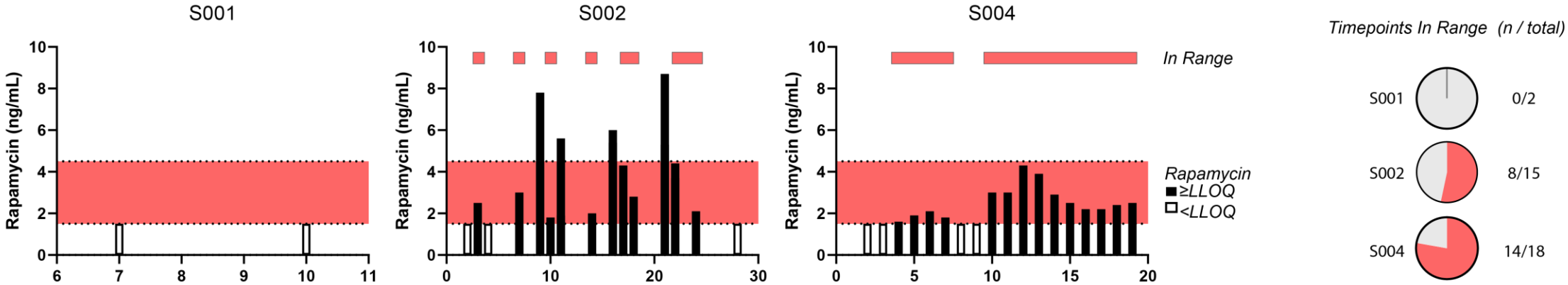
What are we looking for in the early days of this trial

1. Can we dose Rapa to maintain levels within target range for DARIC activation?
2. Does that result in DARIC dimerization, activation and expansion?
3. Do the DARIC cells engage antigen and mediate target cell cytotoxicity?

1 Can we dose Rapa to maintain levels within target range for DARIC activation?

As of March 17, 2023, three patients had received lymphodepletion (LD) and SC-DARIC33 therapy at dose level 1 (1 x 10^6 SC-DARIC33 T cells/kg). Rapamycin dosing was adjusted by the treating physician to attain target levels.

Infusions were generally well tolerated without occurrence of dose limiting toxicities.



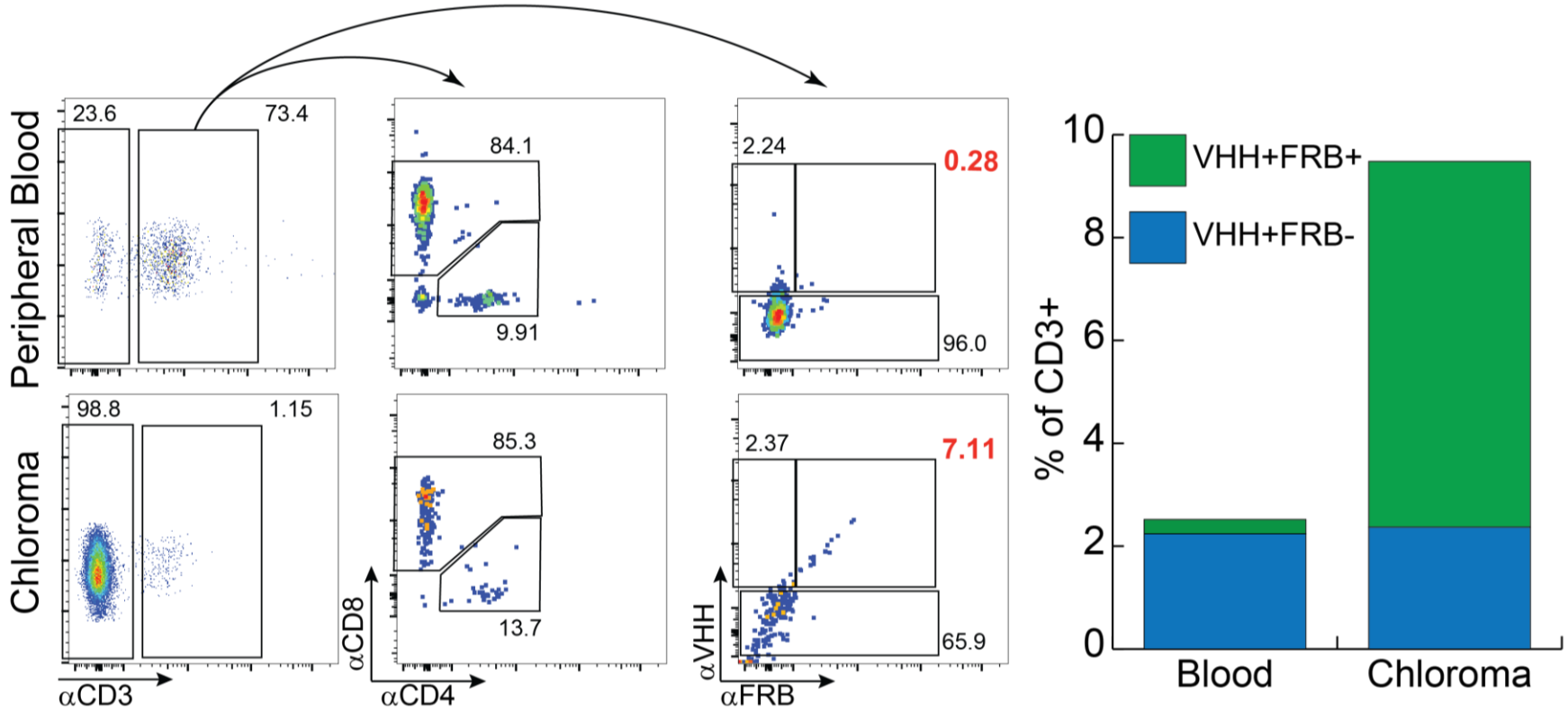
Improvement in Rapamycin targeting

2seventybio

2 Do therapeutic Rapa levels result in DARIC dimerization, activation and expansion?

Patient S002

Compared to blood, SC-DARIC33 T cells (VHH+FRB+) were increased among T cells in tumor tissue.

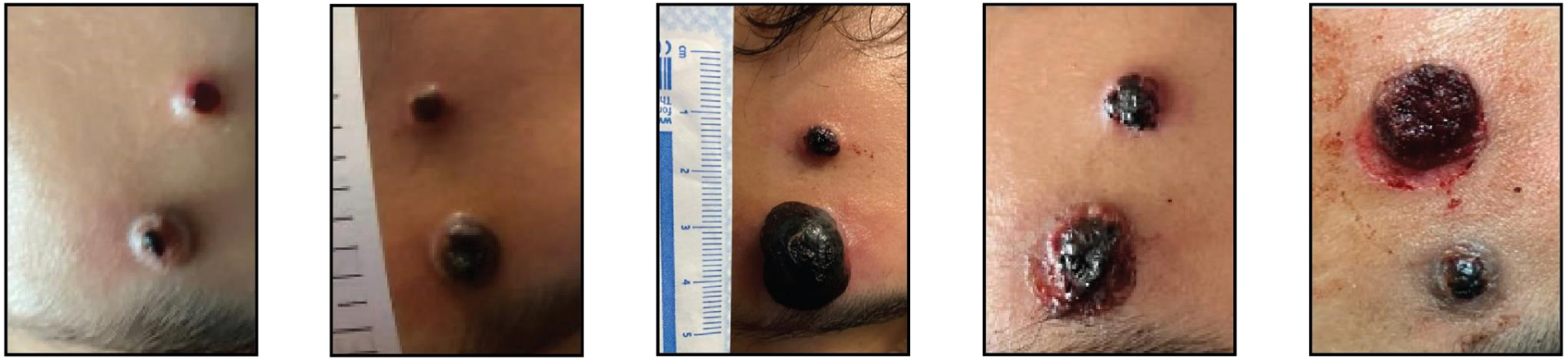


2seventybio

3 Do the DARIC cells engage antigen and mediate target cell cytotoxicity?

Patient S002

Chloroma: Two extramedullary leukemic “tumors” in the skin above the eyelid

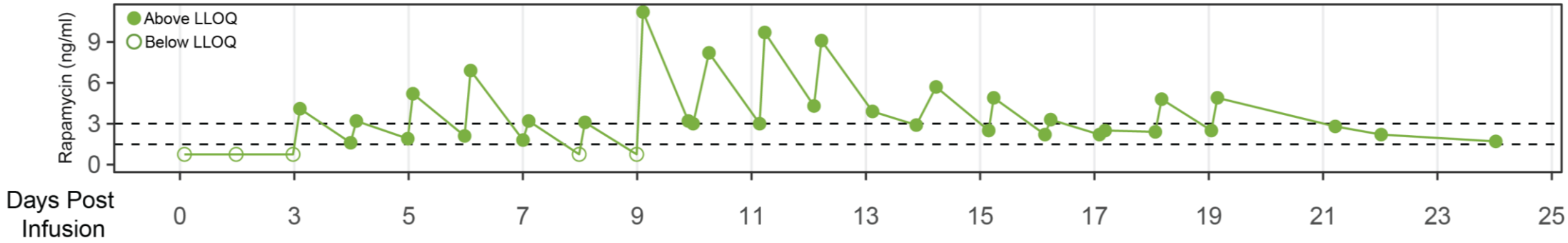


Day 3 | Day 4 | Day 8 | Day 13 | Day 22

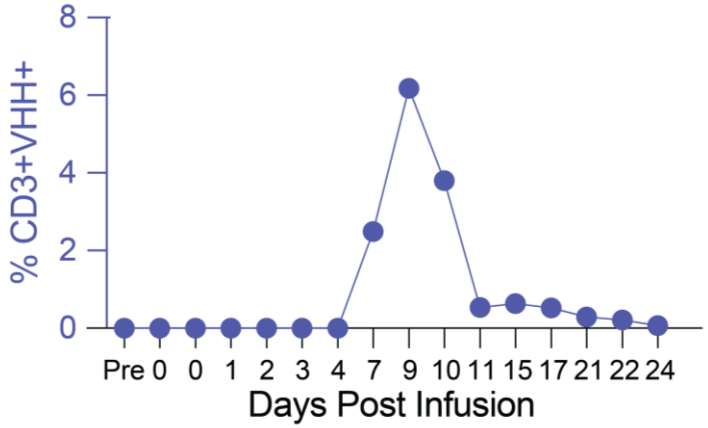
Progressive hemorrhagic necrosis of the chloromas

2 Does therapeutic Rapa levels result in DARIC dimerization, activation and expansion?

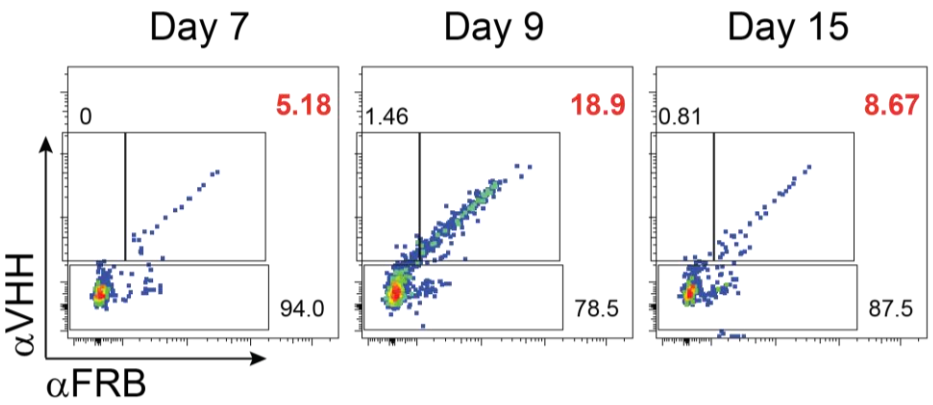
Patient S004



Percentage of total lymphocytes that are DARIC cells



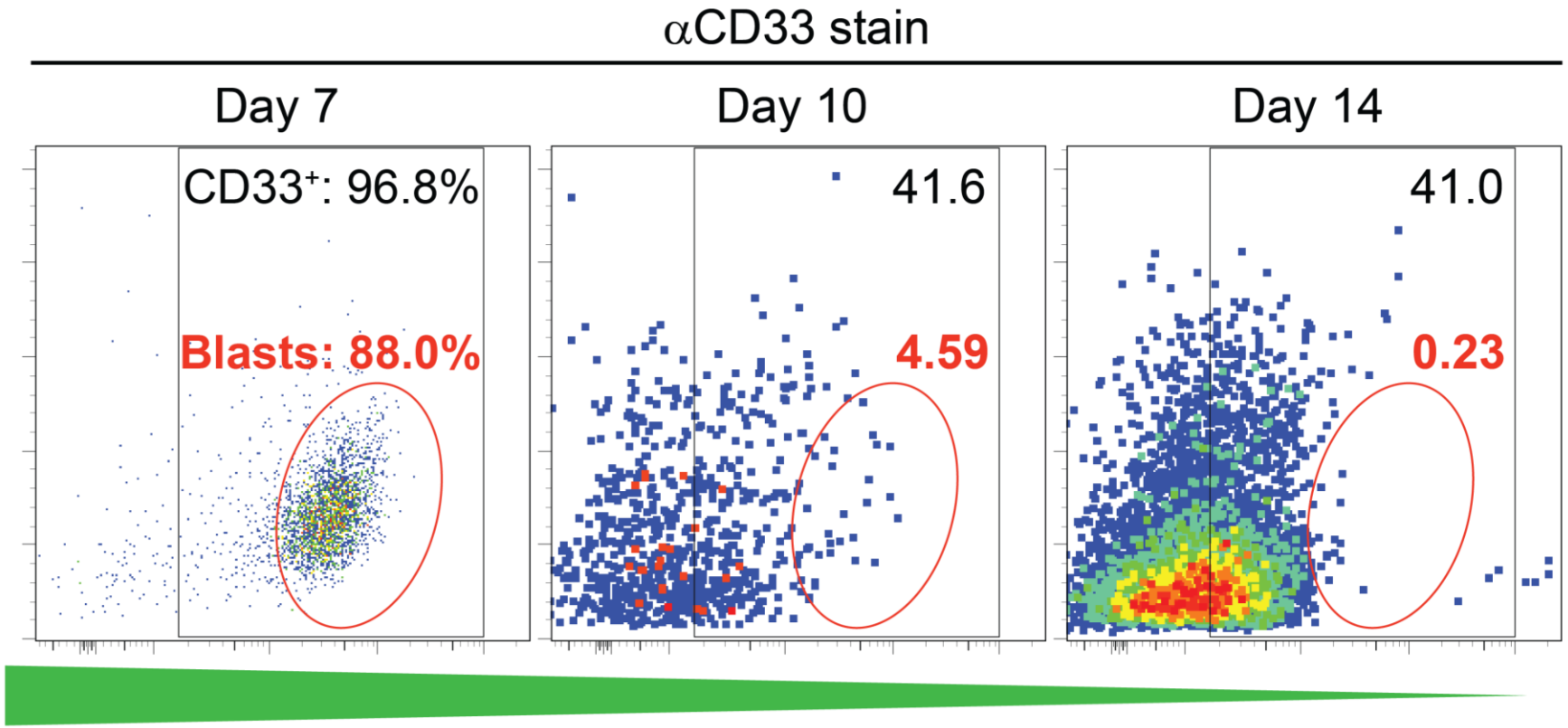
Percentage of CD3+ T-cells that are "turned on" by Rapa (*VHH+FRB+*)



2seventybio

3 Do the DARIC cells engage antigen and mediate target cell cytotoxicity?

Patient S004



Transient clearance of leukemic blasts in blood

Summary of initial PLAT-08 correlative data

First three patients / Dose Level 1

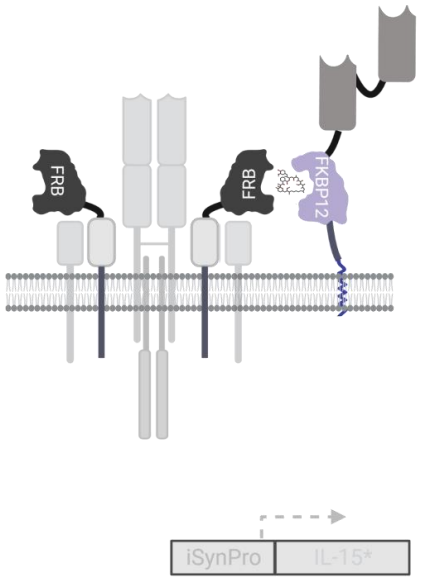
- *Initial safety and tolerability data consistent with CAR T cell approaches*
- *We can dose RAPA to target levels and turn the system on*
- *SC-DARIC33 T cells activate and expand*
- *SC-DARIC33 T cells traffic to, engage and kill target cells*

Next Steps

- Explore SC-DARIC33 at DL2 (5e6 cells/kg) and continue dose escalation
- Continue to develop next generation solutions to the additional problems that may limit efficacy

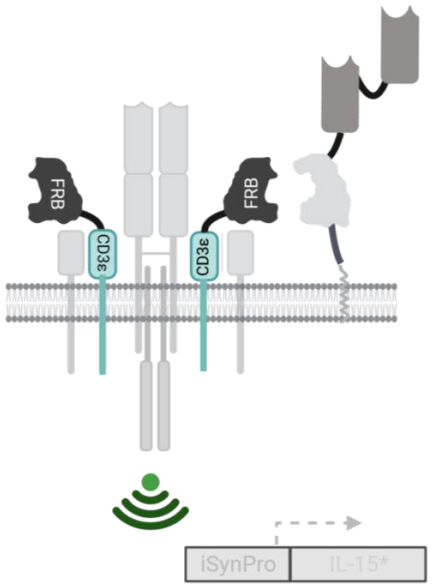
Our Next-Gen AML (NG-AML) program builds on SC-DARIC33 success

1 Rapamycin-based CAR regulation



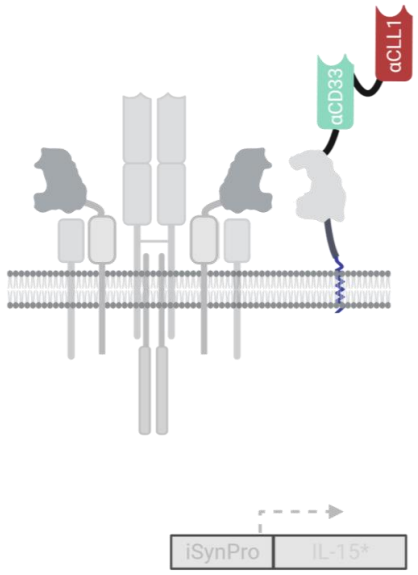
Solving for aplasia risk

2 Signaling via the native T Cell Receptor



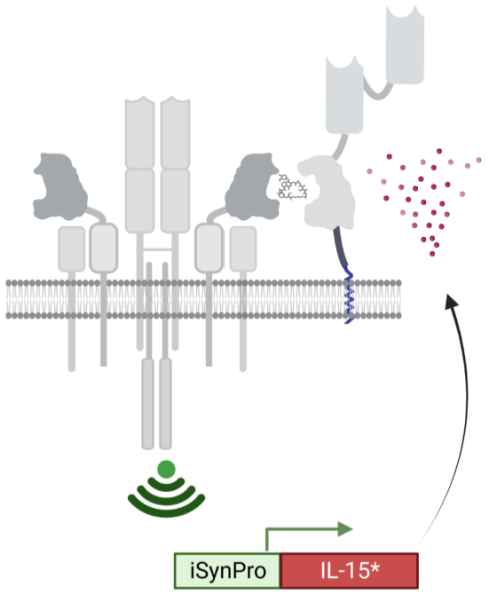
Solving for reduced antigen expression

3 Dual Antigen Targeting



Solving for disease heterogeneity

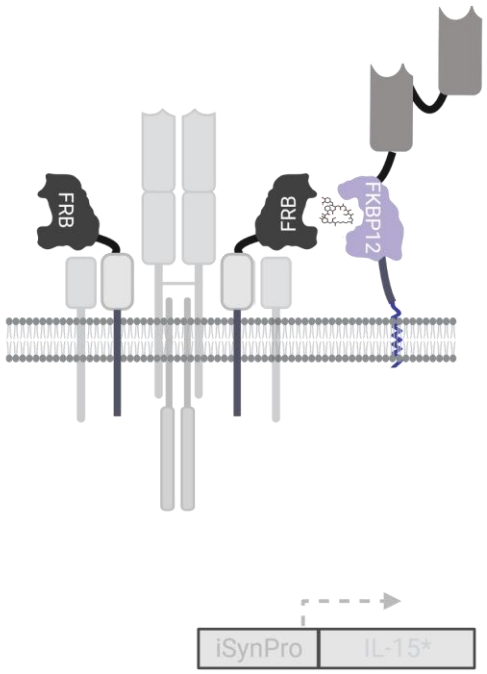
4 Soluble IL-15 for better T cell persistence

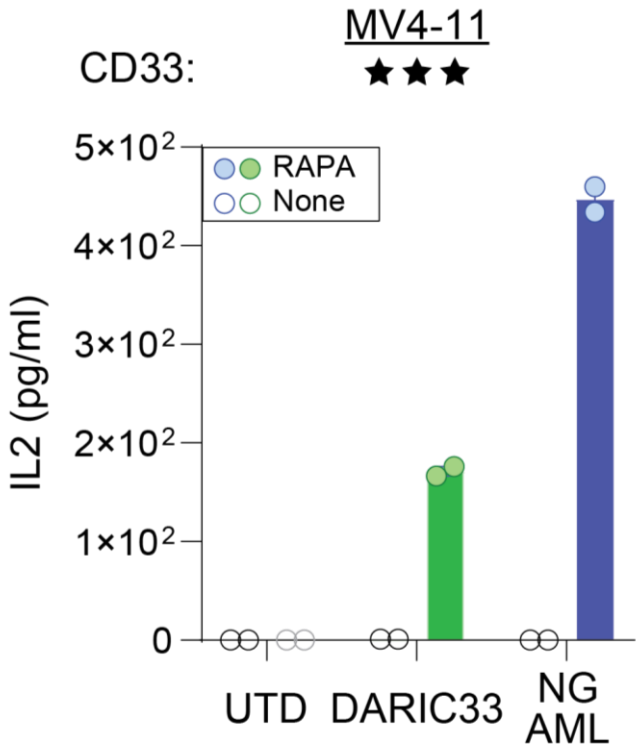


Solving for T cell persistence

The NG-AML CAR is tightly controlled by rapamycin dosing

1 Rapamycin-based CAR regulation

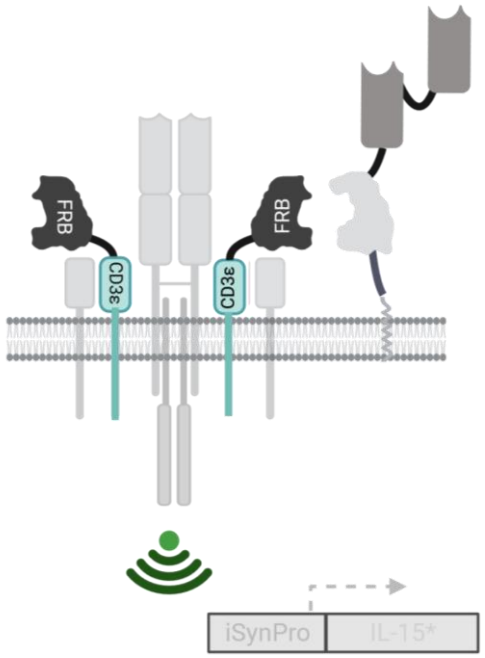


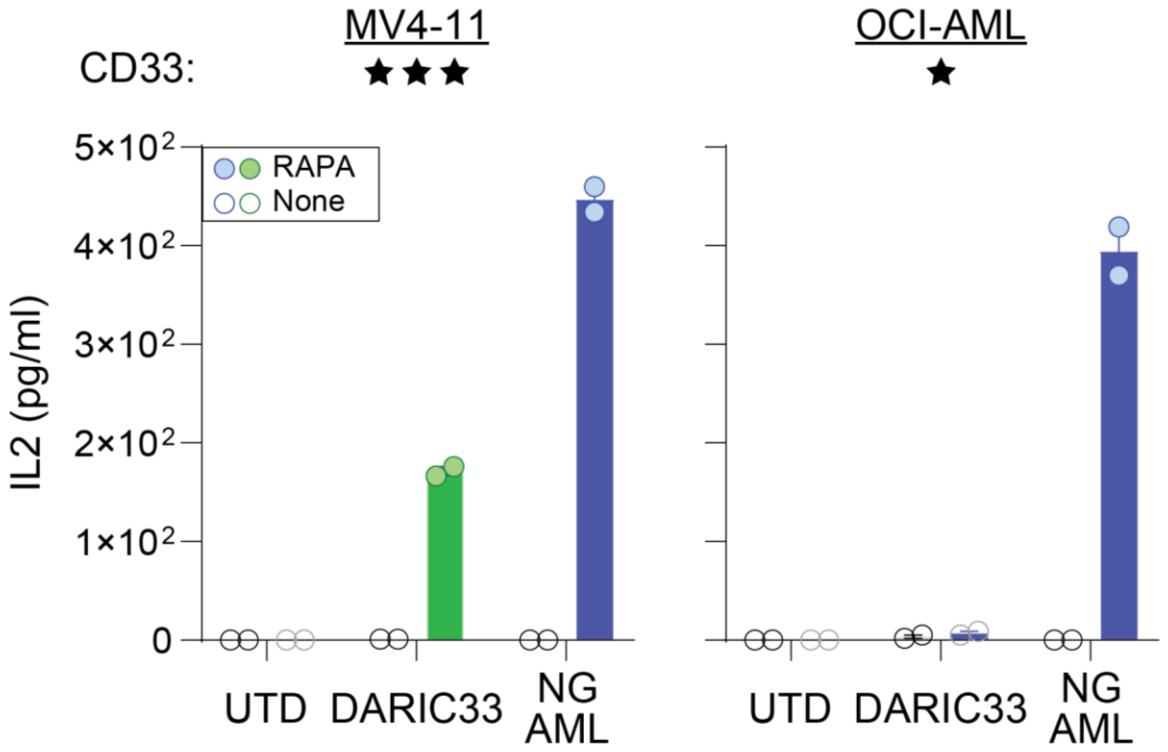


2seventybio

The NG-AML CAR uses the RESET architecture for higher antigen sensitivity

2 Signaling via the native T Cell Receptor

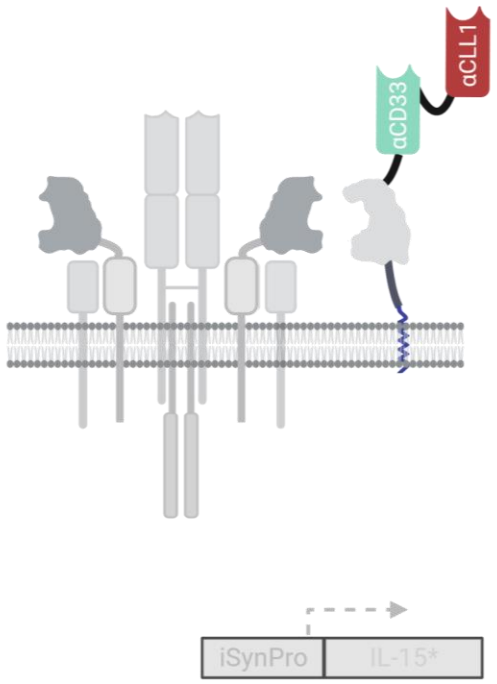


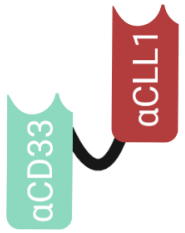


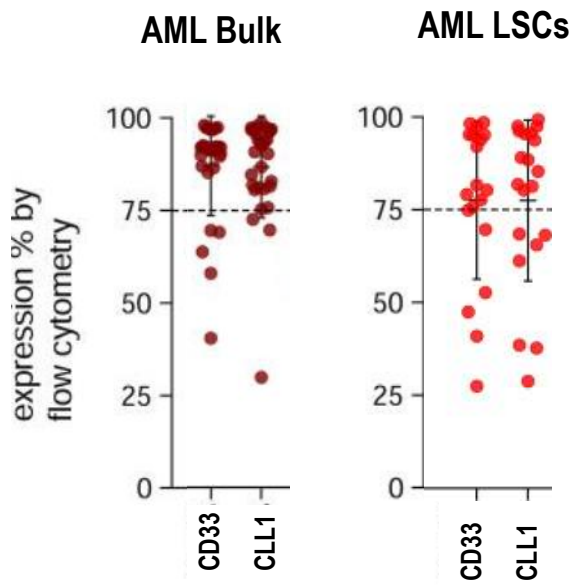
The **Rapamycin-Enabled, Switchable Endogenous TCR (RESET)** architecture demonstrates **enhanced sensitivity** to low target density limiting low antigen escape

The NG-AML CAR recognizes CD33 and CLL-1 to address AML heterogeneity

3 Dual Antigen Targeting

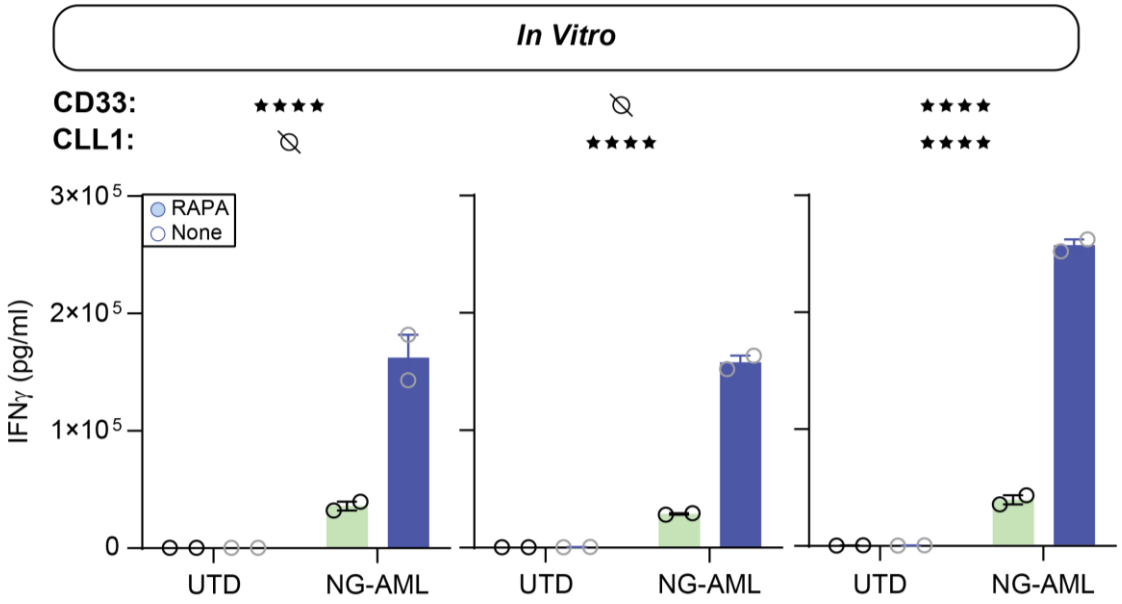






Perna et al, Cancer Cell 2017

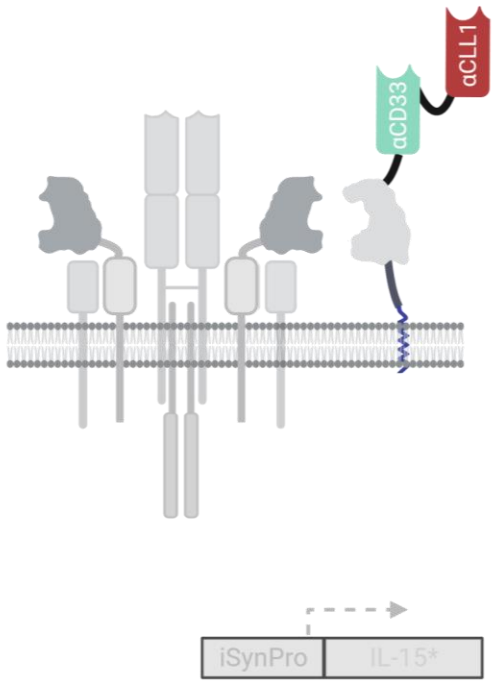
- CD33 and CLL-1 have high expression and prevalence in AML blasts and Leukemic Stem Cells (LSCs)
- CD33 binder targets the conserved C2 domain

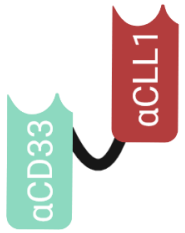


2seventybio

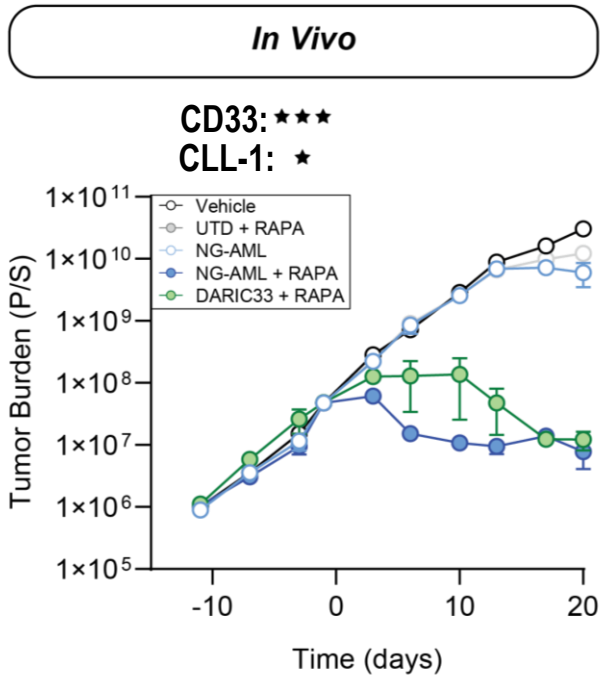
The NG-AML CAR recognizes CD33 and CLL-1 to address AML heterogeneity

3 Dual Antigen Targeting





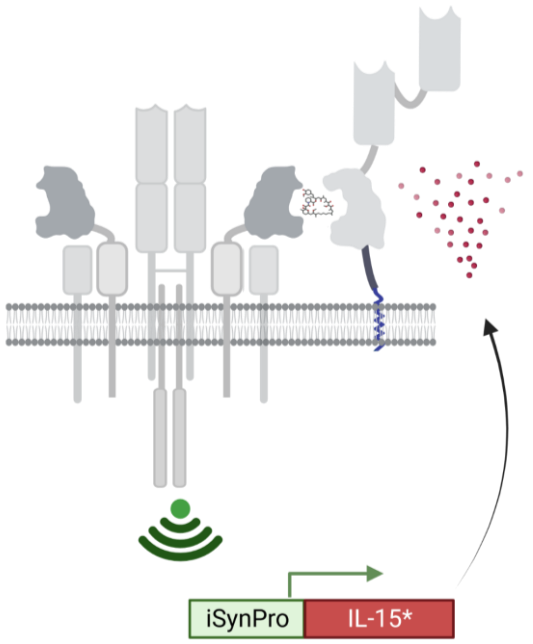
- CD33 and CLL-1 have high expression and prevalence in AML blasts and Leukemic Stem Cells (LSCs)
- CD33 binder targets the conserved C2 domain



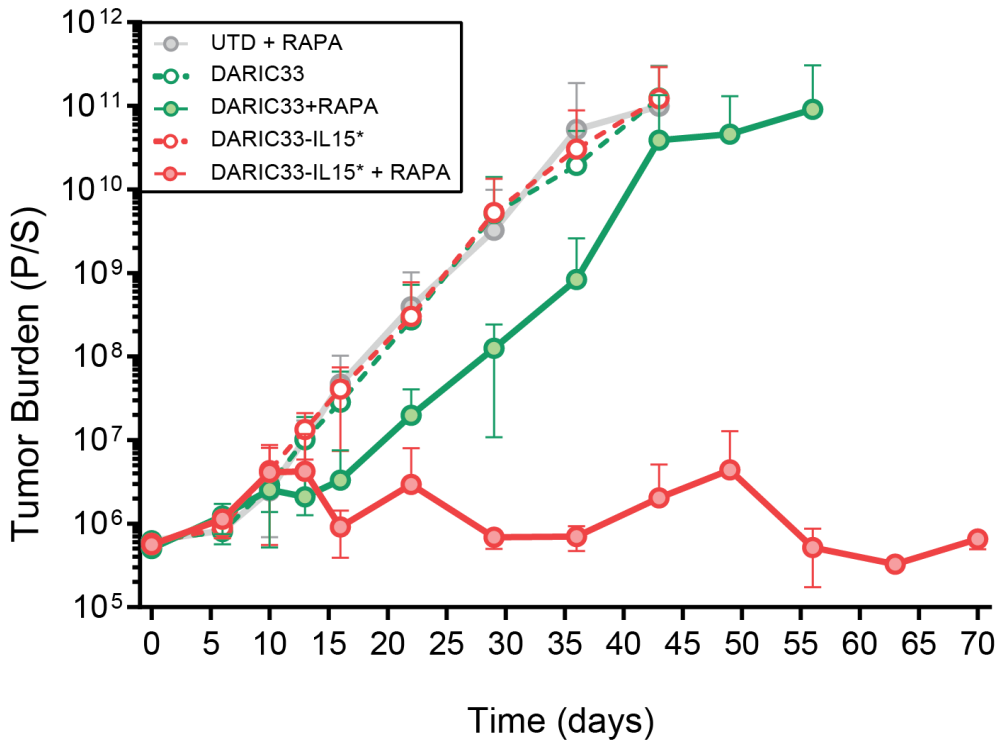
2seventybio

The NG-AML CAR incorporates IL-15, resulting in more potent T cells

4 Soluble IL-15 for better T cell persistence



IL-15 activity is regulated by a T cell activation-dependent synthetic promoter



Addition of iSynPro-IL15* improves in vivo AML tumor control

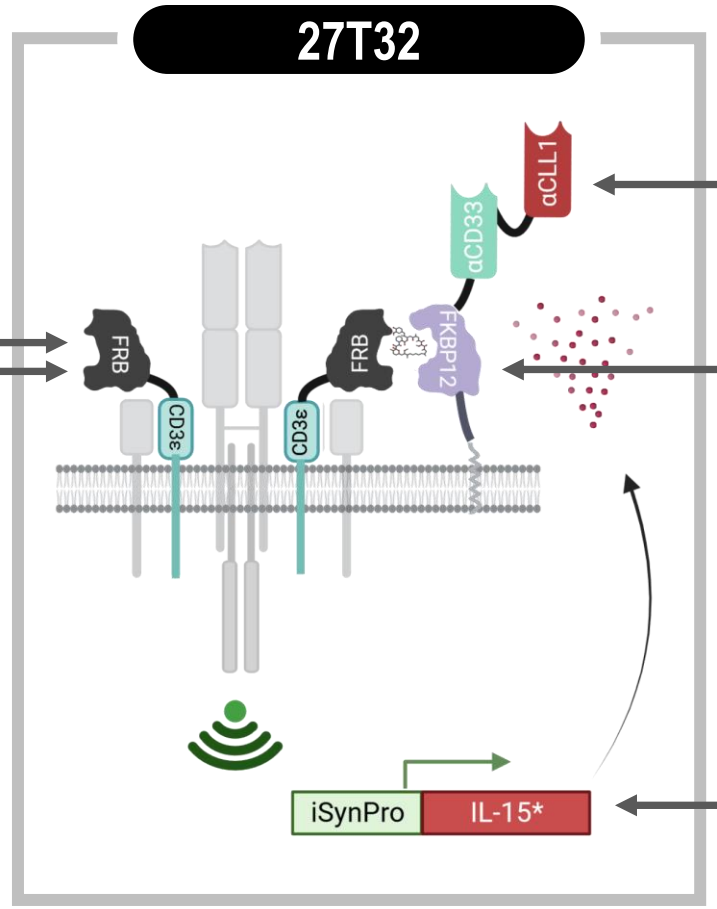
27T32 Our Next-Gen CAR T for AML: Bold and packed with innovations

Solving reduced antigen expression

Novel architecture
enhances sensitivity to low target density

Solving T cell exhaustion

Regulatable system
reduces T cell exhaustion and promotes memory



Solving disease heterogeneity

Dual-targeting
limits potential antigen escape

Solving aplasia risk

Regulatable system
reduces risks from long term myelodysplasia

Solving T cell persistence

Inducible IL-15
Increases activation-dependent expansion & function

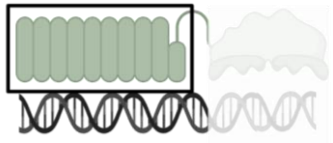
Ex Vivo and *In Vivo* Gene Editing Applications

Mike Certo, Ph.D., VP, head of genome editing

megaTAL Platform: Engineering activity and specificity

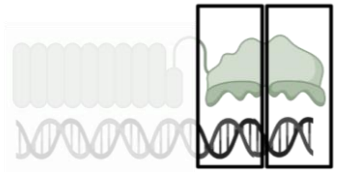
Gene Editing Architecture

TAL Array Anchor



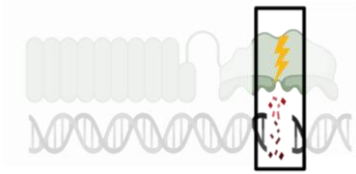
10-12 bp TAL target recognition

Meganuclease Binding



22 bp MN target recognition

Meganuclease Cleavage

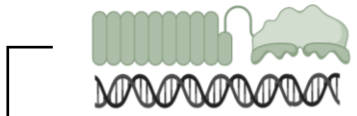


Creates a 4 bp, 3' overhang DSB

megaTAL attributes

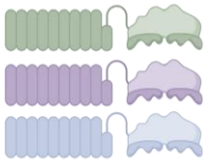
Small size compatable with *ex* and *in vivo* delivery modalities including AAV

2.5 kb



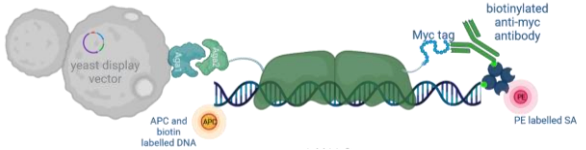
10-12 bp TAL target recognition

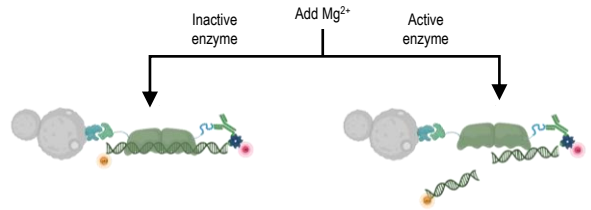
Each megaTAL is a fully orthogonal reagent



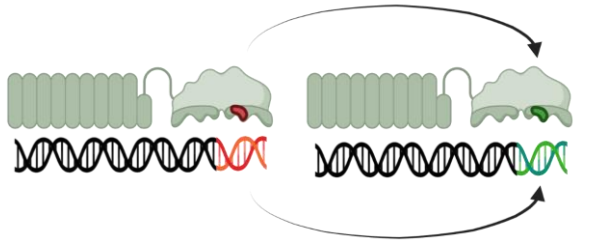
Single, monomeric component drives target recognition and cleavage

Protein Engineering for Activity and Specificity





Unbiased off-target discovery



In silico off-target discovery

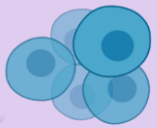
megaTAL refinement

Gene Editing
Ex Vivo vs In Vivo

Ex Vivo

2 Extract cell

1 Collect blood



Engineer cells through viral or nonviral methods

3 Grow culture

4 Re-introduce modified cells

In Vivo

1 Direct delivery using viral or non-viral vehicle

Viral delivery

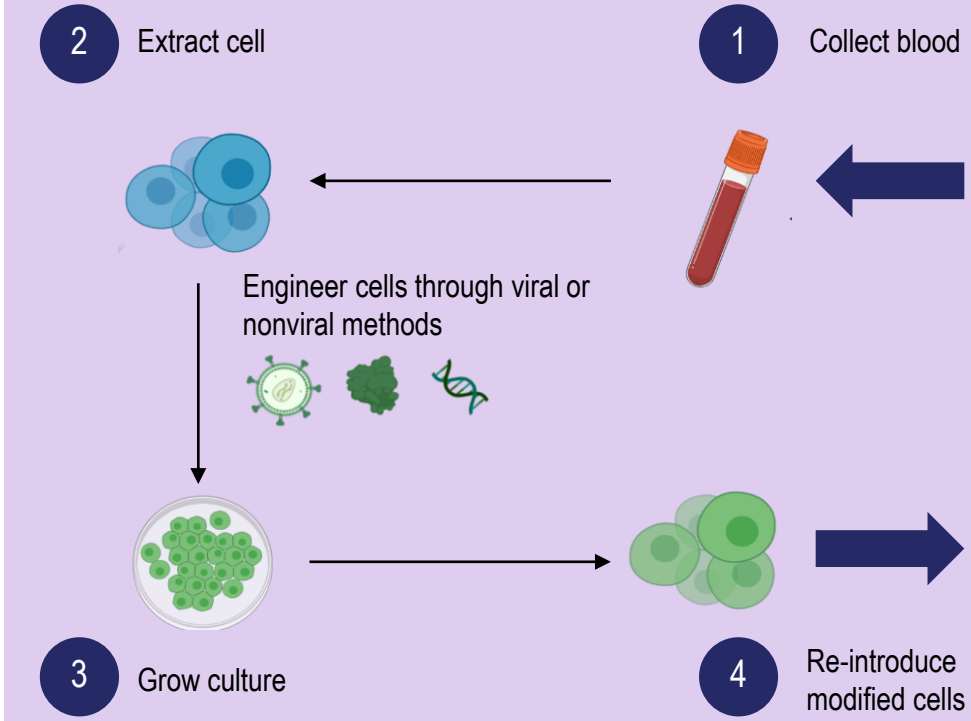
Adeno Associated Virus (AAV)

Non-viral delivery

Lipid nanoparticle (LNP)

Gene Editing
Ex Vivo vs In Vivo

Ex Vivo



In Vivo

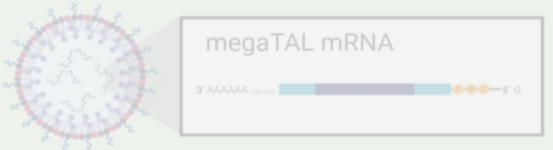
1 Direct delivery using viral or non-viral vehicle

Viral delivery

Adeno Associated Virus (AAV)

Non-viral delivery

Lipid nanoparticle (LNP)

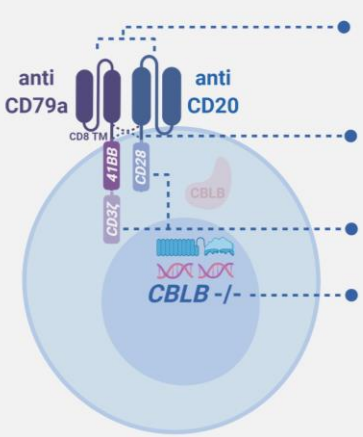


bbT369: Autologous CAR T product purpose-built to address significant need in b-NHL

CD19 CAR T cells have improved outcomes for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), but 60-70% of patients do not achieve a long-term durable remission, highlighting the need for additional treatment options that provide more deep, durable complete responses.[1-2]

Challenges in bNHL CAR T	Description of issue
1 CD19 Loss	~30% of CD19 CAR T relapse patients have CD19 negative disease.
2 Target-Antigen Downregulation	CD19-Low tumors have been shown to escape CAR T detection and killing.
3 Poor outcomes in patients with Challenging TME and/or Aggressive disease	PFS / OS in patients with aggressive disease characteristics, such as higher disease burden and extra-nodal sites have significantly worse outcomes

2seventy cell therapy solution: bbT369



- Novel combination of antigens to address antigen escape.
- Shared CD8 TM domain facilitates heterodimirization of CARS via di-sulphide bond
- Optimized antigen receptor signaling domains to augment T cell activation.
- Gene edit to enhance potency and reduce T cell exhaustion.

TARGET(S)	Dual target: CD20, CD79a
TECH	Dual targeting with split 41BB and CD28 costim Cblb gene edit for expansion, antigen sensitivity, performance
INDICATION	B-NHL
STATUS	Ph1 trial active
PARTNER	2seventy owned

References
1. Neelapu et. al., NEJM 2018
2. Schuster et al. NEJM 2019

Data presented at ASGCT demonstrate potential of the CBLB edit to maintain CAR T activity across multiple challenging tumor scenarios

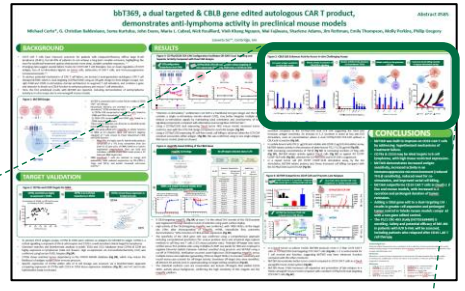
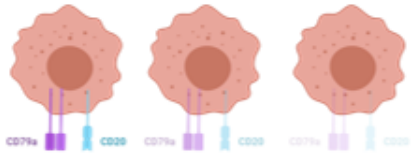
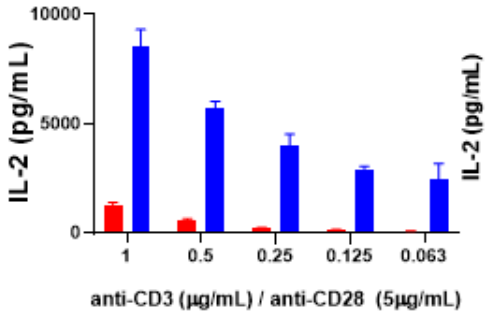


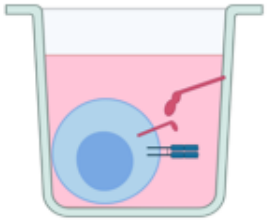
Figure 5: CBLB Edit Enhances Activity Across *in vitro* Challenging Assays

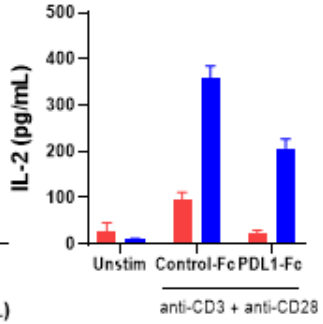
A) **Increased antigen sensitivity in bead-stim model**



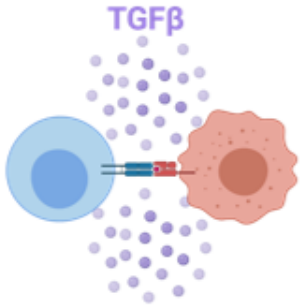


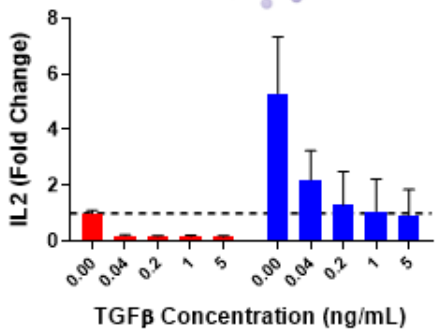
B) **Retain activity in presence of PDL1/PD-1 signaling**



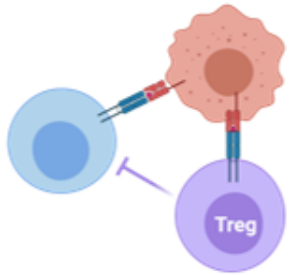


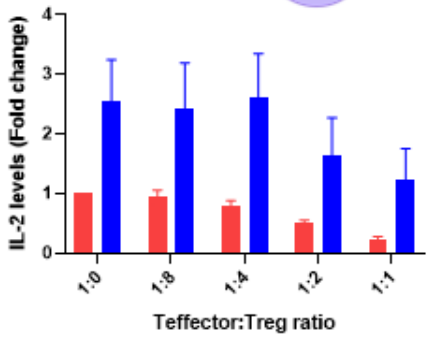
C) **Retains activity in the presence of recombinant TGF-β**



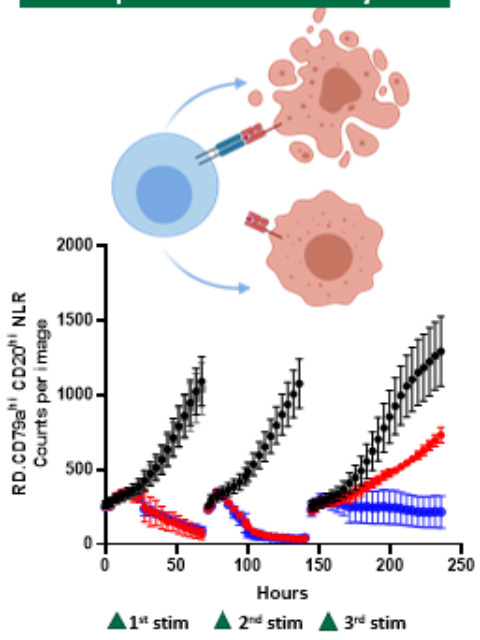


D) **Retain activity in the presence of Tregs**





E) **Improved serial killing capacity in repeat-stimulation assays**



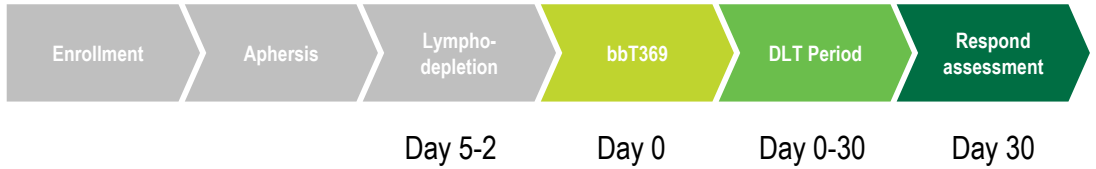
CD79a/CD20 Dual CCR CAR

bbT369

2seventybio

CRC-403 study in B-NHL open and enrolling

CRC-403: A Phase 1/2 Study of bbT369 in Relapsed and/or Refractory B-Cell Non-Hodgkin Lymphoma (B-NHL)



STUDY DESIGN

- Target enrollment: n=50
- 4 study sites
- Relapsed/Refractory B-cell NHL after autologous SCT or ≥ 2 prior lines of therapy
- B-cell NHL according to WHO 2017 classification
- Prior CD19 CAR-T therapy is permitted

Key Questions / Features

QUESTIONS

- Is the safety and tolerability of bbT369 in line with prior CAR Ts?
- Does bbT369 show anti-B cell activity in R/R B-NHL patients?
- Does bbT369 show deep and durable responses?
- Does the dual-targeting CAR architecture limit antigen escape?
- Do CBLB edited T cells expand and persist?

FEATURES

- First in human application of four 2seventy bio innovations:
  - Dual targeted T cell
  - Split-costimulation signaling architecture
  - MegaTAL gene editing tech
  - CBLB edited T cell
- All four are believed to have application across our research pipeline, including enhanced liquid tumor settings and solid tumors

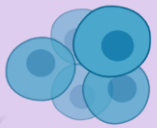
Update from Phase I CRC-403 study anticipated by the end of 2023

Gene Editing
Ex Vivo vs In Vivo

Ex Vivo

2 Extract cell

1 Collect blood



Engineer cells through viral or nonviral methods

3 Grow culture

4 Re-introduce modified cells

In Vivo

1 Direct delivery using viral or non-viral vehicle

Viral delivery

Adeno Associated Virus (AAV)

Non-viral delivery

Lipid nanoparticle (LNP)

Gene Editing
Ex Vivo vs In Vivo

Ex Vivo

2 Extract cell

1 Collect blood

Engineer cells through viral or nonviral methods

3 Grow culture

4 Re-introduce modified cells

In Vivo

1 Direct delivery using viral or non-viral vehicle

Viral delivery

Adeno Associated Virus (AAV)

Non-viral delivery

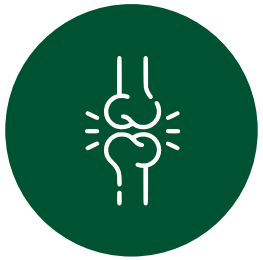
Lipid nanoparticle (LNP)

Hemophilia A

Severe and debilitating genetic bleeding disease caused by the absence of the critical clotting molecule Factor VIII

Phenotypes

BRUISING
that can lead to hematoma



REPEATED BLEEDING
into muscles and joints, which can lead to disability and arthropathy

SPONTANEOUS INTERNAL BLEEDING
which can be life threatening if in vital organs

EXCESSIVE BLEEDING
following injury or surgery

Therapies

FVIII replacement therapy can be given in response to an injury or prophylactically to prevent bleeding

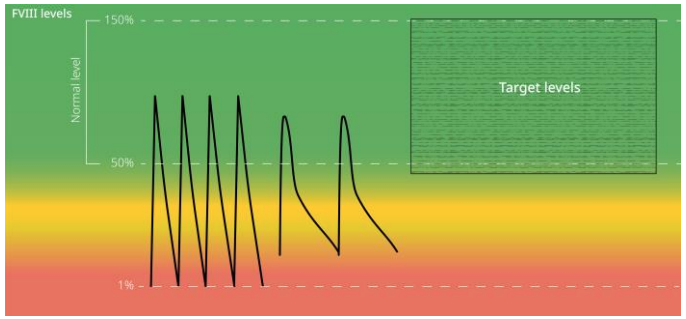
Bispecific antibodies can be used to replace FVIII function and prophylactically prevent bleeds, but is not suitable for traumatic and surgical bleed management

Addresses gaps in SOC and AAV Only Hem A approaches

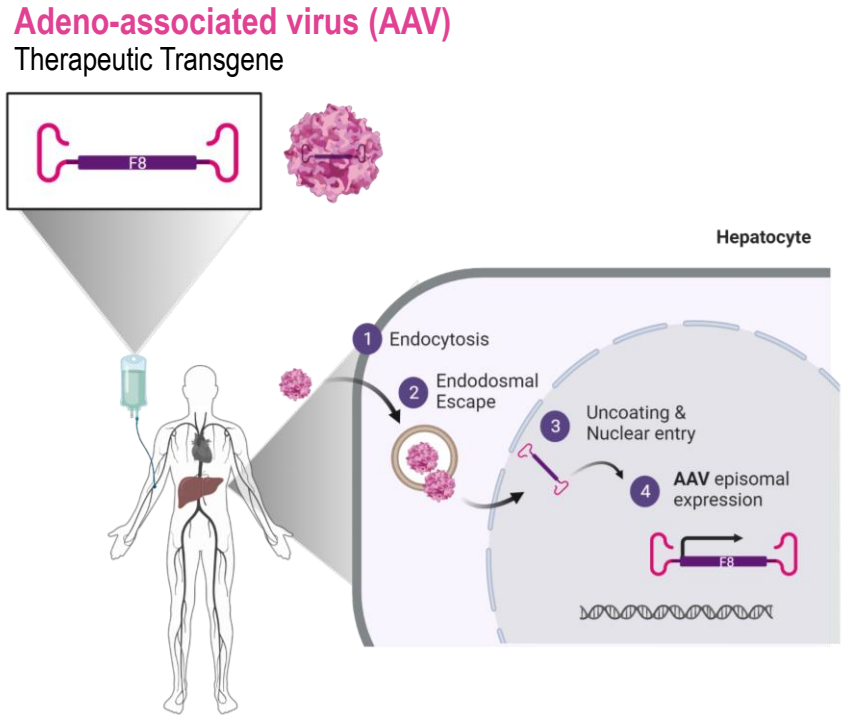
DURABLE expression without activity Troughs

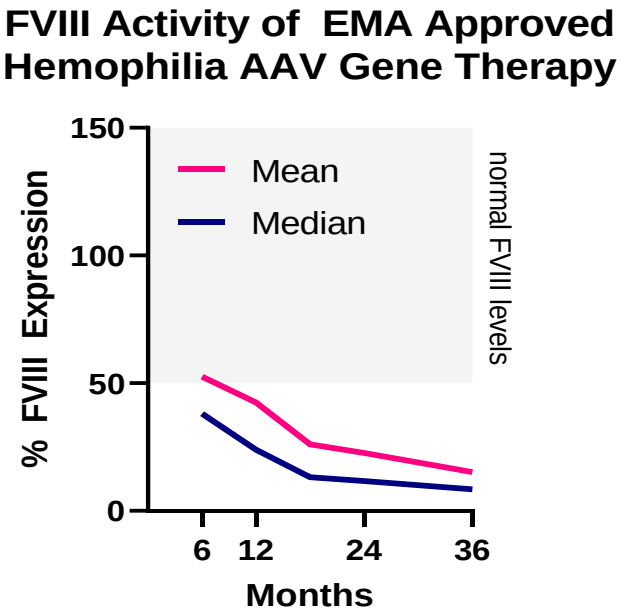
ERT SoC leaves gaps in protection that GTx tries to address

- i.v. FVIII ERT requires repeat dosing and has deep troughs – acute bleeds and joint deterioration over time.
- Extended half-life products reduce injections but still have gaps
- GTx intends to have durable normalized FVIII expression



AAV Episomal transgene expression declines, cannot be redosed and not suitable for Pediatrics

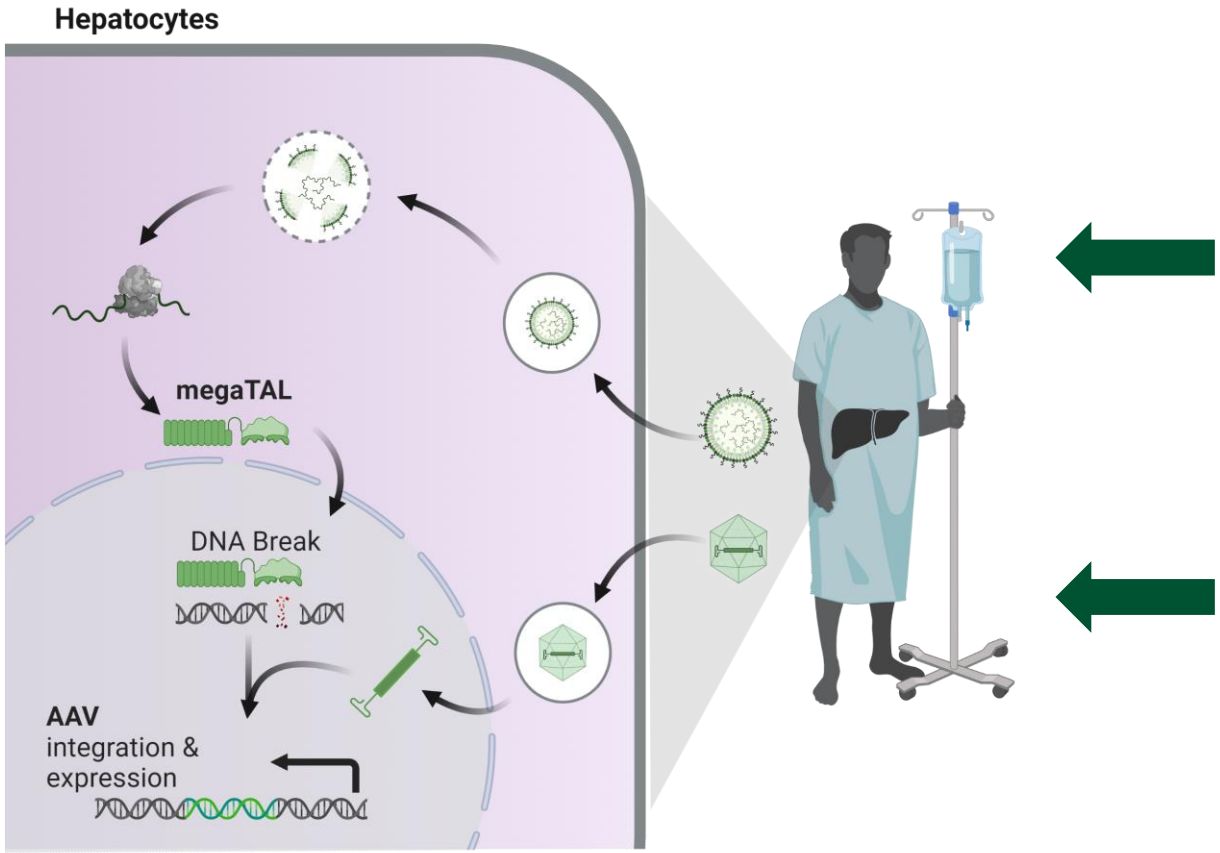




Sources: EMA EPAR ,

In Vivo Gene Therapy for Hemophilia A

Product concept

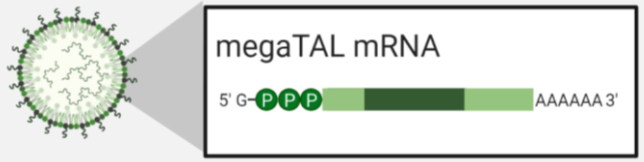


In Vivo Gene Therapy

Direct delivery using viral or non-viral vehicle

Non-viral delivery

Lipid nanoparticle (LNP)

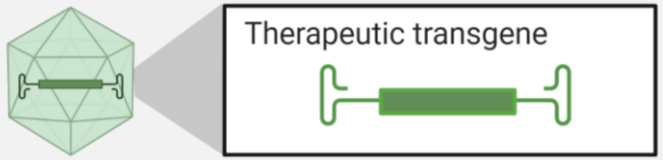


Development Responsibilities

2seventybio in partnership with GENEVANT

Viral delivery

Adeno Associated Virus (AAV)



novo nordisk

Potentially lifelong correction of FVIII deficiency

2seventybio

2seventy & Novo Nordisk
Collaboration Overview

Complimentary co-creation partnership to bring next-generation Hemophilia therapies to patients:

- Built around shared vision and transformational science
- Leveraging 2seventy's gene therapy expertise and Novo's deep clinical experience in hemophilia

Partnership launched with Research Agreement to "make things happen fast"!

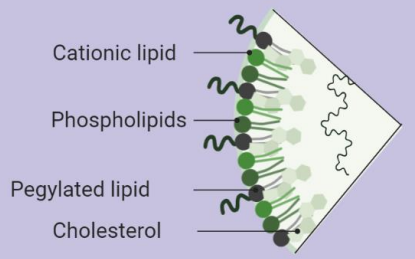
Team health, program success and scientific progress provided opportunity to enter Collaboration Agreement with defined development milestones

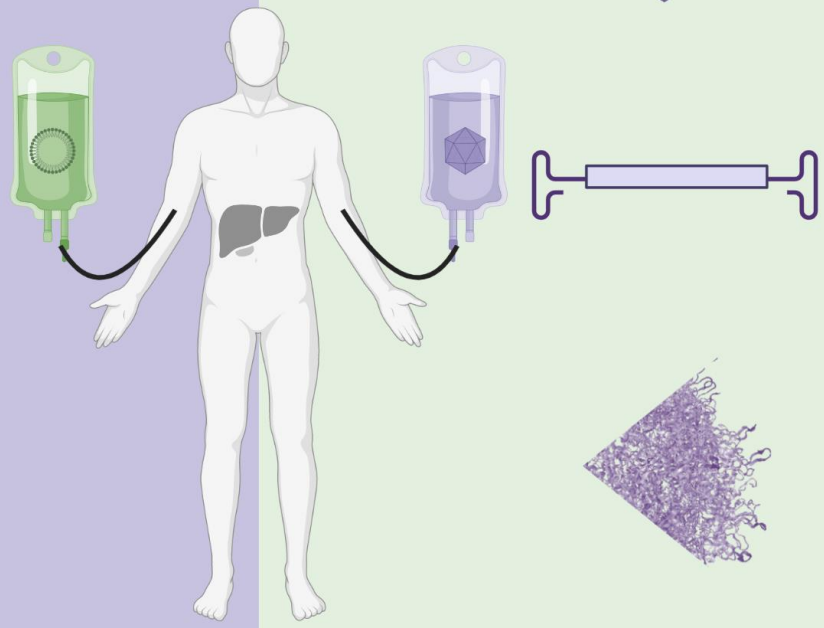
Research Agreement → Collaboration Agreement

Delivering best-in-class liver knock-in approaches for Hemophilia A

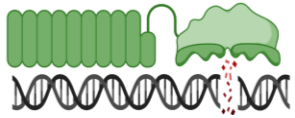
Scientific Considerations

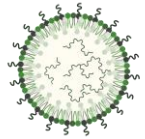
LNP/megaTAL - mRNA	AAV-Transgene
megaTAL	Vector
mRNA	Genome
LNP	Capsid



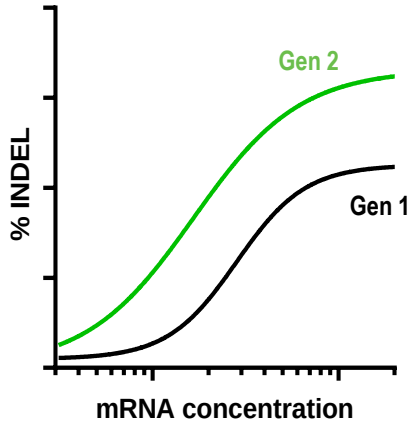


Exploring Product Component Designs

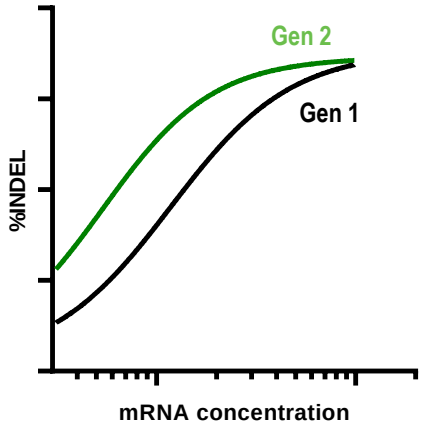




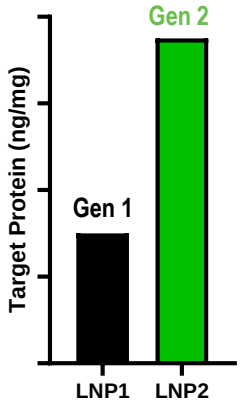
megaTAL Enzyme



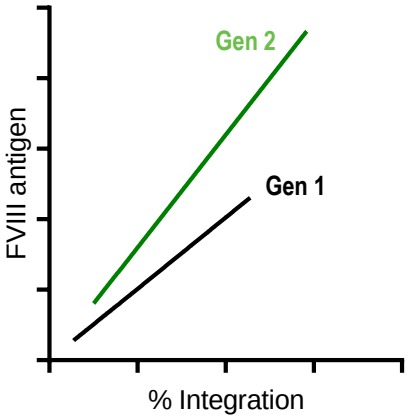
mRNA



LNP Formulations

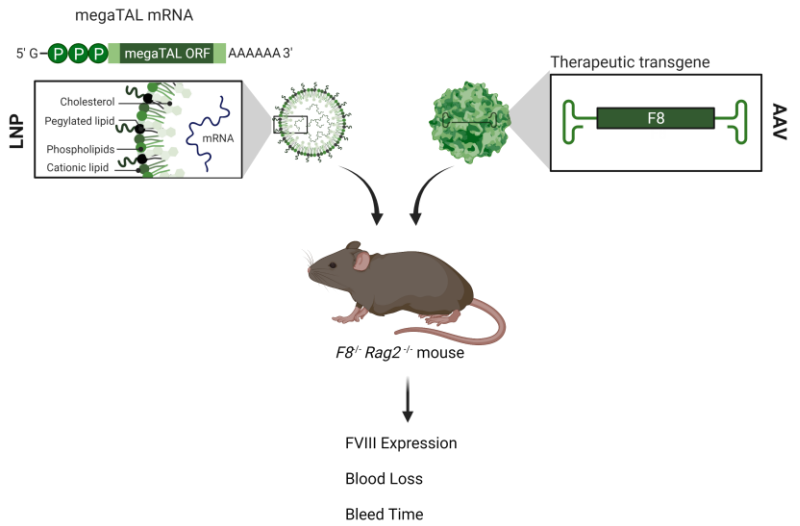


AAV - genome

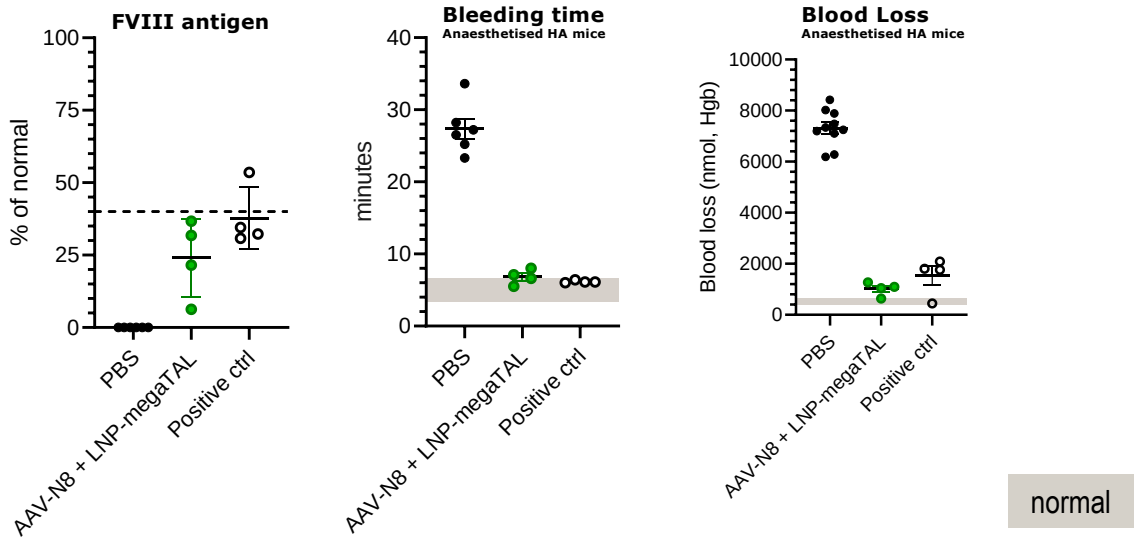


Mouse proof-of-concept
Bleed normalization

In vivo gene editing PoC for FVIII expression



In vivo gene editing PoC for FVIII expression*



Key Characteristics of the preclinical study

- AAV-N8 + LNP-megaTAL leads to integration of N8 gene in surrogate mouse alleles
- Duration of effect is not addressed in this study
- 1st-Gen mouse-model specific megaTAL reagent and AAV

**Positive ctrl - FVIII sequence anticipated from literature, delivered by AAV8 vector; Bleeding under anaesthesia. Data from 1 week post treatment.*

Data generated to date reach pre-established POC milestone criteria

- Pre-clinical proof of concept achieved across several metrics including integration, tolerability, LNP delivery technology and robust efficacy in multiple different animal models
  - Collaboration will continue to optimize the drug product towards pre-defined “option” criteria
- $15 Million Preclinical Milestone triggered in the Novo Nordisk collaboration on Hemophilia A
- Data show further validation of our megaTAL gene editing and in vivo mRNA platforms
  - Learnings and platform improvements can be leveraged for future oncology applications within 2seventy
- Potential for expansion of our in vivo editing platform into additional indications.

2seventybio

2seventy bio and Novo Nordisk Collaboration Delivers Key Proof of Concept Data, Triggering $15 Million Preclinical Milestone in In Vivo Gene Editing Hemophilia A Program

May 1, 2023 11:00 AM EDT

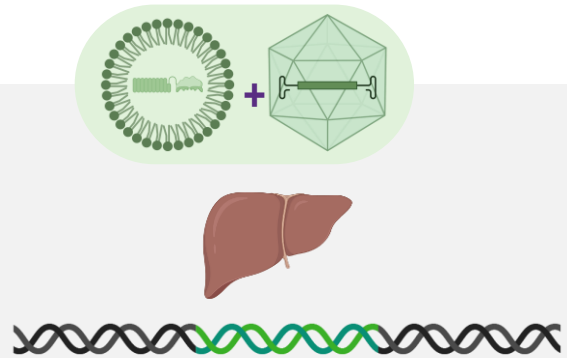
☑ Integration Metrics	☑ Efficacy Metrics	☑ Tolerability Metrics	☑ LNP Metrics

“Novo Nordisk is proud to work in such close and creative collaboration with the team at 2seventy. We are thrilled this program has achieved the strong proof of concept data, triggering this important milestone event.”

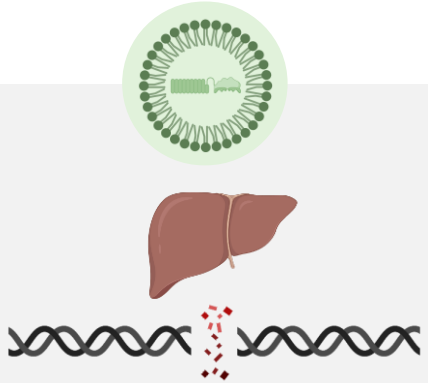
– Marcus Schindler, Executive vice president research and early development, and chief scientific officer, Novo Nordisk

novo nordisk®

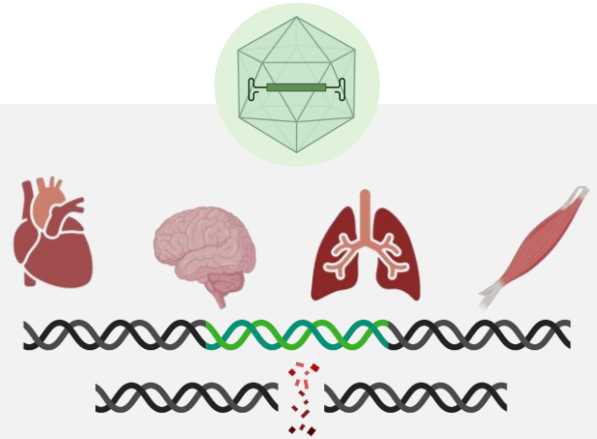
In vivo gene editing approaches
potential platform expansion



Liver Knock In



Liver Knock Out



Ex-Liver Knock Out/In

Development Considerations

- Same approach used for Heme A allows leveraging existing megaTAL, LNP, and AAV improvements
- POC with the Hem A program provides a development path.

- Simpler LNP/mRNA only drug product
- Leverage LNP IVGE progress in HemeA, lead LNP and mRNA process remains the same

- Delivery to non-liver tissue opens up broader indication potential
- Small monomeric megaTAL is easily packaged and delivered by AAV
- Other emerging delivery modalities offer optionality

Summary

Clinical progress with SC-DARIC33 in patients with AML

- First regulatable CAR T cell data from the clinical trial*
- Key questions addressed:
  - *Initial safety and tolerability in line with CAR T cell approaches*
  - *We can dose RAPA to target levels and turn the system on*
  - *SC-DARIC33 T cells activate and expand*
  - *SC-DARIC33 T cells traffic to, engage and kill target cells*

Potency of *ex vivo* CBL-B gene editing in CAR T cells

- Preclinical impact of CBL-B edits in CAR T cells*
- Supports enthusiasm for CBL-B gene editing in bbT369 (B-NHL program)
- First **clinical** application of our megaTAL technology

2seventy bio's NextGen AML approach…. *packed with innovation*

- Integration of innovations to create product 27T32 for AML:
  - Signal 1: Dual targeted
  - Signal 2: Novel high antigen sensitivity regulatable CAR architecture (RESET)*
  - Signal 3: Inducible IL15 cytokine support*

Progress on our Hemophilia A Collaboration with Novo Nordisk

- First direct *in vivo* application of the megaTAL technology
- Key proof of concept data and pre-clinical milestones achieved
- Supports additional applications of our mRNA and megaTAL technology

* *Presentations given at* ASGCT 26TH ANNUAL MEETING Los Angeles

2seventy bio's R&D philosophy

Identify the Key Problem

Understand **tumor** resistance
Explore new biology
Focus on the **hard problem**

Layer Innovations

Define clear hypotheses
Deploy our **unique** toolbox
Deliver **multi-nodal** solutions

Learn Fast in the Clinic

270-MPH (Internal DP Mfg)
Turbo-charge Clin. Translation
Operational **flex & efficiency**

Accelerate with Industry Leading Partnerships

Bristol Myers Squibb · gritstone ONCOLOGY · INHIBRX · 药明巨诺 JW Therapeutics · medigene · novo nordisk® · REGENERON

Q&A